Ultrasound characteristics of thyroid nodules facilitate interpretation of the malignant risk of Bethesda system III/IV thyroid nodules and inform therapeutic schedule

Fu Li¹ | Denghua Pan² | Yuquan Wu² | Jinbo Peng² | Qing Li² | Xiaolong Gui¹ | Wei Ma³ | Hong Yang² | Yun He² | Junqiang Chen¹

¹Department of Gastrointestinal Surgery, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, People’s Republic of China
²Department of Ultrasonography, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, People’s Republic of China
³Department of Pathology, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, People’s Republic of China

Abstract

Background: This study was designed to explore whether ultrasound of thyroid nodules facilitates the interpretation of the malignant risk of Bethesda III/IV thyroid nodules to inform further therapies.

Methods: We reviewed patient records in which the results of ultrasound-guided fine-needle aspiration (US-FNA) were classified by the Bethesda III/IV in our institution between January 2016 and June 2018. Studies were retrieved from PubMed, Cochrane Central Register of Controlled Trials, ISI Web of Science, Science Direct, Wiley Online Library, EMBASE, China National Knowledge Infrastructure, WanFang, and Chinese VIP. The odds ratio (OR) was used to measure associations between risk factors and thyroid nodule malignancy.

Results: Fifty-nine cases of Bethesda III/IV with corresponding surgeries were included, and the malignancy risk was 54.2%. Meta-analysis revealed irregular borders, solitary nodules, hypoechogenicity, microcalcifications, and being taller than wide, all of which increased the malignancy risk of thyroid nodules. Combined ORs for these factors were 4.08 (95% CI: 2.34-7.14, P < .001), 2.18 (95% CI: 1.39-3.42, P = .001), 2.02 (95% CI: 1.35-3.01, P = .001), 3.21 (95% CI: 2.26-4.56, P < .001), and 4.35 (95% CI: 3.07-6.15, P < .001), respectively.

Conclusion: As the risk of malignancy for papillary thyroid carcinoma (PTC) is high, when any one of the five ultrasound features of malignancy were confirmed, repeated FNA is recommended to confirm PTC-type malignancy, even though nodules were Bethesda III/IV classification. However, repeated FNA should be avoided when none of these ultrasound features are identified because repeated FNA does not contribute to identifying non-PTC type malignancies, such as follicular thyroid carcinoma and poorly differentiated thyroid carcinoma.

Keywords

Bethesda system III/IV, thyroid nodule, ultrasound characteristics, US-FNA

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2019 The Authors. Diagnostic Cytopathology published by Wiley Periodicals, Inc.
1 | INTRODUCTION

Thyroid nodules are clinically common; however, the occurrence of malignancy in thyroid nodules remains relatively low, ranging between 5% and 7%. Ultrasound-guided fine-needle aspiration (US-FNA) is a useful test for the evaluation of thyroid nodules that has been widely applied as the primary diagnostic procedure. FNA results are standardized by the Bethesda System for Reporting Thyroid Cytopathology, which promotes effective communication between clinicians and are divided into six types. Benign nodules are classified as Bethesda II, suspicious nodules are classified as Bethesda V, and malignant nodules are classified as Bethesda VI. Undetermined nodules are classified as either Bethesda III (atypia of undetermined significance or follicular lesion of undetermined significance [AUS/FLUS]) or Bethesda IV (follicular neoplasm or suspicious for follicular neoplasm [FN/SFN]). Thyroid nodules classified as Bethesda II, V, and VI have prescribed management strategies; in contrast, optimal management strategies for uncertain nodules (Bethesda III and IV) remain unclear. The risk of malignancy for Bethesda III is estimated at 5%-15% and 10%-40% of Bethesda IV nodules are malignant. Due to the large range of malignancy risk, repeated FNA or surgery is recommended, and more than half have a determined diagnostic result. Approximately 15.6%-48.6% of nodules remain AUS/FLUS upon repeat FNA, indicating a need to assess the risk of malignancy in Bethesda system III/IV nodules.

