Effect of Thyroid Gland Volume in Preoperative Detection of Suspected Malignant Thyroid Nodules in a Multinodular Goiter

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Hypothesis: The detection of suspected malignant thyroid nodules by ultrasonography is associated with thyroid gland volume and tumor size.

Design: Prospective clinical trial.

Setting: A tertiary referral center.

Patients: Three hundred sixty-five patients with a multinodular goiter with coexistent dominant nodules.

Main Outcome Measures: The correlation between thyroid gland volume and tumor size and the detection of suspected malignant thyroid nodules by ultrasonography. The incidence of thyroid carcinoma inside and outside the dominant nodules and thyroid gland volume and tumor size in suspected or unsuspected malignant thyroid nodules by ultrasonography were determined. Receiver operating characteristic analysis was used to identify the cutoffs of the tumor size and thyroid gland volume.

Results: One hundred thyroid carcinomas were found in 69 (18.9%) patients. Forty-one of these carcinomas were inside the dominant nodule, whereas 59 were outside the dominant nodule. Only 9 of the 59 thyroid carcinomas outside the dominant nodules were suspected of being malignant by ultrasonography. Thyroid gland volume less than 38 mL and tumor size larger than 7 mm had 48-fold (odds ratio, 48; P < .001) and 21.5-fold (odds ratio, 21.5; P < .001) increased rates, respectively, of detecting suspected malignant thyroid nodules by ultrasonography.

Conclusions: Thyroid gland volume and tumor size were significantly associated with detection of suspected malignant thyroid nodules by ultrasonography. Small thyroid gland volume was associated with detection of suspected malignant thyroid nodules in multinodular goiters.

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THYROID NODULES OCCUR frequently, especially in middle-aged to elderly women.1,2 The prevalence of thyroid nodules rises from 5% using palpation alone to 30% to 50% using ultrasonography. However, only 5% of these thyroid nodules have been found to be malignant.3-5 Ultrasonography is a useful tool for tumor evaluation because of its safety, noninvasiveness, lack of radiation, and effectiveness.7-9 Using a high-resolution probe, it not only detects the presence, site, number, and size of thyroid nodules, but also clearly documents their characteristics. Ultrasonography has a high sensitivity for detecting nodules as small as 2 to 3 mm. Incidental thyroid nodules are an increasingly common finding because of the expanding use of high-resolution ultrasonography. However, it is important to differentiate malignant nodular lesions from benign nodules to avoid unnecessary thyroidectomies.9,10 The microcalcification, hypoechogeticity, and intranodular vascularity detected by ultrasonography are generally accepted as the most reliable indicators of malignancy; however, the overall sensitivity is low.9-10

Fine-needle aspiration biopsy (FNAB) is considered the most reliable test for the diagnosis of malignant nodular lesions.11-15 Although most clinicians recommend FNAB for a single nodule,16,17 this consensus does not include multinodular goiters (MNGs).18-20 Puncturing all of the palpable nodules is not practical when the clinical suspicion of malignancy is low.20,21 The problem for clinicians is selecting nodules for FNAB, because FNAB

See Invited Critique at end of article

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is not useful for differentiating an MNG with a malignant nodular lesion from a benign MNG. The aims of this prospective clinical study were (1) to evaluate the utility of preoperative FNAB on the dominant nodule and nodules sonographically suspected of being malignant in the MNG and (2) to investigate whether thyroid gland volume and tumor size might affect the detection of suspected malignant nodular lesions using ultrasonography. To our knowledge, this is the first study performed to evaluate the utility of thyroid gland volume in detecting suspected malignant thyroid nodules in MNGs.

METHODS

PATIENTS

We performed a prospective clinical study in 402 consecutive patients undergoing an operation for an MNG at the Istanbul Medical Faculty between September 2005 and September 2006. This study included 365 patients with an MNG with coexistent dominant nodules. Thirty-seven patients were excluded owing to a history of head and neck irradiation; a family history of thyroid carcinoma; suspicious symptoms; or clinical findings that would suggest thyroid malignancy, such as a rapidly enlarging nodule, throat hoarseness, or palpable lymph nodes. None of the patients refused to participate. Of 365 patients, 336 (92.1%) had a euthyroid MNG and 29 (7.9%) had a toxic MNG. None of the patients refused to participate. Of 365 patients, 336 (92.1%) had a euthyroid MNG and 29 (7.9%) had a toxic MNG.

