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# Prevalence and Distribution of Carcinoma in Patients with Solitary and Multiple Thyroid Nodules on Sonography

Mary C. Frates, Carol B. Benson, Peter M. Doubilet, Elizabeth Kunreuther, Maricela Contreras, Edmund S. Cibas, Joseph Orcutt, Francis D. Moore, Jr., P. Reed Larsen, Ellen Marqusee, and Erik K. Alexander

*Department of Radiology (M.C.F., C.B.B., P.M.D., M.C.); Thyroid Section, Division of Endocrinology, Hypertension and Diabetes, Department of Medicine (E.K., J.O., P.R.L., E.M., E.K.A.); Department of Pathology (E.S.C.); and Department of Surgery (F.D.M), Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115*

**Context:** Controversy remains as to the optimal management of patients with multiple thyroid nodules.

**Objective:** The objective of this study was to determine the prevalence, distribution, and sonographic features of thyroid cancer in patients with solitary and multiple thyroid nodules.

**Design:** We describe a retrospective observational cohort study that was carried out from 1995 to 2003.

**Setting:** The study was conducted in a tertiary care hospital.

**Patients:** Patients with one or more thyroid nodules larger than 10 mm in diameter who had ultrasound-guided fine needle aspiration (FNA) were included in the study.

**Main Outcome Measures:** The main outcome measures were prevalence and distribution of thyroid cancer and the predictive value of demographic and sonographic features.

**Results:** A total of 1985 patients underwent FNA of 3483 nodules. The prevalence of thyroid cancer was similar between patients with a solitary nodule (175 of 1181 patients, 14.8%) and patients with multiple nodules (120 of 804, 14.9%) ($P = 0.95$, $\chi^2$). A solitary nodule had a higher likelihood of malignancy than a nonsolitary nodule ($P < 0.01$). In patients with multiple nodules larger than 10 mm, cancer was multifocal in 46%, and 72% of cancers occurred in the largest nodule. Multiple logistic regression analysis of statistically significant features demonstrates that the combination of patient gender ($P < 0.02$), whether a nodule is solitary *vs.* one of multiple ($P < 0.002$), nodule composition ($P < 0.01$), and presence of calcifications ($P < 0.001$) can be used to assign risk of cancer to each individual nodule. Risk ranges from a 48% likelihood of malignancy in a solitary solid nodule with punctate calcifications in a man to less than 3% in a noncalcified predominantly cystic nodule in a woman.

**Conclusions:** In a patient with one or more thyroid nodules larger than 10 mm in diameter, the likelihood of thyroid cancer per patient is independent of the number of nodules, whereas the likelihood per nodule decreases as the number of nodules increases. For exclusion of cancer in a thyroid with multiple nodules larger than 10 mm, up to four nodules should be considered for FNA. Sonographic characteristics can be used to prioritize nodules for FNA based on their individual risk of cancer. **(*J Clin Endocrinol Metab* 91: 3411–3417, 2006)**

POPULATION STUDIES SUGGEST that 3–8% of asymptomatic adults have thyroid nodules (1–4). The prevalence of such nodules increases with age (5). As increasing numbers of patients undergo imaging studies for medical evaluations, more and more thyroid nodules are being detected. Current diagnostic recommendations for patients with thyroid nodules are based primarily on data obtained from the evaluation of nodules before widespread use of ultrasonography. Based on these studies, nodules have a 5–15% prevalence of malignancy (5–9) and, thus, fine needle aspiration (FNA) of solitary nodules larger than 10–15 mm in maximal diameter is usually recommended if the patient is euthyroid (6, 10, 11).

On ultrasound examination, many patients thought to have a solitary nodule by physical exam are found to have additional nodules larger than 10 mm in diameter (4, 12–15). The recommended diagnostic approach for patients with multiple nodules is variable. Some advocate routine FNA of all nodules larger than 10 mm (16, 17), whereas others recommend FNA of only the largest nodule (18). Still others advocate follow-up alone based on the belief that cancer is rare when multiple nodules are present (19), or they suggest thyroid scintigraphy as an initial diagnostic test even when the patient is biochemically euthyroid (20). This lack of a consistent recommendation stems in part from the absence of studies investigating the prevalence and location of thyroid cancer in patients with multiple thyroid nodules.