Ultrasound is the preferred method to detect thyroid nodules, and ultrasound factors, such as hypoechoigenicity, irregular shape, being taller than wide and microcalcifications, are considered to be features of malignant nodules. Some studies have demonstrated the use of ultrasound to predict the risk of malignancy in Bethesda III and IV thyroid nodules during the initial US-FNA. However, one study demonstrated that the thyroid ultrasound risk stratification system has poor specificity and accuracy for classifying indeterminate lesions. Another study reported that age and gender, but not ultrasound characteristics, influence the decision to perform surgery in AUS/FLUS patients. Since then, no clear guidelines have been established to manage Bethesda III and IV nodules. The purpose of this study was to explore whether ultrasound characteristics of thyroid nodules may facilitate clinicians interpreting the risk of malignancy for Bethesda system III/IV thyroid nodules to inform choices for future therapies.

2 | MATERIALS AND METHODS

2.1 | Sonographic evaluation

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. All US-FNA reports and histopathological diagnoses from 1147 patients who were admitted and received surgery from thyroid nodules in the First Affiliated Hospital of Guangxi Medical University from January 2016 to June 2018 were retrospectively reviewed. US-FNA results were described using the Bethesda System for Reporting Thyroid Cytology (TBSRTC), and patients defined as Bethesda system III/IV were enrolled in our study. Patient thyroid nodules were measured using LOGIE9 (GE Healthcare, Wauwatosa, Wisconsin). The transducer was a 5-12 MHz linear transducer. The following ultrasound imaging features of nodules were evaluated: size, shape, being taller than wide, solitary nodules, echogenicity, and calcification. Malignant imaging features included irregular shape, hypoechoegenicity, being taller than wide, and microcalcification.

2.2 | Search strategy

A literature search was performed to identify all articles related to ultrasound parameters in Bethesda system III/IV nodules in the following databases: PubMed, Cochrane Central Register of Controlled Trials, ISI Web of Science, Science Direct, Wiley Online Library, EMBASE, China National Knowledge Infrastructure, WanFang, and Chinese VIP from inception to August 2018 using the keywords: “thyroid,” “Bethesda system,” “The Bethesda System for Reporting Thyroid Cytology,” TBSRTC,” “fine-needle aspiration,” “FNA,” and “FNAC.” Inclusion criteria were studies using ultrasound to estimate the malignancy of Bethesda III/IV nodules in the initial US-FNA. Reviews and references were also evaluated. Reviews, abstracts, letters, and duplicate data were removed. No language restrictions were applied.

Two authors (Fu Li and Denghua Pan) independently performed the literature search and data screening. When there was controversy, the disagreement was resolved by a third reviewer (Yun He).

2.3 | Data extraction

Two investigators (Fu Li and Denghua Pan) independently extracted data from eligible studies. The following characteristics were extracted: first author’s name, year of publication, country, and number of patients. To evaluate risk factors associated with thyroid cancer, the following ultrasound parameters were extracted: irregular borders, solitary nodule, hypoechoegenicity, microcalcifications, and being taller than wide.

2.4 | Statistical analysis

Two independent t-tests and chi-square test were applied to analyze differences between benign and malignant groups using SPSS22.0 (SPSS Inc., Chicago, Illinois). For meta-analysis, the odds ratio (OR) was used to explore associations between risk factors and thyroid nodule malignancy. OR > 1 indicates that risk factors were more likely to correlate with the malignancy of thyroid nodules. For heterogeneity analysis, chi-squared test was used to assess heterogeneity among studies. P < .05 was considered to represent significant heterogeneity, and then a fixed effect model was used. Otherwise, a random effects model was used. Publication bias was measured using funnel plots. Meta-analysis was conducted in STATA12.0 (STATA Corp., College, Texas). P < .05 was considered statistically significant.
RESULTS