The mean dominant nodule size was 33.4 (6.7) mm in diameter, with a female to male ratio of 7.1:1 (n=320:45). The median age of the patients was 49 years (range, 17-75 years), with a female to male ratio of 7.1:1 (n=320:45). The median age of the patients was 49 years (range, 17-75 years), with a female to male ratio of 7.1:1 (n=320:45).

THYROID VOLUME

Total thyroid gland volume was evaluated by ultrasonography. A radiologist (A.S.) experienced in sonography conducted the examinations using different sonographic equipment (Siemens, Erlangen, Germany; Logic 7, General Electric, Milwaukee, Wisconsin; Sonoline Antares, Siemens) with high-frequency (13 MHz) linear probes. Volumetric measurements were made from remnant tissue in 3 perpendicular planes using axial and sagittal images and volume-calculation software available within the equipment. Thyroid volume was estimated through the following equation: volume = length x width x depth x 0.5233.

ULTRASONOGRAPHY FNAB

A single radiologist (A.S.) performed ultrasonography FNAB on all patients by using a broad-band linear transducer (VFX 13-5, Sonoline Antares, Siemens). Ultrasonography FNAB was routinely employed for dominant nodules whether or not they were palpated. Fine-needle aspiration biopsy was also performed when ultrasonography had suspicious findings (ie, a hypoechoic nodule with punctuate calcifications and/or irregular borders). Experienced endocrine cytopathologists performed cytologic examinations on the FNAB specimens. During the procedure, the patient was kept in the supine position with a slight hyperextension of the neck. Local anesthesia was routinely applied. After aspiration, samples were placed on slides and dried. One to 3 slides from each patient were stained with hematoxylin-eosin to confirm the presence of thyroid follicular cells. If the number of follicular cells was insufficient, the procedure was repeated.

EVALUATION OF CYTOLOGICAL DIAGNOSIS

The nodules were classified as benign (typical follicular cells), malignant (atypical follicular cells with malignant nuclear features), indeterminate (follicular neoplasms or suspicious for malignancy), or nondiagnostic (< 6 clusters of follicular cells visualized on ≥ 2 samples). Suspicious or indeterminate FNAB, suggesting follicular proliferation, was considered positive. All thyroidectomy specimens underwent histopathologic examination. On gross examination, all occult lesions were sampled. Tissue samples were embedded into paraffin blocks, from which ultrathin sections of 3 to 5 µm were obtained.

Sensitivity (%) = (True-Positive/True-Positive + False-Negative) × 100

Specificity (%) = (True-Negative/True-Negative + False-Positive) × 100

Positive Predictive Value (%) = (True-Positive/True-Positive + False-Positive) × 100

Negative Predictive Value (%) = (True-Negative/True-Negative + False-Negative) × 100

Statistical Analysis

Data were analyzed using SPSS, version 11.0 (SPSS Inc, Chicago, Illinois). Results were expressed as mean (SD). Comparisons of data were carried out using Mann-Whitney U and χ² tests. Receiver operating characteristic analysis was used to identify the cutoff values of the tumor size and thyroid gland volume. The Spearman test was used for correlation analyses. Results were considered statistically significant at P < .05 (2-tailed).

RESULTS

PATIENTS

The median age of the patients was 49 years (range, 17-75 years), with a female to male ratio of 7.1:1 (n=320:45). The mean dominant nodule size was 33.4 (6.7) mm
(range, 15-80 mm). Total and near-total thyroidectomies were performed in all patients. The mean thyroid volume was 66.6 (46) mL (range, 10-365 mL).

EVALUATION ACCORDING TO BENIGN/MALIGN PATHOLOGY

Of 365 patients, 69 (18.9%) patients had thyroid carcinoma and 296 (81.1%) patients had benign MNGs. There were no significant differences in age or sex between patients with thyroid carcinoma and patients with MNG (48.4 [13.7] years, 58 women and 11 men vs 47.7 [12.6] years, 262 women and 34 men, respectively, P > .05). The mean dominant nodule size and thyroid volume in patients with thyroid carcinoma were significantly lower than in patients with benign pathology (22.19 [14] mm and 38.05 [18] mL vs 30.1 [12] mm and 73.3 [48] mL, respectively, P < .001).