FNA of a thyroid nodule is the method of choice for determining the risk that a given nodule is malignant (6, 7, 21, 22). A number of studies have also assessed various sonographic characteristics as predictors of thyroid cancer. Sonographic features reported to be associated with an increased risk of cancer include nodule size, presence of microcalcifications, hypoechogenicity, solid composition, absence of a halo, and irregular margins, among others (23–30). However, most of these studies involved small patient populations, and

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Abbreviation: FNA, Fine needle aspiration.

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none has systematically compared multiple nodules in the same gland with respect to predicting the risk of thyroid cancer based on combined sonographic criteria.

In our facility we perform a large number of ultrasound-guided FNAs and have routinely recommended FNA for all nodules larger than 10 mm regardless of the sonographic appearance or number of nodules. Thus, this patient population provides a large, unbiased sample to assess the risk of cancer in patients with thyroid nodules with various combinations of sonographic findings.

In this study, we retrospectively reviewed the records of all patients with one or more thyroid nodules larger than 10 mm in maximum diameter who had ultrasound-guided FNA. Our goal was to compare the risk of thyroid cancer in patients with solitary nodules to that in patients with multiple nodules. We also wished to determine whether or not sonographic features of thyroid nodules would be useful in predicting the risk of malignancy for a given nodule.

## Patients and Methods

Approximately 3200 patients without prior thyroid surgery or radioiodine exposure were referred to the multidisciplinary Thyroid Nodule Clinic at the Brigham and Women's Hospital (Boston, MA) between 1995 and 2003 for evaluation of suspected thyroid nodular disease. The criteria for referral were suspicion of the presence of one or more thyroid nodules by physical exam or the presence of an "incidental" nodule discovered by an imaging technique such as magnetic resonance imaging, computed tomography, or carotid ultrasound. All patients underwent thyroid sonography as part of their evaluation, and those patients with one or more thyroid nodules larger than 10 mm in diameter who had ultrasound-guided FNA are the subject of this report. Patients whose serum TSH was normal or elevated were advised to have ultrasound-guided FNA of all nodules larger than 10 mm in maximal diameter. If the serum TSH was less than 0.5 $\mu$U/ml, patients had thyroid scintigraphy to identify autonomously functioning nodules, which were not aspirated. Calcitonin measurements were not routinely performed.

Thyroid ultrasonography was performed by one of three radiologists, each with special expertise in thyroid sonography, using a 5- to 15-MHz transducer. Information about the sonographic examination was studied in depth in a subset of the patient population that underwent ultrasound-guided FNA between June 1995 and October 2000. For each nodule, sonographic images were reviewed by at least one of three radiologist participants in the study, and sonographic characteristics were recorded. Nodules were excluded from this part of the study if images were not available for review. For each nodule, the following sonographic characteristics were recorded: size, parenchymal composition, echogenicity, presence or absence of a halo, margin appearance, presence or absence of calcifications, type of calcifications, and presence or absence of other nodules larger than 10 mm in the gland. Size was recorded as three orthogonal dimensions. If a halo was present, measurements included the halo as part of the nodule. Parenchymal composition was classified based on subjective assessment of the approximate portion of the nodule that was cystic, as follows: completely solid, predominantly solid (1–24% cystic), mixed solid/cystic (25–74% cystic), predominantly cystic (75–99% cystic), or completely cystic. Echogenicity of each nodule that was more than 50% solid was determined by comparing the solid portion of the nodule to surrounding thyroid parenchyma and was reported as hyperechoic when more echogenic, isoechoic when similar, or hypoechoic when less echogenic than thyroid tissue. The presence and extent of a halo was classified as present around at least 50% of the nodule, present around less than 50% of the nodule, or absent. Margin appearance was categorized as well defined or poorly defined. Presence or absence of calcifications was noted for each nodule, and calcifications were classified as punctate, coarse, or isolated to the rim of the nodule. A nodule was considered solitary if there were no other nodules in the gland measuring larger than 10 mm in maximum diameter and nonsolitary if the thyroid contained at least one other nodule larger than 10 mm in maximum diameter. If a particular nodule underwent more than one FNA, the nodule was included in the database only once, and the images acquired at the time of the diagnostic aspirate or at the last ultrasound before surgery were used for the analysis. For a small number of nodules, not all sonographic characteristics were recorded.

FNA was performed by one of four thyroidologists under ultrasound guidance as previously described (15, 31). Three to four aspirates were performed per nodule using a 25-gauge needle. A maximum of three nodules was aspirated during a single visit. Most patients requiring more than one visit for complete evaluation of multiple nodules larger than 10 mm in diameter returned within 6 months of their initial evaluation. If the results of the initial FNA were nondiagnostic, a reaspiration was performed one or more times or the patient elected surgical resection.

