Nodule hypoechogenicity, microcalcifications, and a height-to-width ratio ≥1 are independent factors predicting malignancy in thyroid nodules regardless of nodule size

Popowicz B, Klencki M, Lewinski A, Slowinska-Klencka D. The usefulness of sonographic features in selection of thyroid nodules for biopsy in relation to the nodule's size. Eur J Endocrinol 2009;161:103-11.

SUMMARY

BACKGROUND The wide use of neck ultrasonography has altered the diagnostic approach to thyroid nodules, often revealing many small nodules of uncertain clinical significance on the one hand, and multiple large thyroid nodules on the other, posing the question as to which nodules should undergo fine-needle aspiration biopsy (FNAB). The aim of this study was to evaluate the diagnostic efficacy of ultrasound features that are most useful in establishing the indication for FNAB as it relates to the size of thyroid nodules.

METHODS This is a retrospective study of thyroid nodules diagnosed from 2000 through 2005 in 672 patients who were referred to thyroid surgeons for the management of thyroid nodules at the Medical University of Lodz in Poland. Many of these patients had large multinodular goiters, some of which had benign FNAB cytologic features and others that were suspected of having malignancy. Patients with a history of external-beam or ionizing radiation were excluded from the study. All of the ultrasound examinations were performed by three physicians with at least 5 years of experience with the same ultrasound equipment. Based on the postoperative histopathology, the thyroid nodules were classified as malignant or benign to facilitate an analysis of the nodule ultrasound features, including nodule shape, echogenicity, and intranodular blood flow pattern, and the presence of microcalcifications and multiple nodularity and tumor palpability. The following ultrasound features were analyzed: nodule shape (anterior–posterior dimension [height] compared with the transverse dimension [width] of the nodule to provide a height-to-width ratio in two diagnostic categories [≥1 and <1], nodule echogenicity, solidity and hypoechoic patterns, Doppler blood-flow patterns (intranodular vascular vs. other patterns) and the presence of other thyroid nodules in the thyroid gland. The features of malignancy were evaluated separately according to nodule size, which was categorized as small (<15 mm) and large (≥15 mm). In addition, the study included all accompanying nodules described in the ultrasound report and the postoperative histology report. Nodule margins were not described in a uniform fashion and thus could not be included in the analysis.

RESULTS The study comprised 1141 nodules in 672 patients whose mean (±SD) age was 49.5±11.4 years and for whom data on nodule palpability and histopathology were available. The analysis included 316 nodules for which Doppler blood-flow patterns were available and only 210 nodules for which data were available concerning the nodule shape. In all, 881 nodules were benign follicular adenomas and 96 were malignant (72 papillary, 11 medullary, 5 oxyphilic [Hürthle cell], 2 follicular thyroid, and 4 anaplastic thyroid). Among the 96 cancers, 33 (34%) had diameters less than 10 mm. There were 462 large nodules (40.5%) and 679 small nodules (59.5%).The mean nodule diameter was 32.97±14.31 mm (median, 28; range, 15 to 80) in the large-nodule group, and 11.25±2.7 mm (median, 10; range, 4 to 15) in the small-nodule group. As compared with the benign tumors, the malignant tumors were more often hypoechoic (61.5

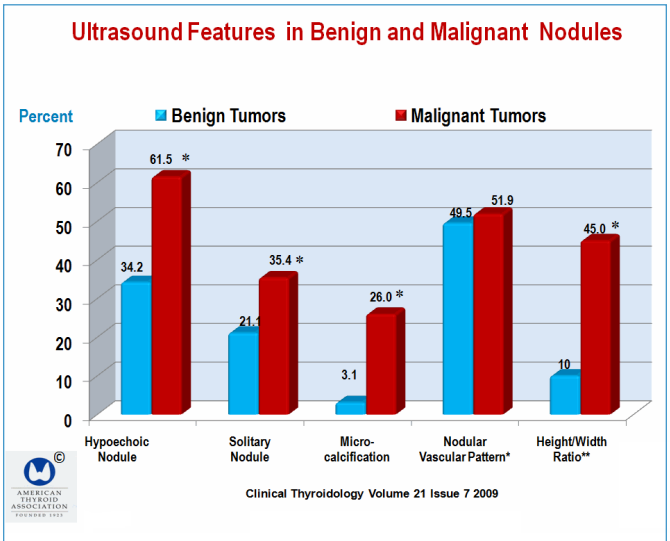

Figure 1. This figure shows the difference in accuracy of sonographic features in benign and malignant tumors, *P <0.001, comparing malignant and benign nodules, regardless of nodule size.