3.1 Clinical and ultrasonographic characteristics of Bethesda system III/IV nodules

From June 2016 to 2018, there were 1147 cases of FNAB performed at our institution. Eighty-nine patients were diagnosed as Bethesda system III thyroid nodules and twenty-nine patients were diagnosed as Bethesda system IV thyroid nodules. The resection rate of Bethesda system III was 43.8% (39/89), the resection rate of Bethesda system IV was 69.0% (20/29). Among 59 patients, 46 were female and 13 were male. Cases were classified into benign and malignant groups based on final histopathologic diagnosis. Table 1 shows clinical and ultrasonographic characteristics of Bethesda system III/IV nodules. In the malignant group, 30 cases were papillary thyroid carcinoma (PTC), one was follicular thyroid carcinoma (FTC), and other was medullary thyroid carcinoma (MTC). The average ages of patients in the benign group were 46.4 and 42.0 years old in malignant group, respectively. No significant difference was observed with respect to age between benign and malignant groups (P > .05). In the benign group, average nodule size was 2.51 cm, and in the malignant group, mean nodule size was 1.44 cm, which were significantly different in two groups (P = .019). Additionally, there was a significant difference between benign and malignant groups with respect to patient sex (P = .013) in thyroid nodules. In the malignant groups of thyroid nodules, the parameters of irregular borders, solitary nodules, hypoechogenicity, microcalcifications and being taller than wide were more common (all P < .05). We also compared clinical ultrasound and ultrasonographic characteristics between PTC and benign thyroid nodules (Table 2). The mean age of PTC cases was 41.27 years old, and the average age of the benign group was 46.41 years old, with no significant difference between the two group (P = .119). Average size in the benign group was larger than in the PTC group (P = .023). In addition, there were significant differences in sex, irregular borders, solitary nodules, hypoechogenicity, microcalcifications, and being taller than wide between PTC and benign groups (all P < .05).

3.2 Characteristics of studies included in this meta-analysis

Figure 1 shows the procedures of this study, which screened 368 studies. After reading full texts of the studies, 16 publications were included in the meta-analysis.9,15-29 Table 3 shows the characteristics included studies. All studies had sufficient data to calculate the associations between risk factors and nodules. This meta-analysis observed significant associations between irregular borders, solitary nodules, hypoechogenicity, microcalcifications and nodules that are being taller than wide or malignant. Combined ORs were 4.08 (95% CI: 2.34-7.14, P < .001; Figure 2A), 2.18 (95% CI: 1.39-3.42, P = .001; Figure 2B), 2.02 (95% CI: 1.35-3.01, P = .001; Figure 2C), 3.21 (95% CI: 2.26-4.56, P < .001; Figure 2D), and 4.35 (95% CI: 3.07-6.15, P < .001), respectively, (Figure 2E; Table 4).

3.3 Publication bias

Begg’s test was performed to measure publication bias of this meta-analysis. Publication bias was found in groups with irregular borders (Figure 3A, P = .003) and microcalcifications (Figure 3B, P = .019). No publication bias was present for solitary nodules (Figure 3C, P = .235),
hypoechogenicity (Figure 3D, $P = .055$), and those that are being taller than wide (Figure 3E, $P = .173$).

3.4 | Discussion

Ultrasound is the preferred method to detect thyroid nodules, and US-FNA is a helpful procedure that provides information for further clinical management. For patients who have thyroid nodules, US-FNA reduces unnecessary surgeries and identifies individuals with a high risk of malignancy. The pathological outcome of US-FNA was classified according to TBSRTC. Ultrasound and cytological findings can help differentiate noninvasive follicular thyroid neoplasms, with papillary-like nuclear features, from the invasive encapsulated follicular variant of PTC.\textsuperscript{30} In addition, ultrasound findings are useful for cytopathologists to manage thyroid nodules with nondiagnostic or unsatisfactory thyroid FNA results.\textsuperscript{31} However, the risk of malignancy of Bethesda system III/IV nodules varies widely. Our study explored whether ultrasound characteristics of thyroid nodules facilitate clinicians interpreting the risk for malignancy of Bethesda system III/IV thyroid nodules to inform further therapies.