All FNA specimens were collected in CytoLyt (Cytyc Corp., Marlborough, MA), and two slides were prepared using Thin-Prep 2000 (Cytyc Corp.). Thin-Prep slides were stained with a modified Papanicolaou procedure. In cases with residual cell sediment, a cell block was prepared by sedimentation, and two cell block sections were stained with hematoxylin and eosin. Specimens were considered nondiagnostic if insufficient cellular material (fewer than six groups of cells containing >10 cells each) was present and no evidence of cellular atypia was found. Diagnostic aspiration was classified as follows: benign, atypical cells of undetermined significance, suggestive of follicular neoplasm, suspicious for papillary carcinoma, or positive for papillary carcinoma. We recommended repeat FNA of nodules with a diagnosis of atypical cells of undetermined significance ("atypical" cytology). If "atypical" on repeat FNA, surgery was recommended. Nodules with FNA cytology suspicious or positive for papillary carcinoma or suggestive of a follicular neoplasm were referred for surgical resection. In all cases in which surgery was performed, the final diagnosis for each nodule larger than 10 mm in the gland was based on histopathological examination of the entire gland (32, 33).

Nodules larger than 10 mm were classified as benign if the FNA diagnosis was benign on an adequate FNA specimen, if no evidence of cancer was found on histological evaluation of a resected nodule, if thyroid scintigraphy indicated that the nodule functioned autonomously, or, if cystic, there was greater than a 50% reduction in maximum nodule diameter on follow-up ultrasound examination. In patients with multiple nodules, each nodule larger than 10 mm was individually classified as benign or malignant based on the above-described criteria. Thyroid cancers 10 mm or less in maximal diameter incidentally discovered on histopathological examination were excluded from analysis. Permission from the Investigational Review Board at the Brigham and Women's Hospital was granted to perform this review and analysis.

We analyzed our results on both a per-patient and a per-nodule basis. To determine which sonographic features were associated with thyroid cancer, $\chi^2$ analyses were used for categorical variables and the Student's $t$ test for continuous variables. $P < 0.05$ was accepted as significant. Statistically significant individual variables were then evaluated using multiple logistic regression analysis to generate a table that specifies the risk of malignancy based on a combination of nodule characteristics.

## Results

### *Prevalence of thyroid cancer in the study population*

Approximately 3200 patients were referred to the Nodule Clinic for diagnostic thyroid ultrasound and possible FNA from 1995–2003. About two thirds (2208) had at least one thyroid nodule larger than 10 mm in maximal diameter and underwent FNA. Of these, 223 patients were excluded from analysis because of the absence of a histopathological diagnosis. This resulted in a study population of 1985 patients with a total of 3483 nodules larger than 10 mm in largest dimension (Fig. 1). Two hundred forty-three (12.2%) of the 1985 patients were male, and 1742 (87.8%) were female. Fewer than 1% of patients reported exposure to childhood head or neck irradiation, and no patients had a familial history of medullary carcinoma of the thyroid.