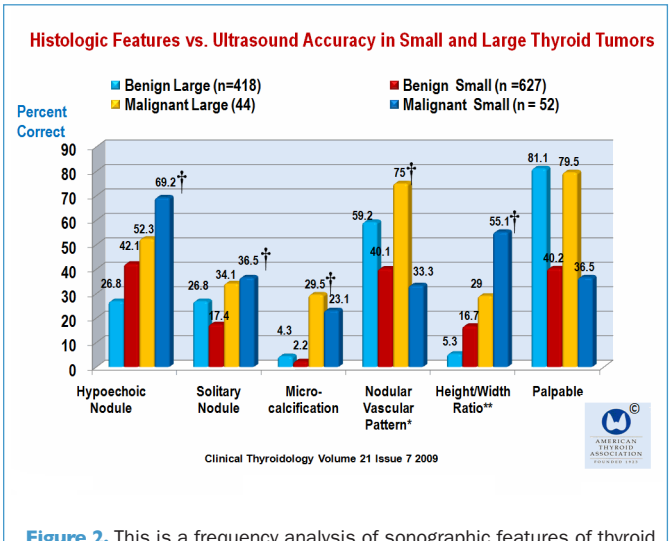

Figure 2. This is a frequency analysis of sonographic features of thyroid nodules and their size in groups of benign and malignant tumors. Small = <10 mm; large = ≥10 mm. * 316 nodules; ** 210 nodules. †P < 0.001, comparing malignant small nodules with malignant large nodules. Data for this figure is derived from Table 1 of Popowicz et al.

vs. 34.2%, P<0.0001) and solitary (35.4 vs. 21.1%, P<0.005) and more contained small calcifications (26.0 vs. 3.1%, P<0.001), and the malignant nodules more often had a height-to-width ratio that was ≥1, versus <1 (45.0 vs. 10%, P<0.0001) (Figure 1). Also, in a separate analysis of the malignant and benign nodules, the same ultrasound features were found in the small nodules as compared with the large nodules. As compared with small benign tumors, small malignant tumors were more likely to be hypoechoic (P<0.001), to have a height-to-width ratio ≥1 (P<0.0001), and to have microcalcifications (P<0.001). As compared with the benign nodules, small malignant tumors were more often solitary (36.5 vs. 17.4%; P<0.001), but this was found only with large nodules. An intranodular vascular pattern was significantly more common in large nodules as compared with small nodules (75 vs. 33.3%, P<0.05); however, there were no significant differences in Doppler blood flow in malignant and benign nodules (Figure 2).

The small nodules were divided by size into two groups: ≤10 mm and 11 to 15 mm. Features such as hypoechogenicity, solitary occurrence. and height-to-width ratio ≥1 tended to be more sensitive for the diagnosis of thyroid cancer in smaller nodules (Figure 3) The single most sensitive ultrasound feature allowing selection of nodules for FNAB in both small and large nodules was hypoechogenicity (Figures 4 and 5). Nonetheless, selecting only hypoechoic nodules for biopsy would have missed 31% of the small malignant tumors and 49% of the large tumors. The specificity of this criterion was significantly lower for small nodules than for large nodules (57.9 vs. 77.7%, P<0.0001) (Figures 5 and 6). Although the most specific criterion for malignancy in both small and large tumors was the presence of microcalcifications (>95%), the sensitivity of this feature was only 29.5% in both small and large tumors. The height-to-width ratio of a nodule had a higher sensitivity for malignant tumors in the large tumor group than the small tumor group (55.1 vs. 29.0%, P<0.002) (Figure 4) but had lower specificity (83.3%). A solitary nodule was more specific for malignancy in a small nodule than in a large tumor (82.6 vs. 73.2%, P<0.001).

Multivariate logistic-regression analysis (Figure 7) found in the small-nodule group that at least one of the ultrasound tumor features significantly differentiated malignant and benign nodules, which would have led to aspiration of 98% of malignant nodules, while lowering the number of examinations by 24.3%. Also in the small-tumor group, a sensitivity of >90% was found for an FNAB selection of malignant tumors that included all hypoechoic nodules and those with a height-to-width ratio ≥1. However, with these selection criteria, the specificity would be only 46.3% and the number of FNABs would decline by 28%. In the group of small nodules with diameters ≤10 mm, these ultrasound selection criteria (hypoechogenicity and height-to-width ratio ≥1) would result in a sensitivity of 90% with a specificity as low as 34.6%. If the selection criteria included