HISTOPATHOLOGIC FINDINGS

Histopathologic examination revealed thyroid carcinoma in 69 (18.9%) patients, follicular adenoma in 10 (2.7%) patients, and colloid nodular goiters in 286 (78.3%) patients. Of 365 patients, 14 (4.8%) had chronic lymphocytic thyroiditis. Three patients with chronic lymphocytic thyroiditis had thyroid carcinoma; the remaining 11 patients had benign pathology. All patients with chronic lymphocytic thyroiditis had positive thyroid antibodies.

Of the 69 patients with thyroid carcinoma, 63 (91%) had papillary carcinoma, 5 (5%) had follicular carcinoma, and 1 (1%) had medullary thyroid carcinoma. The mean tumor size of thyroid carcinomas, either inside or outside the dominant nodule, was 12.4 (12) mm (range, 1-80 mm). The histopathologic criteria of thyroid carcinomas showed that thyroid capsule invasion was present in 38 patients (55%) and vascular invasion was present in 3 (4.3%) patients. Forty-one of the 69 patients (59.4%) with thyroid carcinoma had carcinoma inside and 28 (40.6%) patients had carcinoma outside the dominant nodule. Seventeen patients had thyroid carcinoma both inside and outside the dominant nodule. The carcinomas were multifocal in 12 patients (2 foci in 8 patients and 3 foci in 4 patients). One hundred foci of thyroid carcinomas, including those that were inside and outside the dominant nodule, were found in the 69 patients with thyroid carcinoma.

| Table 1. Characteristics of Thyroid Carcinoma Inside or Outside the Dominant Nodule |
|---------------------------------------------------|---------------------------------|---------------------------------|-----------------|
| Characteristic                                    | Inside the Dominant Nodule (n=41) | Outside the Dominant Nodule (n=59) | P Value         |
| Tumor size, mean (SD), range, mm                  | 22.19 (14), 15-80                 | 5.7 (4.4), 1-22                  | .001            |
| Capsular invasion, %                              | 53.6                             | 27.1                             | .007            |
| Follicular variant, %                             | 7.3                              | 0                                | .03             |
| Vascular invasion, %                              | 9.7                              | 8.7                              | .82             |

| Table 2. Characteristics of Thyroid Carcinoma Suspected or Unsuspected of Being a Malignant Nodule by Ultrasonography |
|---------------------------------------------------------------|-----------------|-----------------|-----------------|
| Characteristic                                                        | Suspected Malignant (n=9) | Unsuspected Malignant (n=50) | Z Score | P Value |
| Mean (SD), Range                                                     |                  |                  |                |         |
| Tumor size, mm                                                       | 13.2 (5.6), 12-22 | 4.4 (2.3), 1-22  | 4.29           | <.001   |
| Thyroid gland volume, mL                                            | 27.66 (13), 10-48 | 69.84 (29), 35-365 | 4.31           | <.001   |

THYROID CARCINOMA INSIDE AND OUTSIDE THE DOMINANT NODULE

Of 100 thyroid carcinomas, 41 (41%) were inside the dominant nodule and 59 (59%) were outside. The incidence of thyroid carcinoma outside the dominant nodule was significantly higher than that inside (z=-6.48, P < .01). Of 59 thyroid carcinomas outside the dominant nodule, 52 (88.1%) had tumor sizes smaller than 1 cm. The mean tumor size of thyroid carcinoma inside the dominant nodule was significantly larger than thyroid carcinoma outside the dominant nodule (22.19 [14] mm vs 5.7 [4.4] mm, respectively, z=-7.554, P < .001). The prevalences of capsular and vascular invasions for thyroid carcinoma inside the dominant nodule were significantly higher than that of thyroid carcinoma outside the dominant nodule (53.6% vs 27.1%, P < .007, and 7.3% vs 0%, P = .03, respectively) (Table 1).

HISTOPATHOLOGIC FINDINGS CORRELATED WITH PREOPERATIVE FNAB

Fine-needle aspiration biopsy was performed in 389 nodules in 365 patients. The dominant node was sampled in all of them and in another 24 thyroid nodules owing to suspected malignancy by ultrasonography findings. Analysis of the FNAB parameters obtained and compared with the histologic findings to rule out malignancy yielded a sensitivity of 76%, a specificity of 86%, and a diagnostic accuracy of 87%, with a positive predictive value of 47% and a negative predictive value of 96%.