Among the 1985 study patients, 295 (14.9%) had thyroid

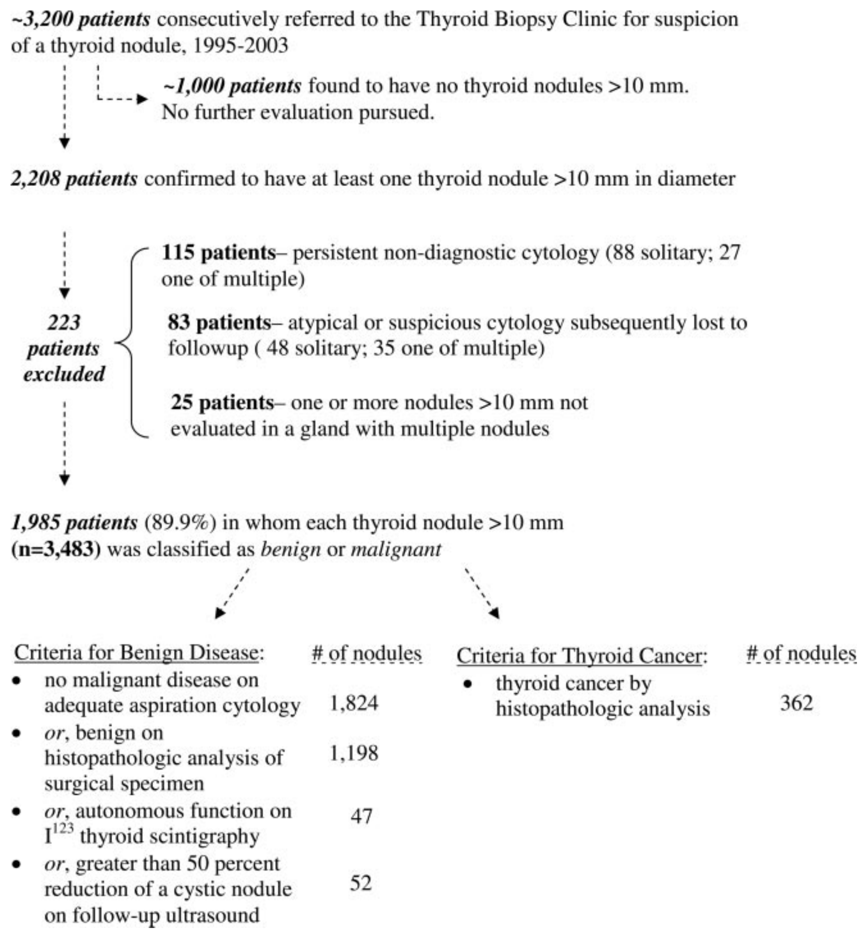


FIG. 1. Study population.

cancer, including 261 cases of papillary carcinoma, 27 of follicular carcinoma, three of medullary carcinoma, two of anaplastic carcinoma, and two of metastatic disease to the thyroid. One hundred eighty-eight of the 227 patients with thyroid cancer (82.8%) had American Joint Committee on Cancer (6th edition) stage I or II disease, and the remainder had stage III or IV disease. The mean age of patients with thyroid cancer was 46.2 ± 0.9 yr (mean ± SD) compared with 40.1 ± 0.3 yr in those without cancer ($P < 0.01$, *t* test). The rate of cancer in a man with nodules (49 of 243, or 20.2%) was higher than in a woman with nodules (246 of 1742, or 14.1%) ($P < 0.03$, $\chi^2$).

The 1985 study patients included 1181 (59.5%) with a solitary nodule larger than 10 mm in largest dimension and 804 (40.5%) who had two or more such nodules. There was no significant difference in sex distribution between the groups [females constituted 1035 (87.6%) of 1182 patients with a solitary nodule *vs.* 708 (88.1%) of the 804 patients with multiple nodules; $P = 0.74$, $\chi^2$]. Patients with solitary nodules were younger (48 ± 15 yr) than those with more than one nodule larger than 10 mm (53 ± 14 yr) ($P < 0.01$, *t* test).

The prevalence of thyroid cancer (Table 1) did not differ between patients with a solitary thyroid nodule (175 of 1181 patients, 14.8%) and patients with multiple nodules (120 of 804 patients, 14.9%) ($P = 0.95$, $\chi^2$). The types of thyroid cancer were also similar in the two groups: among the 175 solitary nodules that were cancers, 151 (86.3%) were papillary, 21 (12.0%) were follicular, and three (1.7%) were other types of cancer, whereas the corresponding numbers for the 120 cancers in glands with multiple nodules were 110 (91.7%) papillary, six (5.0%) follicular, and four (3.3%) other ($P = 0.09$, $\chi^2$ comparison of papillary *vs.* nonpapillary cancers in the two groups).

**TABLE 1.** Prevalence of thyroid cancer per patient and per nodule according to the number of nodules larger than 10 mm in maximum diameter

| No. of thyroid nodules >10 mm | No. of patients | Patients with thyroid cancer, no. (%) | No. of thyroid nodules | Malignant nodules, no. (%) |
|---|---|---|---|---|
| Single | 1181 | 175 (14.8)[a,b] | 1181 | 175 (14.8)[c,d] |
| Multiple | 804 | 120 (14.9)[a] | 2302 | 187 (8.1)[c] |
| 2 | 425 | 73 (17.2)[b] | 848 | 107 (12.6)[d] |
| 3 | 213 | 27 (12.7)[b] | 639 | 47 (7.4)[d] |
| ≥4 | 166 | 20 (12.1)[b] | 815 | 33 (4.0)[d] |

[a] $P = 0.95$, $\chi^2$ comparing cancer rate per patient in those with single nodules (n = 175 patients) to those with multiple nodules (n = 120 patients).

[b] $P = 0.30$, $\chi^2$ comparing cancer rate per patient in those with one nodule (n = 175 patients), two nodules (n = 73 patients), three nodules (n = 27 patients), and four or more nodules (n = 20 patients).

