

Repeat fine-needle aspiration biopsy (FNAB) should be considered for thyroid nodules with suspicious features on ultrasound, even when the initial FNAB results are benign.

Kwak JY, Koo H, Youk JH, Kim MJ, Moon HJ, Son EJ, Kim EK. Value of US correlation of a thyroid nodule with initially benign cytologic results. *Radiology* 2010;254:292-300.

SUMMARY

BACKGROUND

Fine-needle aspiration biopsy plays a key role in selecting patients for surgery; however, it has some limitations, such as false negative or false positive results or inadequate cytologic specimens. This study was aimed at assessing the value of ultrasound (US) features in thyroid nodules that initially yield benign cytologic results.

METHODS

From October 2003 through February 2006, a total of 6025 consecutive patients who were seen in Severance Hospital in Seoul, Korea, had US-guided FNAB of 6118 nodules, 3540 of which were ≥ 1 cm with benign cytologic results (58%). Benign cytology comprised colloid nodules, adenomatous hyperplasia, lymphocytic thyroiditis, Graves' disease, and postpartum thyroiditis

The Winnowing of Thyroid Nodules for Study (Figure 1)

A total of 2136 nodules were excluded (60%) because no further evaluation results were available, and 60 of the remaining 1404 nodules were excluded because they increased in size on follow-up US without further cytologic or pathologic evaluation, and 1 nodule was excluded because it revealed follicular neoplasm, leaving a total of 1343 nodules for ultrasound analysis in 1324 patients (Figure 1).

Focal thyroid nodules were interpreted by using the following US features: internal nodule echogenicity, the tumor margin,

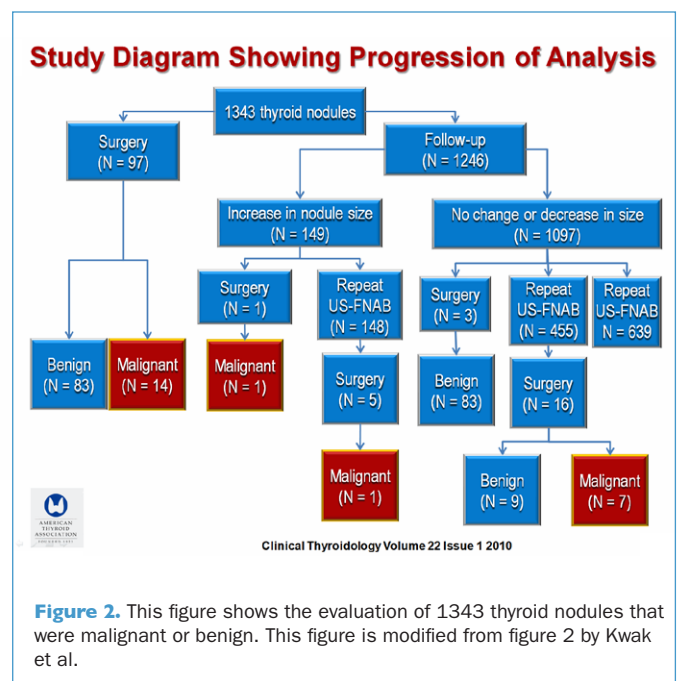
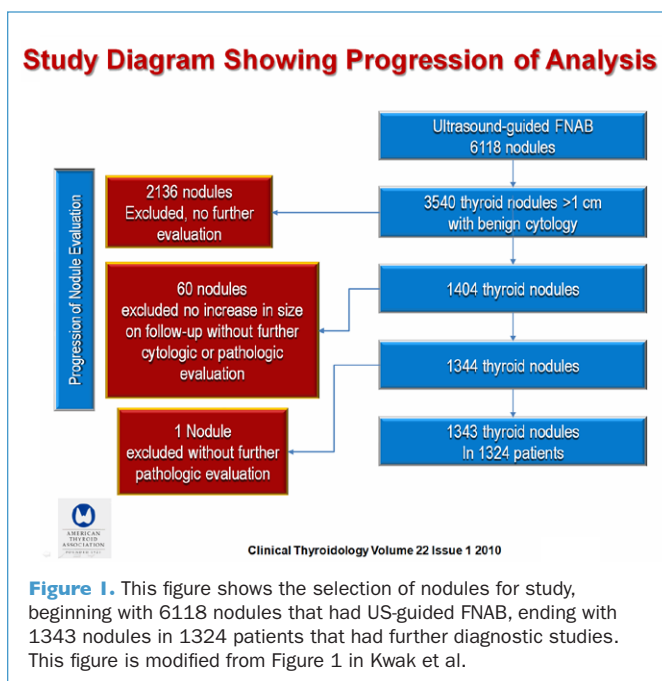
calcifications, and shape. Internal components of the nodule were defined as solid, mixed, or cystic, and a nodule with mixed components was interpreted as a mixed solid-cystic lesion. Nodules with mixed components were evaluated on the basis of the internal solid components. Based on these authors previously published criteria, a nodule was considered suspicious for malignancy if any of the following were found on neck US: marked hypoechoogenicity, microlobulated or irregular margin, microcalcifications, or a greater anteroposterior than transverse configuration.