SUSPECTED VS UNSUSPECTED MALIGNANT THYROID NODULES BY ULTRASONOGRAPHY

Of 59 thyroid carcinomas outside of the dominant nodule, only 9 (15.2%) nodules were suspected of being a malignant nodular lesion by ultrasonography, thus ultrasonography FNAB was performed. The tumor size in suspected malignant nodules was significantly larger than in unsuspected malignant nodules (13.2 [5.6] mm vs 4.2 [2.3] mm, respectively, z=4.29, P < .001). The mean thyroid volume in suspected malignant nodules was significantly smaller than in unsuspected malignant nodules (27.66 [13] mL vs 69.84 [29] mL, respectively, z=4.31, P < .001) (Table 2).
According to receiver operating characteristic analysis, the optimal cutoff values of thyroid gland volume and tumor size were 38 mL and 7 mm, respectively. Thyroid gland volume less than 38 mL had a 48-fold increased rate (odds ratio, 48; 95% confidence interval, 6.62–347.74; P < .001) and tumor size larger than 7 mm had a 21.5-fold increased rate (odds ratio, 21.5; 95% confidence interval, 3.68–125.32; P < .001) of detecting suspected malignant thyroid nodules by ultrasonography. Powers for the thyroid gland volume and tumor size were 0.96 and 0.93, respectively. The detection of suspected malignant thyroid nodules by ultrasonography was significantly and positively correlated with the tumor size (r = 0.56, P < .001), whereas it was significantly and negatively correlated with thyroid gland volume (r = −0.56, P < .001) (Figure).

**COMMENT**

We found that thyroid volume and tumor size were significantly associated with detection of suspected malignant thyroid nodules by ultrasonography. When the thyroid volume was less than 38 mL, the rate of detection of suspected malignant thyroid nodules by ultrasonography increased. Moreover, when the tumor size was larger than 7 mm, the rate of detection of suspected malignant thyroid nodules by ultrasonography increased.

Thyroid nodules are common in the adult population, and their prevalence is seemingly dependent on the method of detection.[1,6] Palpation findings in iodine-sufficient geographic areas revealed a nodule prevalence of 5%.[5,7] Even in iodine-sufficient regions, the prevalence of thyroid nodules in the general population detected by ultrasonography is as high as 50%. Thyroid nodules are encountered 2 to 3 times more frequently in endemic areas.[5,6] Several autopsy studies have estimated thyroid nodule prevalence to range from 40% to 50%.[6,10]

Thyroid nodules found incidentally are increasingly common because of the expanding use of imaging studies.[7,8] Ultrasonography characteristics proved to be predictive of the risk of malignancy.[9,10] Thyroid ultrasonography permits the detection of thyroid nodules as small as a few millimeters. Most of these lesions are benign, but the clinical problem is distinguishing those nodules from benign nodules. Contradictory methods for the management of nonpalpable thyroid nodules have been proposed.[1,2,14] Some authors recommend ultrasonography FNAB in nonpalpable thyroid nodules, whereas others consider a simple follow-up with neck palpation to be sufficient when there is no family history of thyroid cancer or head/neck irradiation.[6,17] Fine-needle aspiration biopsy is not useful for differentiating an MNG with malignant foci from a benign MNG.[22,23] The problem for clinicians and radiologists is selecting nodules for FNAB. We are frequently confronted with this problem, as biopsies of all nodules are not possible.

In our study, ultrasonography FNAB was routinely employed for dominant nodules and also performed for suspected malignant nodular lesions when ultrasonography indicated suspicious findings, including a hypoechoic nodule in association with punctuate calcifications and/or irregular borders. Of 365 patients with MNGs associated with a dominant nodule, only 41 (11.2%) patients had thyroid carcinomas in the dominant nodule. We found that ultrasonography FNAB had a sensitivity of 76% and a positive predictive value of 47%.

In a recent study, FNAB guided by manual palpation was carried out on the dominant nodule and any other nodules with clinical features suggesting malignancy.[24] Fine-needle aspiration biopsy positively identified 16.6% of confirmed malignancies; 55% of patients with malignancy had a benign FNAB result. Overall sensitivity and the positive predictive value of FNAB was 17% and 32%, respectively.[24] Consequently, FNAB was not useful for
differentiating an MNG with malignant foci from a benign MNG. An indeterminate result of FNAB was considered negative. If this result of FNAB was considered positive, the sensitivity for detecting carcinomas increased from 17% to 34%.