[c] $P < 0.001$, $\chi^2$ comparing cancer rate per nodule in those with single nodules (n = 175 nodules) to those with multiple nodules (n = 187 nodules).

[d] $P < 0.001$, $\chi^2$ comparing cancer rate per nodule in those with one nodule (n = 175 nodules), two nodules (n = 107 nodules), three nodules (n = 47 nodules), and four or more nodules (n = 33).

Unlike the per-patient comparison, a nodule that is one of several had a lower likelihood of being malignant than did a solitary nodule: 175 of 1181 solitary nodules (14.8%) were malignant, as opposed to 187 of 2302 nonsolitary nodules (8.1%) ($P < 0.001$, $\chi^2$). The per-nodule likelihood of cancer decreased progressively as the number of nodules larger than 10 mm increased (Table 1).

Of the 120 patients with thyroid cancer in a gland with more than one nodule, 87 (72.5%) had cancer in the largest thyroid nodule (Table 2). When more than two nodules larger than 10 mm were present, the malignancy was in the largest nodule about half the time. As the number of nodules increased, the frequency of cancer in the largest nodule decreased ($P = 0.03$), thus reducing the predictive value of FNA of the largest nodule. Sixty-five of the 120 patients (54.2%) with cancer in a gland with more than one nodule had a unifocal cancer, whereas the cancer was multifocal in 55 patients.

A strategy of biopsying the largest nodule would have detected only 86% of patients with two nodules who had cancer and approximately 50% of patients with three or more nodules who had cancer (Table 3).

*Prediction of cancer based on sonographic characteristics*

To determine the predictive value of sonographic features, we reviewed a subset of the nodules in the total population. Of the 1201 nodules that underwent FNA between June 1995 and October 2000, 201 were excluded because images could not be retrieved for review. Another 135 were excluded because pathological diagnosis was not available. The remaining 865 nodules (~70% of those aspirated during this period) comprised the study set for evaluation of sonographic features. Of these 865 nodules, 771 (89.1%) were benign and 94 (10.9%) were malignant, including 80 papillary cancers, 12 follicular cancers, and two anaplastic cancers.

In this study set, 780 of the nodules (90.2%) occurred in women and 85 (9.8%) in men. As in the larger group, the cancer was more likely in a nodule in a man (16 of 85, or 18.8%) than in a woman (78 of 780, or 10%) ($P < 0.02$, $\chi^2$).

To determine whether the likelihood of cancer was associated with nodule size (measured as maximum diameter), we divided nodules into size categories by 5-mm increments (Table 4) and compared size to rate of malignancy. There was no significant relationship between nodule size and likelihood of thyroid cancer ($P = 0.48$, $\chi^2$).

Those individual sonographic characteristics that had a statistically significant association with thyroid cancer included nodule composition (cystic *vs.* solid component), echogenicity (hypoechoic), presence and type of calcifications, and whether or not the nodule was solitary (Table 4).

**TABLE 2.** Location of cancer in 120 patients with multiple nodules and thyroid cancer

| No. of thyroid nodules >10 mm | No. of patients | Cancer in largest nodule, no. (%) | Cancer in two or more nodules, no. (%) |
|---|---|---|---|
| 2 | 73 | 63 (86.3) | 34 (46.6) |
| 3 | 27 | 16 (59.2) | 13 (48.1) |
| ≥4 | 20 | 8 (40.0) | 8 (40.0) |
| Total | 120 | 87 (72.5) | 55 (45.8) |

**TABLE 3.** Diagnostic yield of sequential aspiration strategies in 120 patients with multiple nodules and cancer

| FNA performed on | No. of nodules >10 mm | | |
|---|---|---|---|
| | 2 (n = 73) | 3 (n = 27) | ≥4 (n = 20) |
| Largest nodule | 86.3 | 51.8 | 55.0 |
| Largest 2 nodules | 100 | 81.5 | 85.0 |
| Largest 3 nodules | | 100 | 95.0 |
| Largest 4 nodules | | | 100 |

Results are percentages.

In particular, the more cystic a nodule was, the lower the likelihood of cancer. Hypoechoic nodules had a higher rate of malignancy than nodules that were isoechoic or hyperechoic. When compared with the malignancy rate for nodules without calcifications, the presence of coarse or rim calcifications increased the likelihood of cancer almost 2-fold, and punctate calcifications increased the likelihood almost 3-fold. As in the entire study population, the rate of cancer per nodule was nearly double in solitary nodules compared with nonsolitary nodules. The presence and extent of a halo around a nodule and the appearance of a nodule's margin (well defined or poorly defined) were not significantly associated with presence or absence of thyroid cancer.