A calculation of the likelihood of having a benign nodule was subdivided into various subgroups, including the number of aspirations, US features, and follow-up data. After this estimation, the likelihood of benign thyroid nodules in the group with benign cytologic results was compared with those of the remaining subgroups. The likelihood of thyroid nodules with benign cytologic results on at least two FNAB aspirations was compared with benign nodules from the remaining subgroups. Finally, a comparison was made of the likelihood of negative US results in nodules with initially benign cytologic results, and during follow-up US with nodules that had initially showed benign cytologic results, negative US results, and increased size at follow-up US.

RESULTS

Patient Nodule Demographics (Figures 2 and 3)

The mean age of all study patients was 48.9 years (range, 14 to 81); the mean age for men was 49.3 (range, 16 to 76), and for women 48.8 (range, 14 to 81). The mean thyroid nodule



size was 22.2 mm (range, 10 to 60). Malignant nodules were confirmed by surgery or repeat FNAB, and nodules were confirmed as benign by surgery or repeat FNAB or no change or a decrease in nodule size during US follow-up.

Of the 1343 nodules, 97 (7.2%) were surgically excised without follow-up US or FNAB, and the histologic results of this group were benign in 83 of the 1343 nodules (86%) and malignant in 14 (14%). Of the 1246 nodules that had follow-up, 149 (12%) increased in size and 1097 (88%) had no change or decreased in size. Of the 149 nodules that increased in size, 1 had surgery (0.7%) and 148 (99%) had repeat aspiration or surgery; 5 of the 149 patients were found to have malignant tumors (3%). Thus, of the total of 1343 nodules that were initially considered benign on FNAB, 23 (1.7%) had malignant tumors (Figure 2).

The diagnosis of 1343 nodules was confirmed by surgery in 122, by repeat FNAB in 543, and by follow-up US in 678 (Figure 2). Of 122 patients who had surgery, there were 122 nodules, 23 of which were malignant and 99 benign. Of the malignancies, 83% were papillary thyroid cancer, 13% were follicular variant papillary thyroid cancer, and 4% were minimally invasive follicular thyroid cancer. Of the 99 benign nodules, 87 (88%) were caused by benign adenomatous hyperplasia, 8 were follicular adenoma (8%), and 4 (4%) were thyroiditis (Figure 3).

Outcome on the Basis of Ultrasonography (Figure 4)

Based on the US findings, there were 93 nodules with positive features and 1250 with negative features, and the final rate of malignancy was 1.9%. The histopathologic results in 122 patients were confirmed by surgery, 543 by repeat FNAB, and 678 by follow-up US. The mean interval between the initial and follow-up FNAB was 15.6 months (range, 3 to 51) in 543 nodules. The time between the first and repeated FNABs was >90 days for all patients, and 94 of 753 (12%) had more than two follow-up FNABs. The mean time between initial and follow-up US was 26.7 months (range, 3 to 60) in 678 nodules. Of the 122 nodules treated surgically, 23 (19%) were histopathologically malignant, and 99 (81%) were histologically benign (Figure 4).