In our study, thyroid nodules with relatively TI-RADS high scores received FNA, so total ROM of Bethesda system III/IV was 54.2%, which was significantly higher than those from Western practice,\textsuperscript{29,32-34} demonstrating that TI-RADS reduces the number of unnecessary thyroid nodule FNAs.\textsuperscript{35} Second, as we know differentiated thyroid carcinoma (DTC) accounts for more than 90% of all thyroid cancers and DTC is an indolent carcinoma, our practice of triaging patients with Bethesda system III/IV nodules is as follows: $\geq$TI-RADS 4c with Bethesda system III/IV nodules were referred to surgery; $\leq$TI-RADS 4a with Bethesda system III/IV nodules were referred for routine observation, with the exception of benign thyroid nodules, which were referred to surgery; for TI-RADS 4b with Bethesda system III/IV nodules needing further discussion with the patients, possible advice included repeat FNA diagnostic surgery, routine observation, use of other imaging modalities, and so on based on patient preference.\textsuperscript{36,37}
In general, ultrasound features suspicious for malignancy include hypoechogenicity, irregular borders, being taller than wide, microcalcifications, and components of the nodules.\textsuperscript{38,39} In our study, differences were observed in the rates of hypoechogenicity, irregular borders, being taller than wide, microcalcifications and components of nodules between benign and malignant groups. Reports indicated that being taller than wide, irregular margins and hypoechogenicity were all associated with malignancy in thyroid nodules, with irregular margins having the highest positive predictive value for malignancy.\textsuperscript{38} This observation was also reported by Maia et al\textsuperscript{40} in 80 patients surgically treated at a single center. In the present study, we observed irregular borders, hypoechogenicity, microcalcifications, being taller than wide, and components of the nodules all increased the risk for malignancy in thyroid nodules. This finding is in accordance with a study by Kure et al\textsuperscript{41,42} Brito et al\textsuperscript{43} demonstrated that being taller than wide had the highest diagnostic OR for judging the malignancy of thyroid nodules compared to other graphic ultrasound features. In our study, a relationship between the dimension of being taller than wide and risk of cancer was observed.

Several studies have confirmed that the majority of malignant thyroid nodules are solid.\textsuperscript{44} However, the presence of microcalcifications in partial cystic lesions increase the risk of malignancy.\textsuperscript{45} Furthermore, a totally cystic lesion conveys a very low risk of malignancy and can be treated as benign disease.\textsuperscript{43} In our study, 93.8% (30/32) of patients had solitary nodules in the two malignancy subgroups, and 48.1% (13/27) had solitary nodules in the two benign subgroups. We found that solitary nodules increased the risk for malignancy in patients.

The risk and incidence of malignancy in Bethesda system III/IV nodules varies widely. When nodules are diagnosed as Bethesda system III/IV, it is a challenge for clinicians to decide whether to recommend surgery, repeated US-FNA or follow-up. One study reported that repeated US-FNA can be performed 6 months or more after initial AUS/FLUS.\textsuperscript{46} Rossi Met et al\textsuperscript{47} attempted to better define the management of Bethesda system III/IV nodules by introducing cytological subcategories, concluding that surgery may be applied in part

### TABLE 3 Characteristics of included studies

| First author       | Year | Country          | Bethesda category |
|--------------------|------|------------------|-------------------|
| Gweon et al\textsuperscript{9} | 2013 | South Korea      | III               |
| Carr et al\textsuperscript{15}  | 2013 | American         | IIIS              |
| Yoo et al\textsuperscript{16}   | 2014 | Korea            | III               |
| Lee et al\textsuperscript{17}   | 2014 | Korea            | AUS               |
| Yoon et al\textsuperscript{18}  | 2014 | Seoul Korea      | III               |
| Kim et al\textsuperscript{19}   | 2014 | Korea            | AUS               |
| Iskandar et al\textsuperscript{20} | 2015 | American         | III/IV            |
| Park et al\textsuperscript{21}  | 2015 | Seoul, Republic of Korea | III |
| Yoo et al\textsuperscript{22}   | 2015 | Seoul, Republic of Korea | III |
| De Napoli et al\textsuperscript{23} | 2016 | Italy            | IV                |
| Lee et al\textsuperscript{24}   | 2015 | Seoul, Korea     | III               |
| Topaloglu et al\textsuperscript{25} | 2016 | Turkey           | III               |
| Baser et al\textsuperscript{26} | 2017 | Turkey           | FLUS              |
| Turkyilmaz et al\textsuperscript{27} | 2017 | Turkey          | III               |
| Lim et al\textsuperscript{28}   | 2018 | Singapore        | III               |
| Kaliszewski et al\textsuperscript{29} | 2018 | Poland           | III               |

Abbreviation: AUS/FLUS, atypia of undetermined significance or follicular lesion of undetermined significance.