The results listed above pertain to the relationship between an individual nodule characteristic and thyroid can-

**TABLE 4.** Relationship between sonographic characteristics of a thyroid nodule and its likelihood of malignancy

| Characteristic | No. benign[a] | No. malignant[a] | % Malignant | $P$ value[b] |
|---|---|---|---|---|
| Size (mm) | | | | 0.48 |
| 11–14.9 | 135 | 15 | 10.0 | |
| 15–19.9 | 167 | 16 | 8.7 | |
| 20–24.9 | 149 | 19 | 11.3 | |
| 25–29.9 | 112 | 11 | 8.9 | |
| ≥ 30 | 208 | 33 | 13.7 | |
| Composition | | | | <0.01 |
| Completely solid | 330 | 55 | 14.3 | |
| Predominantly solid | 209 | 24 | 10.3 | |
| Mixed solid and cystic | 129 | 8 | 5.8 | |
| Predominantly cystic | 85 | 2 | 2.3 | |
| Completely cystic | 7 | 0 | 0.0 | |
| Echogenicity | | | | <0.02 |
| Hypoechoic | 295 | 53 | 15.2 | |
| Hyper/isoechoic | 317 | 32 | 9.2 | |
| Calcifications | | | | <0.001 |
| Punctate | 79 | 24 | 23.3 | |
| Coarse | 50 | 10 | 16.7 | |
| Rim only | 5 | 1 | 16.7 | |
| None | 626 | 58 | 8.5 | |
| Solitary *vs.* multiple | | | | <0.002 |
| Solitary | 393 | 64 | 14.0 | |
| Multiple | 378 | 30 | 7.4 | |
| Halo | | | | 0.32 |
| None | 460 | 49 | 9.6 | |
| Present around <50% | 179 | 23 | 11.4 | |
| Present around ≥50% | 116 | 19 | 14.1 | |
| Margin | | | | 0.23 |
| Poorly defined | 153 | 14 | 8.4 | |
| Well defined | 592 | 78 | 11.6 | |

[a] Numbers of benign and malignant nodules for each characteristic do not always add up to the total number of benign and malignant nodules in the study sample, because information was not available for all characteristics of all nodules.
[b] $P$ value via $\chi^2$ test.

cer. To assess how the likelihood of malignancy can be determined based on a nodule's characteristics in combination, we applied multiple logistic regression analysis to those characteristics with the strongest association with malignancy, including female *vs.* male gender, solitary *vs.* nonsolitary status, cystic *vs.* solid composition, and presence and type of calcifications. This analysis yielded a table that specifies the risk of malignancy based on nodule characteristics in solitary and nonsolitary (Table 5) nodules. For any set of sonographic characteristics, the likelihood of a nodule being malignant is approximately twice as high in a solitary compared with a nonsolitary nodule and more than 1.5 times as high in a man compared with a woman.

## Discussion

This analysis of 1985 patients with one or more thyroid nodules larger than 10 mm evaluated by ultrasound and ultrasound-guided FNA demonstrates that the likelihood of thyroid cancer in a patient with one or more nodules larger than 10 mm is independent of the number of nodules and that sonographic characteristics are unable to accurately distinguish benign from malignant disease. In our cohort, 15% of patients had thyroid cancer, a prevalence that applied whether the patient had a solitary nodule or multiple nodules. Thus, the presence of multiple nodules was not more associated with a lower risk of thyroid cancer than was the presence of a solitary thyroid nodule. In patients with two or more nodules, aspiration of only the largest nodule would have missed almost one third of the malignancies.

In studies performed before ultrasound or without ultrasound-guided FNA, thyroid cancer was detected in approximately 5–9% of patients (8, 34, 35). More recent studies using ultrasound-guided FNA report a 7–14% prevalence of thyroid cancer, but none has evaluated all nodules larger than 10 mm in a large cohort of patients including those with multiple nodules (36–38). The prevalence of thyroid cancer in thyroidectomy specimens from patients with one or more thyroid nodules has been reported (38). Similar to our results, 14% of patients in that study had thyroid cancer, and no difference was found between those with solitary or multiple nodules. However, only 132 nodules were analyzed in 132 patients, suggesting that only one nodule was assessed per patient, even though multiple nodules were reported to be present in 47%. To the best of our knowledge, no other investigations have provided a complete malignancy assessment of all thyroid nodules larger than 10 mm.

