Outcome of Bethesda III thyroid nodules and its correlation with ultrasonographic features and BRAF$^{600E}$ analysis

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Purpose

To establish the malignancy rate of initially Bethesda III (atypia of undetermined significance or follicular lesions of undetermined significance) thyroid nodules and whether they differ according to histological subcategories. To investigate the value of ultrasonographic (US) features that predict malignancy, and BRAF$^{600E}$ analysis, and to suggest management of AUS/FLUS nodules.
Methods and Materials

From January 2010 to June 2012, 6118 focal thyroid nodules underwent US-guided FNA. A total of 411 of 6118 (6.7%) focal thyroid nodules were diagnosed as AUS/FLUS, and 246 were excluded because of a lack of further evaluation, such as surgery, rFNA, or follow-up US (n=240) or because further FNA showed AUS/FLUS again without additional histological confirmation (n=6). A total of 162 patients (146 women and 16 men) with 165 thyroid nodules were analyzed in the present study. The mean age of patients was 49 years (range, 22 - 76 years). The mean lesion size was 13 mm in longest diameter (range, 3 - 52 mm).

There were nine histological subcategories of AUS/FLUS nodules (1): microfollicles in a sparsely cellular aspirate with scant colloid (group 1, n=2), Hurthle cells in a sparsely cellular aspirate with scant colloid (group 2, n=3), mild follicular cell atypia with drying/clotting artifact (group 3, n=17), Hurthle cells in a cellular aspirate (group 4, n=3), focal features of papillary carcinoma in an otherwise predominantly benign-appearing (group 5, n=71), cyst-lining cells with nuclear atypia in an otherwise predominantly benign-appearing (group 6, n=0), follicular cells with regenerative atypia (group 7, n=3), atypical lymphoid infiltrate (group 8, n=1), not otherwise categorized (group 9, n=65).

We confirmed diagnosis by surgery (n = 100), rFNA (n = 42), rFNA with surgery (n = 23).Malignant nodules were confirmed by surgery (n=88) or rFNA(n=3). Nodules were deemed benign if confirmed as benign using surgery (n=35) or rFNA (n=39).

The interval between initial FNA and rFNA were three to six months in thyroid nodules that suspicious malignant US features and six months in that indeterminate US features (2).

The #2 test was used to compare the risk of malignancy according to US features and BRAF analysis.

Logistic regression analysis was performed to assess the odds ratio for the risk of malignancy according to specific US features (shape, margin, echogenecity, calcification). Relative 95% confidence intervals (CIs) were also calculated. The analysis was performed using the STATA software (version 9.0, StataCorp).

In all analyses, $P < 0.05$ was taken to indicate statistical significance.
Results

The malignancy rate of initially AUS/FLUS nodules was 55.2% (91/165). The malignancy rates were 0% in groups 1(0/2), 2(0/3), 4(0/3), 7 (0/3) and 8(0/1), 76.5% (13/17) in group 3, 83.1% (59/71) in group 5, and 29.2% (19/65) in group 9. The malignancy rate of nodules with suspicious US features was 79.3% (73/92) and the malignancy rate with intermediate US features was 24.7% (18/73).

Among suspicious US features, nodules with a taller-than-wide shape showed a significantly higher odds ratio compared to those with an oval shape (odds ratio: 11.25; \( P = 0.00 \)); however, round and irregularly shaped nodules did not show significantly higher odds ratios \( (P = 0.13 \) and \( 0.11, \) respectively). An ill-defined margin showed a higher odds compared with an oval shape however, the \( P\)-value was 0.06, which was not statistically significant. (odds ratio: 1.83). Microlobulated and spiculated nodules showed no significant difference \( (P = 0.06 \) and 0.24, respectively). Micro- and macrocalcifications showed significantly higher odds compared with no calcification (odds ratios: 5.17 and 12.22, respectively; \( P = 0.00, \) respectively), whereas rim calcifications showed no significant difference \( (P = 0.91) \). Marked hypoechogenicity showed a higher odds ratio compared with hyperechogenicity(odds ratio: 6.40); however, the \( P\)-value was 0.17, which was not statistically significant. In the present study, the presence of micro- and macrocalcifications and a taller-than-wide shape showed higher odds ratios and were significantly correlated with malignancy.

The likelihood of malignant thyroid nodule in BRAF\(^{600E}\)-positive nodules was 97.5% (39/40) and 39.7% (25/63) in BRAF\(^{V600E}\) negative nodules \( (P < 0.05) \).
Images for this section:

**Fig. 1:** 63-year-old woman. Transverse image. US scans show a 9-mm round, ill-defined, taller-than-wide hypoechoic solid nodule with intranodular vascularity (suspicious malignant US features) in the right-upper lobe of the thyroid gland. Initial cytological result was AUS/FLUS (focal features of papillary carcinoma, in an otherwise predominantly benign-appearing) and was confirmed by surgery as papillary microcarcinoma.

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**Fig. 2:** Longitudinal view of the same nodule of Fig 1.

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Fig. 3: 31-year-old woman. Transverse image. US scans show a 39-mm oval, well-defined, isoechoic solid nodule with intranodular vascularity (intermediate US features) in the left lobe of the thyroid gland. Initial cytological result was AUS/FLUS (not otherwise categorized) and was confirmed by surgery as minimal invasive follicular carcinoma.

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**Fig. 4:** Longitudinal view of the same nodule of Fig 3.

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Fig. 5: Color doppler image of the same nodule of Fig 3.

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Conclusion

In our study, the malignancy rate of AUS/FLUS thyroid nodules was higher than that reported previously. Nodules with suspicious US features showed a significantly higher malignancy rate than indeterminate nodules. In addition, the malignancy rate was different among histological subcategories of AUS/FLUS thyroid nodules. Thus, management of these nodules should be tailored according to histological subcategory.

For management of AUS/FLUS nodules, we suggest the following:

- Bethesda III nodules should be histologically subcategorized and in group 3 and 5, the malignancy rate is high and we recommend surgery rather than repeat FNA in these groups. In group 9, the malignancy rate is 29.2% and relatively low compare with group 3 or 5. Thus, management of these nodules will depend on the physician or institution’s preference, including follow-up US, repeat US-FNA, US-CNB, and thyroid surgery. US features and additional molecular study may be useful in predicting malignancy in AUS/FLUS thyroid nodules and could be helpful in planning management.
- In cases of group 1, 2, 4, 6, 7 and 8, there was no malignancy in this study but the total number of these groups is small (n=12) so more study needed.
- The malignancy rate of nodules resulting in FLUS again at rFNA was 88.9%. Thus, for nodules that result in FLUS again at rFNA, we recommend surgery rather than a third FNA or F/U.
- The frequencies of malignant thyroid nodules in BRAF<sup>600E</sup>-positive and BRAF<sup>600E</sup>-negative nodules were 97.5% (39/40) and 39.7% (25/63), respectively (P < 0.05). Thus, BRAF<sup>600E</sup> analysis should be considered for thyroid nodules with malignant US findings. Several studies also proved the roles of BRAF<sup>600E</sup> mutation status and sonographic findings as adjuncts to FNA cytological diagnosis (3,4).
References


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