**FIGURE 2** Meta-analysis of included studies assessing the association between risk factors and thyroid cancer. A, Irregular borders. B, Solitary nodule. C, Hypoechoic. D, Microcalcifications. E, Being taller than wide [Color figure can be viewed at wileyonlinelibrary.com]
of Bethesda system III and all Bethesda system IV nodules and that repeated FNA and follow-up may be useful in part of Bethesda system III nodules. Vargas-Salas et al\(^48\) addressed three critical topics for clinicians to facilitate improved decisions for treating thyroid nodules. They think molecular testing should be considered a public health measure, avoiding unnecessary surgical risk and cost. In the United States, molecular testing has become widely used to measure the risk of AUS/FLUS and FN/SFN. However, genetic tests have not been used in thyroid practice or included in the health insurance system in some areas of China and other countries. Meanwhile, when we emphasize molecular testing in the diagnosis of thyroid carcinoma, being mindful of expenses to the patient and health care costs to society were considered because it is equally important to avoid overuse of molecular tests.\(^49\) Another study concluded that clinical features, such as gender, nodule size, and age, should be considered in patients with undetermined thyroid nodule.\(^50\) However, in clinical practice, ultrasound features of thyroid nodules influence patient decisions, and final assessment of the nodules is based on various ultrasound features. Figures 4 and 5 show two patients with Bethesda system III/IV thyroid nodules. Figure 4A shows that a solid thyroid nodule was located in the left lobe of the thyroid. The nodule was a hypoechoic nodule with irregular border and microcalcifications (TI-RADS 4c). FNA was conducted, and results revealed cytological atypia: focal nuclear changes with extensive but mild nuclear changes (Figure 4B, Figure 4C). Therefore, we diagnosed this thyroid nodule as AUS/FLUS. Finally, the patient decided to undergo surgery to resect this nodule, and the histopathology was PTC (Figure 4D). Figure 5 was a case of an FN/SFN thyroid nodule. Figure 5A shows a solid thyroid nodule located in the right lobe of the thyroid. The nodule was hypoechoic with irregular border and macrocalcifications (TI-RADS 4b). FNA results showed mild nuclear changes (increased nuclear size, nuclear contour irregularity) without true papillae and intranuclear pseudoinclusions (Figure 5B,C). We diagnosed this thyroid nodule as FN/SFN and recommended surgery for this patient. Histopathology of this thyroid nodule was FTC (Figure 5D). In this study, we unveiled significant associations between solitary nodules, hypochoegenicity, irregular borders, being taller than wide, microcalcifications, and malignant nodules.

### Table 4 Risk factors associated with thyroid cancer

| Risk factor                  | Malignant total | Benign total | Heterogeneity $I^2$ | $P$ value | Meta-analysis model | Odds ratio (95% confidence interval) | $P$ value |
|------------------------------|-----------------|--------------|----------------------|-----------|--------------------|--------------------------------------|-----------|
| Irregular borders            | 1092            | 513          | 1894                 | 576       |                    | 83.50%                               | <.001     |
| Solitary nodule              | 940             | 824          | 1695                 | 1399      |                    | 51.80%                               | .013      |
| Hypoechoic                   | 1163            | 558          | 2070                 | 665       |                    | 70.70%                               | <.001     |
| Microcalcifications          | 1208            | 438          | 2094                 | 353       |                    | 66.40%                               | <.001     |
| Being taller than wide       | 565             | 174          | 766                  | 79        |                    | 20.50%                               | .261      |

### Figure 3

Funnel plots were used to estimate potential publication bias. A, Irregular borders. B, Microcalcifications. C, Solitary nodule. D, Hypoechoic. E, Being taller than wide. Begg’s method was applied.
In conclusion, hypoechogenicity, irregular borders, being taller than wide, microcalcifications and solid nodules are ultrasound characteristics of malignant thyroid nodules. As the ROM of PTC was high, when any one of the five ultrasound features of malignancy was confirmed, repeated FNA is recommended to confirm or rule out PTC malignancy, even for Bethesda III/IV nodules. However, repeated FNA should be avoided when none of these ultrasound features are identified because a repeated FNA does not contribute to identifying non-PTC malignancies, such as follicular thyroid carcinoma and poorly DTC.