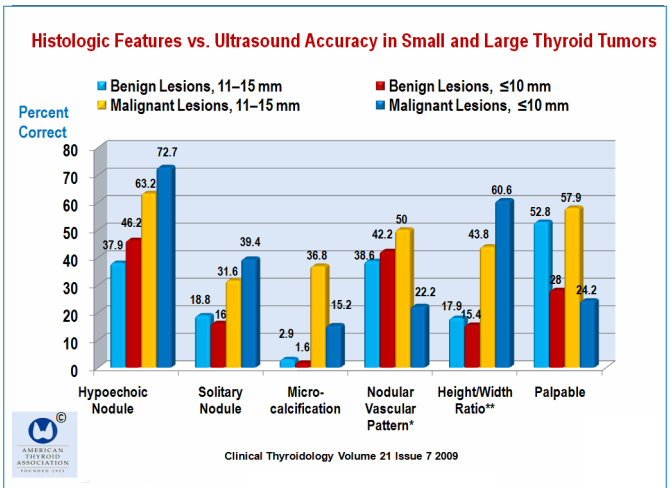

Figure 3. This figure shows the results of a detailed analysis of small nodules divided into lesions with diameters ≤ 10 mm and 11-15 mm. It shows that features like hypogenicity, solitary nodules, and height-to-width ratio ≥ 1 tended to be more sensitive in smaller nodules whereas nodule microcalcifications were less sensitive. Neither nodule palpability nor size > 10 mm was significantly associated with the histology diagnosis. * 3125 nodules; ** 103 nodules. Data for this figure were derived from Table 2 of Popowicz et al.

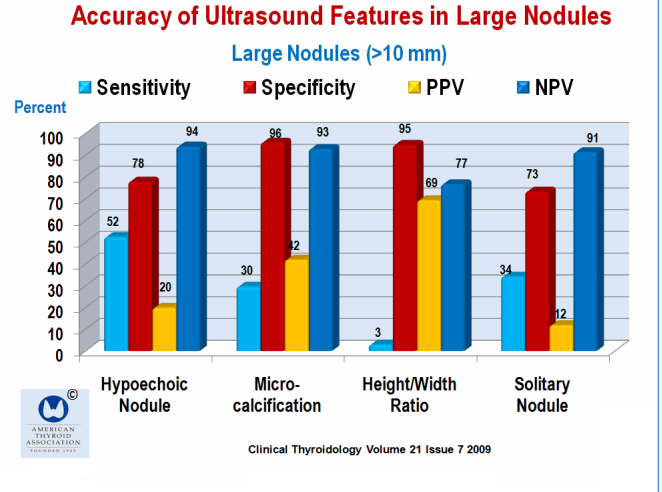

Figure 4. This figure shows the diagnostic accuracy of the ultrasound features in large thyroid nodules. Data for this figure were derived from Table 3 of Popowicz et al.

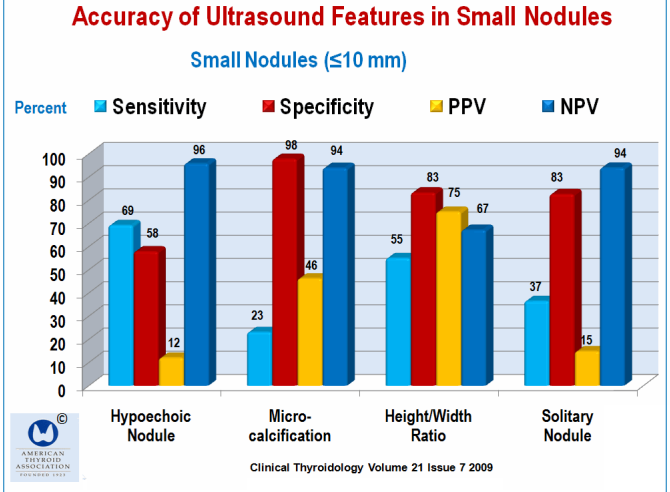

Figure 5. This figure shows the diagnostic accuracy of the ultrasound features in small thyroid nodules. Data for this figure were derived from Table 4 of Popowicz et al.