Numerous studies have examined the relationship between sonographic features of thyroid cancer and malignancy. Although certain sonographic criteria are associated with increasing cancer risk, the predictive value of these criteria is not sufficiently high or low to preclude the necessity of FNA. Most studies of sonographic features have been based on small patient populations (27, 29, 30, 39) or were subject to ascertainment bias, in that definitive pathology was available for only a select subset of patients that was skewed toward those with the most suspicious nodules (23, 28, 30, 40, 41). Other studies have been limited to univariate analyses that evaluate one sonographic feature at a time (25, 42). This last issue is especially limiting, because in clinical practice each individual nodule has a constellation of sonographic features (*e.g.* solitary, predominately solid, with punctate calcifications), and its likelihood of malignancy depends on all of its characteristics. Our study of sonographic characteristics addresses, and largely overcomes, these limitations. Our sample is large, and we avoided ascertainment bias by performing FNA on all nodules, with further pathological information derived from the surgical specimen if the patient underwent thyroidectomy. Although sonographic criteria were analyzed in only about one third of our cohort, these subjects appear to be representative of the entire cohort.

In our study, patients were referred for ultrasound by primary care physicians because of an abnormal physical examination or an incidental imaging finding of a possible nodule. Only two thirds of the referred patients were found to have one or more nodules larger than 1 cm in diameter. We analyzed data from 90% of these patients. Therefore, we know of no selection or sample bias. Among those excluded from the final analysis, the proportion of patients with solitary and multiple nodules was nearly equal. Furthermore, all thyroid nodules were classified based on cytological or histopathological analysis. The rate of false-negative results at cytology has been shown to be very low (0.3–1.0%) (43, 44), making it unlikely many cancers were missed.

There is considerable variation among published recommendations and guidelines for appropriate evaluation of patients with more than one thyroid nodule. Some advocate no FNA unless worrisome ultrasound features are detected (19), whereas others suggest routine aspiration of only the

**TABLE 5.** Likelihood of malignancy in a thyroid nodule: results of multiple logistic regression of sonographic characteristics

| Nodule composition | Women | | | Men (%) | | |
|---|---|---|---|---|---|---|
| | Punctate calcifications (%) | Coarse or rim calcifications (%) | No calcifications (%) | Punctate calcifications (%) | Coarse or rim calcifications (%) | No calcifications (%) |
| Solitary nodule | | | | | | |
| Completely solid | 32.7 | 26.1 | 14.3 | 47.8 | 39.9 | 23.9 |
| Predominantly solid | 25.2 | 19.6 | 10.3 | 38.7 | 31.4 | 17.8 |
| Mixed solid and cystic | 15.7 | 11.9 | 6.0 | 25.9 | 20.3 | 10.7 |
| Predominantly cystic | 6.4 | 4.7 | 2.3 | 11.3 | 8.5 | 4.2 |
| Completely cystic | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| One of multiple nodules | | | | | | |
| Completely solid | 17.9 | 13.7 | 7.0 | 29.1 | 23.0 | 12.3 |
| Predominantly solid | 13.1 | 9.9 | 4.9 | 22.1 | 17.1 | 8.9 |
| Mixed solid and cystic | 7.7 | 5.7 | 2.8 | 13.6 | 10.2 | 5.1 |
| Predominantly cystic | 3.0 | 2.2 | 1.0 | 5.4 | 4.0 | 1.9 |
| Completely cystic | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |

largest nodule (18). The American Association of Clinical Endocrinologists has recommended "FNA of all thyroid nodules when the possibility of malignancy is appreciable" (16). Sampling of only one or two nodules was considered reasonable according to one survey of endocrinologists in the United States (45). Recent recommendations suggest FNA of most nodules greater than 10–15 mm, particularly those with worrisome sonographic characteristics (10, 11).

FNA of more than one nodule is uncomfortable, time consuming, costly, and carries a small but finite risk. It would be desirable to be able to identify nodules with either a very high or very low risk of malignancy to permit prioritization for FNA. Our univariate analyses of sonographic features demonstrated that a number of characteristics correlate with the chance a nodule is cancer, whereas others do not. The sonographic feature most closely associated with malignancy is nodule composition: the more cystic a nodule, the less likely it is to be malignant, and completely cystic nodules were never malignant in our study population. Other sonographic characteristics that correlate with malignancy include the presence and nature of calcifications, whether the nodule is solitary or not, and (in nodules that are >50% solid) the nodule's echogenicity. In contrast, nodule size, margin definition, and presence and extent of a halo around the nodule are all unrelated to its risk of malignancy, at least among nodules with maximum diameter larger than 10 mm. Among nonsonographic features, patient age does not correlate with the likelihood of malignancy, but gender does. A nodule in a man is significantly more likely to be malignant than is a similar nodule in a woman.