Comparison of US Findings and the Risk for Malignancy in a Thyroid Nodule (Figure 5)

Results of the analysis of benign and malignant thyroid nodules determined that the mean (±SD) diameter of benign nodules was 22.3 ±10.8 mm, which was significantly larger than the size of malignant nodules (18.2±8.7 mm) (P<0.001). There was no significant relationship between the risk of malignancy and patient sex or age. In the final analysis, 26 (1.9%) malignant and 1317 (98.1%) benign nodules were found according to reference standards established by the investigators. If the initial cytologic results showed benign thyroid nodules, the likelihood of the nodule actually being benign was 98.1%, and when a thyroid nodule had benign results at both initial and repeat FNAB, the likelihood increased to 100%. The likelihood of having a benign thyroid nodule with suspicious US features was lower

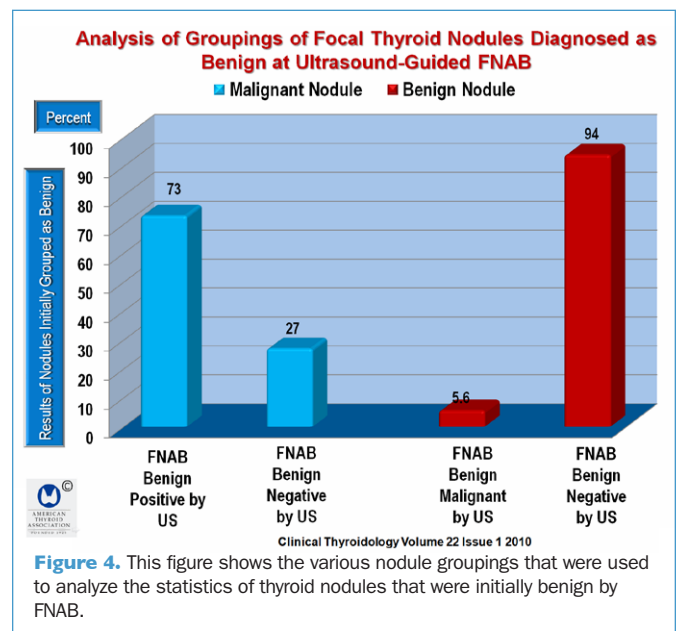


Figure 4. This figure shows the various nodule groupings that were used to analyze the statistics of thyroid nodules that were initially benign by FNAB.

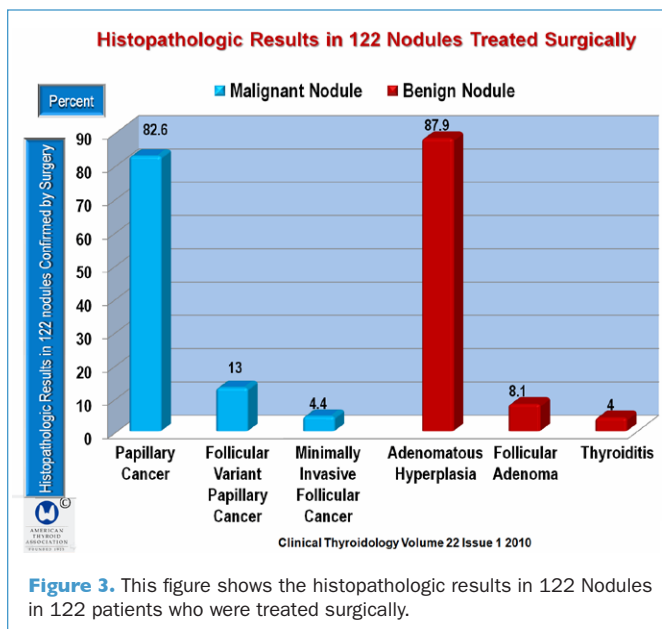


Figure 3. This figure shows the histopathologic results in 122 Nodules in 122 patients who were treated surgically.