In several studies, the improved resolution of the ultrasonography and the use of FNAB, usually under ultrasound guidance, enabled the preoperative diagnosis of extremely small papillary thyroid carcinomas. Moreover, a significant number of patients with papillary microcarcinomas had locally advanced disease at the time of surgery. This finding suggests that the small size cannot guarantee low risk of thyroid papillary carcinoma found incidentally. The treatment of thyroid microcarcinomas is still a matter of discussion. Many microcarcinomas may remain occult and are diagnosed as an incidental finding during surgery for benign thyroid disorders. However, some microcarcinomas may result in a negative outcome, including distant metastasis and patient death.

The wide application of screening ultrasonography for the evaluation of thyroid or carotid artery lesions; the use of FNAB, usually under ultrasonographic guidance; and the refinement of pathologic procedures have led to an increase in the diagnosis of incidental thyroid carcinoma. In these studies, the malignancy rate within thyroid incidentalomas was between 13% and 28.8%, all nodules were incidentally found, and incidental carcinoma was diagnosed following FNAB. There was not any information regarding the thyroid volumes in those particular patients.

In conclusion, this is the first study to evaluate the effects of thyroid gland volume and tumor size on the detection of suspected malignant thyroid nodules outside the dominant nodule in MNGs. In patients having MNGs with coexistent dominant nodules, ultrasonography might not be useful in detecting the suspected malignant thyroid nodules when the thyroid gland volume is high.

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REFERENCES


Erbil and colleagues have noted that thyroid cancer occurred more often in smaller thyroid glands and in bigger thyroid nodules. They report that 69 of 365 consecutive patients (18.9%) undergoing thyroidectomy for an MNG and a dominant thyroid nodule without a history of exposure to low-dose therapeutic radiation; clinical manifestations suggesting thyroid cancer, such as ipsilateral lymph adenopathy or hoarseness; or a family history of thyroid cancer had thyroid cancer. Overall, 100 thyroid cancers were identified in these 69 patients, 41 in the dominant nodule and 59 elsewhere in the thyroid gland. Smaller thyroid glands (<38 mL) had a 48-fold increased rate of malignancy, whereas large nodules (>7 mm) also had a significantly increased rate of being thyroid cancer. This overall cancer rate of 18.9% seems a little higher than expected. This may be due to the use of fine-needle aspiration cytology. The increased rate of thyroid cancer may also be caused by some selection or referral bias. The authors’ findings seem to make sense, since patients with larger goiters have a reason other than cancer for an enlarged thyroid gland, including growth factors, such as epidermal growth factor, thyroid-stimulating hormone, and insulin like growth factor. When I palpate the pyramidal lobe, I know that there is a general stimulus to the thyroid gland so that a malignant neoplasm is less likely.

Despite this, previous studies report that an MNG increases the risk of thyroid cancer, though many of these carcinomas are incidental; such a situation appears to have occurred in this study, since 59% of the identified thyroid cancers were not in the dominant nodule. The natural history of occult thyroid cancers is unknown, though most are never of clinical consequence.

The authors state that their patients are from an iodine-inadequate area, yet 91% of their patients had papillary thyroid cancer and only 5% had follicular cancer. The frequency of follicular cancer usually increases in patients from iodine-deficient areas.

The authors used ultrasound-directed FNAB for all dominant nodules, and carcinoma was diagnosed in 11.2% of the 365 patients. Although, as the authors report, microcalcification, hypoechogenicity, and intranodular vascularity by ultrasound examination suggest cancer, these findings are not found in many cancers.

Regarding thyroid nodule size, one would expect thyroid cancers to be larger than benign nodules and we know that larger thyroid cancers are more aggressive. Some studies suggest that thyroid cancers in MNGs are frequently not in the largest thyroid nodule.1 On clinical examination, the hard or gritty solitary or dominant nodule is at higher risk of being thyroid cancer and should be biopsied under ultrasound guidance.

This clearly written article by an excellent group of physicians in Istanbul provides useful information regarding the treatment of patients with dominant thyroid nodules in an MNG. Such patients with smaller thyroid glands and larger dominant nodules have the highest risk of having thyroid cancer.

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