**ACKNOWLEDGMENTS**

The study was supported by funds from the Guangxi Scientific Research and Technology Development Plan (1598011-4), and Guangxi National Nature Science Foundation (2017GXNSFAA198253). The funders had no role in the study design, data collection and analysis, the decision to publish or the preparation of the article.

**CONFLICT OF INTEREST**

Fu Li, Denghua Pan, Yuquan Wu, Jinbo Peng, Qing Li, Xiaolong Gui, Wei Ma, Hong Yang, Yun He, Junqiang Chen declare that they have no conflict of interest.

**FIGURE 4** A case with AUS/FLU thyroid nodule. A, Imaging of the thyroid nodule. B, C, Results of FNA. D, Histopathology results. Figure 4A shows a solid thyroid nodule located in the left lobe of the thyroid. The nodule was hypoechogenic with irregular border and microcalcifications (TI-RADS 4c). Figure 4B, C show cytological atypia: focal nuclear changes and extensive but mild nuclear changes ($\times400$). Hence, we diagnosed this thyroid nodule as atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS). Figure 4D shows histopathology of PTC for this thyroid nodule ($\times400$). FNA, fine-needle aspiration [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 5** A case with FN/SFN thyroid nodule. A, Imaging of thyroid nodule. B, C, Results of FNA. D, Histopathology results. Figure 5A shows a solid thyroid nodule located in the right lobe of the thyroid. The nodule was hypoechogenic with irregular border and macrocalcifications (TI-RADS 4b). Figure 5B, C show mild nuclear changes (increased nuclear size, nuclear contour irregularity) without true papillae and intranuclear pseudoinclusions ($\times400$). Hence, we diagnosed this thyroid nodule as follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN). Figure 5D shows the histopathology was FTC for this thyroid nodule ($\times40$) [Color figure can be viewed at wileyonlinelibrary.com]
REFERENCES

1. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214.

2. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. Thyroid. 2009;19(11):1159-1165.

3. Haugen BR, AlexanderEK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1-133.

4. Ervano B, Polat SB, Baser H, et al. Bethesda classification is a valuable guide for fine needle aspiration reports and highly predictive especially for diagnosing aggressive variants of papillary thyroid carcinoma. Cytopathology. 2017;28(4):259-267.

5. Ho AS, Sarti EE, Jain KS, et al. Malignancy rate in thyroid nodules classified as Bethesda category III (AUS/FLUS). Thyroid. 2014;24(5):832-839.

6. Onder S, Firat P, Ates D. The Bethesda system for reporting thyroid cytopathology: an institutional experience of the outcome of indeterminate categories. Cytopathology. 2014;25(3):177-184.

7. Chen JC, Pace SC, Chen BA, Khiyami A, McHenry CR. Yield of repeat fine-needle aspiration biopsy and rate of malignancy in patients with atypia or follicular lesion of undetermined significance: the impact of the Bethesda system for reporting thyroid cytopathology. Surgery. 2012;152(6):1037-1044.

8. Rosario PW. Thyroid nodules with atypia or follicular lesions of undetermined significance (Bethesda category III): importance of ultrasonography and cytological subcategory. Thyroid. 2014;24(7):1115-1120.

9. Gweon HM, Son EJ, Youk JH, Kim JA. Thyroid nodules with Bethesda system III cytology: can ultrasonography guide the next step? Ann Surg Oncol. 2013;20(9):3083-3088.

10. Yoon JH, Kwak JY, Kim EK, et al. How to approach thyroid nodules with indeterminate cytology. Ann Surg Oncol. 2010;17(8):2147-2155.

11. Miller B, Burkey S, Lindberg G, Snyder WH 3rd, Nwariaku FE. Prevalence of malignancy within cytologically indeterminate thyroid nodules. Am J Surg. 2004;188(5):459-462.