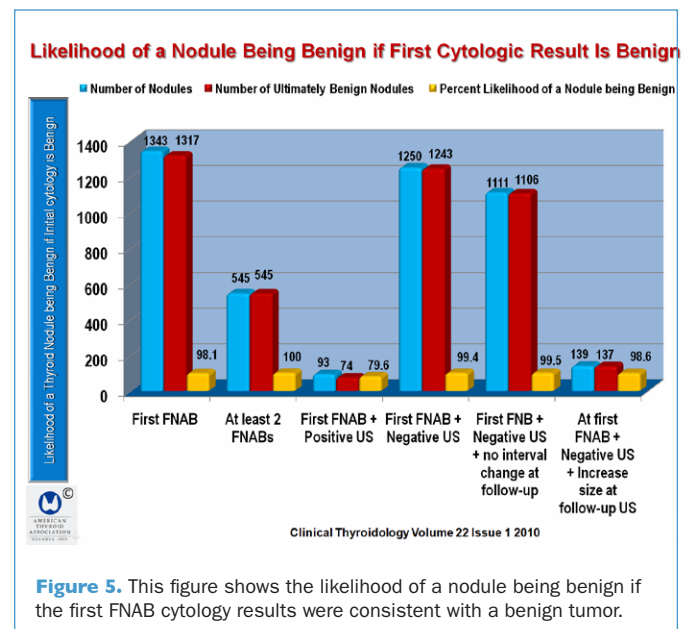


Figure 5. This figure shows the likelihood of a nodule being benign if the first FNAB cytologic results were consistent with a benign tumor.

(80%) than having a benign thyroid nodule with negative US features (99.4%) ($P < 0.001$). The risk for malignancy was slightly higher (1.4%) in a thyroid nodule with benign features on the initial US study and an increase in size during follow-up, and it was slightly higher than that of a thyroid nodule with no change during follow-up, (5%) but the difference was not significant $P = 0.4$ (Figure 5).

Logistic-regression analysis demonstrated that for tumor size, the odds ratios and 95% confidence intervals (CIs) were 0.956 (95% CI, 0.912 to 1.002; $P = 0.06$); for age were 1.021 (95%

CI, 0.987 to 1.057; $P = 0.23$); for sex, were 0.592 (95% CI, 0.201 to 1.745; $P = 0.34$); and for US groupings were 45.588 (95% CI, 18.577 to 111.874; $P < 0.001$)

CONCLUSION

The risk for malignancy is extremely low if the initial FNAB is negative and the US features are not suspicious; however, if there are suspicious US features, the false negative rate of cytology may be as high as 20%. As a consequence, it seems that repeat FNAB should be considered.

COMMENTARY

Fine-needle aspiration biopsy is currently the best diagnostic means of identifying malignant thyroid tumors. Yet the false negative rate can range from 1 to 11% (1). Limitations of FNAB are related to the skill of the operator, the expertise of the cytologist, and the difficulty in distinguishing some benign cellular adenomas from their malignant counterparts. Nonetheless, experts in the field and current American Thyroid Association guidelines recommend that a nodule of any size with sonographically suspicious features can be considered for FNAB (2;3). This includes microcalcifications, hypoechoic solid nodules, irregular or lobulated margins, intranodular vascularity, and nodal metastases (or signs of extracapsular spread). However, this recommendation is controversial because it includes patients with microcarcinomas in whom a survival benefit after an FNAB diagnosis has been challenged. The recent National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science conference indicated that lesions with a maximum diameter greater than 1.0 to 1.5 cm should be considered for biopsy unless they are simple cysts or septated cysts with no

solid elements. FNAB also may be replaced by periodic follow-up of small nodules ranging from 8 mm to 1 cm in diameter if they have sonographic features that are strongly associated with benign cytology. This underscores the clinical importance of US in the management of thyroid nodules. For example, one study concludes that US evaluation changes the management of 63% of patients with palpable thyroid nodules (4;5). Still, the skill of the US operator plays a key role in the decision to rebiopsy nodules based on a US evaluation.

Kwak et al. point out a few limitations of this study, including some variability among the findings of the five cytopathologists, making the precise rate of malignant nodules uncertain.

Nonetheless, the authors provide strong evidence that benign cytologic FNAB results should be repeated if neck ultrasonography is suspicious for malignancy. The 20% rate of false-negative FNAB cytology under these circumstances is a compelling endorsement of their recommendation.

— Ernest L. Mazzaferri, MD, MACP

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