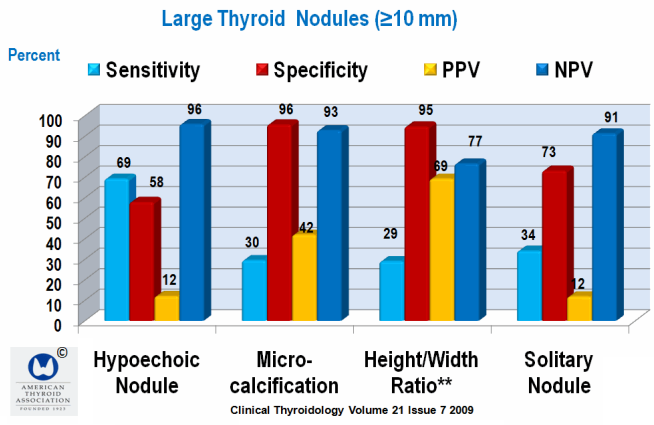

Figure 6. This figure shows the ultrasound features that independently identify malignant thyroid nodules. Data for this figure was derived from Table 5 of Popowicz et al.

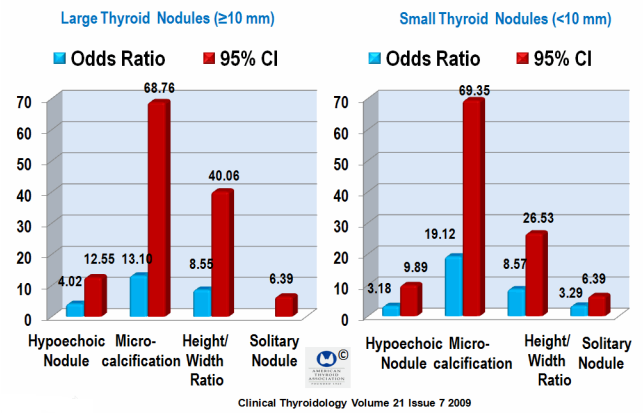

Figure 7. This figure shows the odds ratios for ultrasound features suggesting malignancy in a thyroid nodule in patients with large thyroid nodules or small thyroid nodules. Data for this figure was derived from Table 5 of Popowicz et al.

all nodules that were solitary or had microcalcifications, or had a height-to-width ratio ≥1, the specificity would increase to 77.8% in nodules ≤10 mm with a sensitivity of 81.6%; however, hypoechogenicity was the only feature among those analyzed that differed significantly between invasive and noninvasive cancers. The FNAB of all hypoechoic nodules or those containing calcifications or a height-to-width ratio ≥ 1 would lead to a 55.1% decline in the number of FNABs performed, while maintaining a high sensitivity and specificity of 83.9% and 72.4%, respectively.

CONCLUSION There is strong rationale for using thyroid ultrasound features to select large or small thyroid nodules for fine-needle aspiration biopsy. Nodule hypoechogenicity, microcalcifications, and a height-to-width ratio ≥1 are independent factors predicting malignancy in thyroid nodules regardless of nodule size.

COMMENTARY

A variety of ultrasound findings have been identified as independent features suggesting malignancy in a thyroid nodule. The study by Popowicz et al. provides further insight into this problem. This study found that lesional hypoechogenicity and the presence of microcalcifications were independent factors that suggested malignancy with a high degree of accuracy, regardless of nodule size. Widely recognized features portending malignancy in a thyroid nodule are hypoechogenicity (1-3), microcalcification (1, 3, 4), and irregular nodule margins (3, 4).

In addition to these ultrasound features, Popowicz et al. found on multivariate analysis that the shape of thyroid nodules determined by a height-to-width ratio ≥1 was also an independent factor suggesting malignancy. However, this has not been as widely accepted and varies according to the way it is measured in various studies. For example, Alexander et al. (5) found that a long-to–short-nodule axis ratio >2.5 was 100% predictive of a benign process; however, this was present in only 4% of the study cohort but was confirmed by a prospective validation with consistent results (P<0.01). In another study, Berker et al. (6) found that a long-to-short-nodule axis ratio <1.5 was associated with malignancy in subcentimeter thyroid nodules. Still others have determined the nodule configuration by measuring the anterior–posterior -to-width ratio. For example, Moon et al. (7) found that malignancy was identified by a taller-than-wide shape, which had a specificity of 91%, but a sensitivity of only 40%. Cappelli et al. (8) also found that a nodule shape that was more tall than wide determined by the anteroposterior-transverse diameter ratio >1 was a good predictor of malignancy independent of the nodule size, but concluded that microcalcification, blurred margins, and a hypoechoic nodule pattern was the best compromise between missing cancers and cost–benefit.