12. Mendez W, Rodgers SE, Lew JI, Montano R, Solorzano CC. Role of surgeon-performed ultrasound in predicting malignancy in patients with indeterminate thyroid nodules. Ann Surg Oncol. 2008;15(9):2487-2492.

13. Trimboli P, Fulciniti F, Zilioli V, Ceriani L, Giovanella L. Accuracy of international ultrasound risk stratification systems in thyroid lesions cytologically classified as indeterminate. Diagn Cytopathol. 2017;45(2):113-117.

14. Nagarkatti SS, Faquin WC, Lubitz CC, et al. Management of thyroid nodules with atypical cytology on fine-needle aspiration biopsy. Ann Surg Oncol. 2013;20(1):60-65.

15. Carr R, Ustun B, Chhieng D, et al. Radiologic and clinical predictors of malignancy in the follicular lesion of undetermined significance of the thyroid. Endocr Pathol. 2013;24(2):62-68.

16. Yoo WS, Choi HS, Cho SW, et al. The role of ultrasound findings in the management of thyroid nodules with atypia or follicular lesions of undetermined significance. Clin Endocrinol (Oxf). 2014;80(5):735-742.

17. Lee KH, Shin JH, Oh YL, Hahn SY. Atypia of undetermined significance in thyroid fine-needle aspiration cytology: prediction of malignancy by US and comparison of methods for further management. Ann Surg Oncol. 2014;21(7):2326-2331.

18. Yoon JH, Lee HS, Kim EK, Moon HJ, Kwak JY. A nomogram for predicting malignancy in thyroid nodules diagnosed as atypia of undetermined significance/follicular lesions of undetermined significance on fine needle aspiration. Surgery. 2014;155(6):1006-1013.

19. Kim GR, Yoon JH, Kim EK, Moon HJ, Kwak JY. Benign aspirates on follow-up FNA may be enough in patients with initial Atypia of undetermined significance/follicular lesion of undetermined significance. Int J Endocrinol. 2014;2014:354612.

20. Iskandar ME, Bonomo G, Avadhani V, et al. Evidence for overestimation of the prevalence of malignancy in indeterminate thyroid nodules classified as Bethesda category III. Surgery. 2015;157(3):510-517.

21. Park VY, Kim EK, Kwak JY, Yoon JH, Moon HJ. Malignancy risk and characteristics of thyroid nodules with two consecutive results of atypia of undetermined significance or follicular lesion of undetermined significance on cytology. Eur Radiol. 2015;25(9):2601-2607.

22. Yoo MR, Gweon HM, Park AY, et al. Repeat diagnoses of Bethesda category III thyroid nodules: what to do next? PLoS One. 2015;10(6):e0130138.

23. De Napoli L, Bakkar S, Ambrosini CE, et al. Indeterminate single thyroid nodule: synergistic impact of mutational markers and Sonographic features in triaging patients to appropriate surgery. Thyroid. 2016;26(3):390-394.

24. Lee YS, Kim HK, Chang H, et al. Diagnostic thyroidectomy may be preferable in patients with suspicious ultrasonography features after cytodiagnosis of AUS/FLUS in the Bethesda system. Medicine. 2015;94(51):e2183.

25. Topaloglu O, Baser H, Cuhaci FN, et al. Malignancy is associated with microcalcification and higher AP/T ratio in ultrasonography, but not with Hashimoto’s thyroiditis in histopathology in patients with thyroid nodules evaluated as Bethesda category III (AUS/FLUS) in cytology. Endocrine. 2016;54(1):156-168.

26. Baser H, Cakir B, Topaloglu O, et al. Diagnostic accuracy of thyroid imaging reporting and data system in the prediction of malignancy in nodules with atypia and follicular lesion of undetermined significance cyto logical categories according to nuclear and architectural Atypia of undetermined significance/follicular lesions of undetermined significance cytologies. Clin Endocrinol (Oxf). 2017;86(4):584-590.

27. Turkylmaz S, Ulusahin M, Celebi B, et al. Thyroid nodules classified as atypia or follicular lesions of undetermined significance deserve further research: analysis of 305 surgically confirmed nodules. Cytopathology. 2017;28(5):391-399.