The results of our univariate analyses are concordant with some findings of prior studies but disagree with others. Our findings that predominately solid nodules, hypoechoic nodules, and those with punctate calcifications are more likely to be malignant than are nodules without these characteristics are consistent with prior studies (23, 24, 26, 28, 30). Unlike prior investigations (27, 30, 39, 46–48), however, we did not find that coarse or rim calcifications or a halo around some or all of a nodule are indicators of benignity. Instead, we found that a halo has no prognostic significance and that coarse or rim calcifications double the risk of malignancy compared with a similar nodule without calcifications (although this is lower than the 3-fold increase in risk associated with fine punctuate calcifications).

Several studies have identified a role for color Doppler in the evaluation of thyroid nodules. Nodules with prominent central flow have an increased risk of malignancy (23, 27, 41, 42). It is a limitation of the sonographic portion of this study that Doppler was not included. During the dates of data acquisition, the role of Doppler had not yet been established, and color Doppler of thyroid nodules was not routinely performed in our laboratory. The Doppler results for a small subset of the nodules included in this analysis have been previously published (49).

Using the results of our multivariate analysis of sonographic characteristics, for any thyroid nodule seen on ultrasound with a maximum diameter larger than 10 mm, the likelihood of malignancy can be determined, based on its solid/cystic composition, presence and type of calcifications, whether or not the nodule is solitary, and the gender of the patient. For example, a solitary nodule without calcification that is mixed cystic/solid has a 6.0% likelihood of malignancy if the patient is female and a 10.7% likelihood if the patient is male. If the nodule had punctate calcifications, the risk would increase in a female to 15.7% and in a male to 25.9%. When all factors point toward malignancy (solitary, solid nodule with punctate calcifications in a man) there is a 47.8% likelihood that the nodule is malignant.

The results of our study support recommendations about how many nodules to biopsy when multiple nodules are present and, if only a subset is to be sampled, how to select which nodules to biopsy. In the patient with multiple thyroid nodules, our findings suggest that all nodules should be biopsied when up to three nodules larger than 10 mm in maximal diameter are present, and perhaps four nodules be biopsied when four or more nodules larger than 10 mm in maximal diameter are present. Among our patients with two nodules larger than 10 mm, about 15% of cancers would have been missed if only the largest nodule had been aspirated, and in those with three or more nodules larger than 10 mm, nearly 50% of the cancers in patients would have been missed if only the largest nodule had been aspirated. Approximately 15% of the cancers in patients with more than three nodules would not have been detected if only the two largest nodules had been aspirated. Our data confirm that sonography cannot be used to confidently exclude malignancy based on its negative predictive value.

In some cases, a decision may be made to biopsy only a subset of nodules in a gland with multiple nodules (*e.g.* if there are a large number of nodules >10 mm). In such cases, the results of our multivariate analysis can provide guidance about which nodules should be sampled. The nodule (or nodules) with the highest sonographic risk would be one(s) chosen to undergo biopsy. Our results also call into question whether noncalcified, predominantly or completely cystic nodules need to undergo FNA, because our multivariate analysis indicates that such nodules in a gland with multiple nodules have a less than 2% chance of malignancy.

In summary, in a patient with one or more thyroid nodules larger than 10 mm in maximum diameter, the likelihood of thyroid cancer is independent of the number of thyroid nodules. In patients with a thyroid cancer and multiple thyroid nodules, the cancer is often unifocal but not always present in the largest nodule. Thus, for confident exclusion of thyroid cancer in a gland with multiple nodules larger than 10 mm, up to four nodules larger than 10 mm should be considered for aspiration when present. If the decision is made to biopsy only a subset of nodules in a gland with multiple nodules, the results of our multivariate analysis can be used to prioritize nodules based on their risk of cancer.

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Address all correspondence and requests for reprints to: Erik K. Alexander, M.D., Thyroid Section, Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, 75 Francis Street, PBB-B4, Boston, Massachusetts 02115. E-mail: ekalexander@partners.org.

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Current address for M.C.: Department of Radiology, Madigan Army Medical Center Building, 9040 Fitzsimmons Drive, Tacoma, Washington 98431.

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