Popowicz et al. did not find Doppler blood-flow characteristics of the nodule to be useful for identifying malignancy in small nodules, which is in keeping with the findings in some studies (2, 9, 10) but not in others (8). For example, Papini et al. (11) found that an intranodular vascular pattern, was an independent risk factor of malignancy. Chan et al. (12) also found that hypoechogenicity (86%), microcalcifications (42%) and intranodular hypervascularity (69%) were uncommon features of papillary thyroid cancer. Thus, the findings on this feature are highly variable.

Popowicz et al. also found that a solitary nodule was also an ultrasound feature that suggested malignancy in small nodules, which has been found by some (5, 13) but not all (2,

11) studies. Still other studies (14) find that the cancer risk for patients with one or two nodules >1 cm decreases with three or more thyroid nodules.

Popowicz et al. found no single criterion to be optimal for selecting nodules for FNAB, a conclusion reached by others (8, 11, 15, 16). Popowicz concluded that the results of this study provide a rationale for using ultrasound features in selecting nodules for FNAB, such as the shape of nodules with a height-to-width ratio ≥1, hypoechogenicity, microcalcifications and a solitary nodule, but these ultrasound features have different predictive diagnostic values and different sensitivity and specificity according to nodule size. The authors offer the caveat that although the set of ultrasound features proposed in this study for small nodules is greater than that for large nodules, it does not mean that FNAB of very small nodules (microcarcinomas) should be performed more often than for larger nodules. Rather, it shows what ultrasound features should be considered to obtain the maximal sensitivity, and that small nodules presenting with such features should be biopsied or followed by repeat ultrasound examinations (17).

This is a very thoughtful study that provides important information about ultrasound-guided FNAB, not only in the sense of guiding the biopsy needle, but also in guiding the physician who will be performing the biopsy.

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References

1. Kim EK, Park CS, Chung WY. et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol 2002;178:687-91.

2. Nam-Goong IS, Kim HY, Gong G, et al. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with pathological findings. Clin Endocrinol (Oxf) 2004;60:21-8.

3. Barbaro D, Simi U, Meucci G, et al. Thyroid papillary cancers: microcarcinoma and carcinoma, incidental cancers and non-incidental cancers—are they different diseases? Clin Endocrinol (Oxf) 2005;63:577-81.

4. Kang HW, No JH, Chung JH, et al. Prevalence, clinical and ultrasonographic characteristics of thyroid incidentalomas. Thyroid 2004;14:29-33.

5. Alexander EK, Marqusee E, Orcutt J, et al. Thyroid nodule shape and prediction of malignancy. Thyroid 2004;14:953-8.

6. Berker D, Aydin Y, Ustun I, et al. The value of fine-needle aspiration biopsy in subcentimeter thyroid nodules. Thyroid 2008;18:603-8.

7. Moon WJ, Jung SL, Lee JH, et al. Benign and malignant thyroid nodules: US differentiation—multicenter retrospective study. Radiology 2008;247:762-70.

8. Cappelli C, Castellano M, Pirola I, et al. Thyroid nodule shape suggests malignancy. Eur J Endocrinol 2006;155:27-31.

9. Frates MC, Benson CB, Doubilet PM, et al. Can color Doppler sonography aid in the prediction of malignancy of thyroid nodules? J Ultrasound Med 2003;22:127-31.

10. Rago T, Vitti P, Chiovato L, et al. Role of conventional ultrasonography and color flow-doppler sonography in predicting malignancy in 'cold' thyroid nodules. Eur J Endocrinol 1998;138:41-6.

11. Papini E, Guglielmi R, Bianchini A, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab 2002;87:1941-6.

12. Chan BK, Desser TS, McDougall IR, et al. Common and uncommon sonographic features of papillary thyroid carcinoma. J Ultrasound Med 2003;22:1083-90.

13. Frates MC, Benson CB, Doubilet PM, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab 2006;91:3411-17

14. Barroeta JE, Wang H, Shiina N, et al. Is fine-needle aspiration (FNA) of multiple thyroid nodules justified? Endocr Pathol 2006;17:61-5.

15. Frates MC, Benson CB, Charboneau JW, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005;237:794-800.

16. Peccin S, de Castsro JA, Furlanetto TW, et al. Ultrasonography: is it useful in the diagnosis of cancer in thyroid nodules? J Endocrinol Invest 2002;25:39-43.

17. Mazzaferri EL, Sipos J. Should all patients with subcentimeter thyroid nodules undergo fine-needle aspiration biopsy and preoperative neck ultrasonography to define the extent of tumor invasion? Thyroid 2008;18:597-602.

www.thyroid.org/patients/ct/index.html