28. Lim JXY, Nga ME, Chan DKH, Tan WB, Parameswaran R, Ngiam KY. Subclassification of Bethesda atypical and follicular neoplasm categories according to nuclear and architectural Atypia improves discrimination of thyroid malignancy risk. Thyroid. 2018;28(4):511-521.

29. Kaliszewski K, Diakowska D, Wojtczak B, Forkasiewicz Z. Evaluation of selected ultrasound features of thyroid nodules with atypia of undetermined significance/follicular lesion of undetermined significance for the Bethesda reporting system for thyroid cytol ogy. Cancer Manag Res. 2018;10:2223-2229.

30. Yang GCH, Fried KO, Scognamiglio T. Sonographic and cytopathologic differences of NIFTP from infiltrative or invasive encapsulated follicular variant of papillary thyroid carcinoma: a review of 179 cases. Diagn Cytopathol. 2017;45(6):533-541.

31. Poller DN. Value of cytopathologist review of ultrasound examinations in non-diagnostic/unsatisfactory thyroid FNA. Diagn Cytopathol. 2017;45(12):1084-1087.

32. VanderLaan PA, Marqusee E, Krane JF. Usefulness of diagnostic qualifiers for thyroid fine-needle aspirations with atypia of undetermined significance. Am J Clin Pathol. 2011;134(4):572-577.

33. Guo A, Kaminoh Y, Forw ard T, Schwartz FL, Jenkinson S. Fine needle aspiration of thyroid nodules using the Bethesda system for reporting thyroid cytopathology: an institutional experience in a rural setting. Int J Endocrinol. 2017;2017:9601735.
34. Singh RS, Wang HH. Eliminating the “Atypia of undetermined significance/follicular lesion of undetermined significance” category from the Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol. 2011;136(6):896-902.

35. Grani G, Lamartina L, Ascoli V, et al. Reducing the number of unnecessary thyroid biopsies while improving diagnostic accuracy: toward the “right” TIRADS. J Clin Endocrinol Metab. 2019;104(1):95-102.

36. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid. 2017;27(11):1341-1346.

37. Broome JT, Solorzano CC. The impact of atypia/follicular lesion of undetermined significance on the rate of malignancy in thyroid fine-needle aspiration: evaluation of the Bethesda system for reporting thyroid cytopathology. Surgery. 2011;150(6):1234-1241.

38. Chng CL, Kurzawinski TR, Beale T. Value of sonographic features in predicting malignancy in thyroid nodules diagnosed as follicular neoplasm on cytology. Clin Endocrinol (Oxf). 2015;83(5):711-716.

39. Azar N, Lance C, Nakamoto D, Michael C, Wasman J. Ultrasonographic thyroid findings suspicious for malignancy. Diagn Cytopathol. 2013;41(12):1107-1114.

40. Maia FF, Matos PS, Pavin EJ, Vassallo J, Zantut-Wittmann DE. Value of ultrasound and cytopathological classification system to predict the malignancy of thyroid nodules with indeterminate cytology. Endocr Pathol. 2011;22(2):66-73.

41. Kuru B, Atmaca A, Tarim IA, et al. Risk factors associated with malignancy and with triage to surgery in thyroid nodules classified as Bethesda category III (AUS/FLUS). Eur J Surg Oncol. 2016;42(1):87-93.

42. Kuru B, Kefeli M. Risk factors associated with malignancy and with triage to surgery in thyroid nodules classified as Bethesda category IV (FN/SFN). Diagn Cytopathol. 2018;46(6):489-494.

43. Brito JP, Gionfriddo MR, Al Nofal A, et al. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab. 2014;99(4):1253-1263.

44. Kwak JY, Han KH, Yoon JH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology. 2011;260(3):892-899.

45. Kim DW, Lee EJ, In HS, Kim SJ. Sonographic differentiation of partially cystic thyroid nodules: a prospective study. AJNR am J Neuroradiol. 2010;31(10):1961-1966.

46. Koh J, Kim EK, Kwak JY, Yoon JH, Moon HJ. Repeat fine-needle aspiration can be performed at 6 months or more after initial atypia of undetermined significance or follicular lesion of undetermined significance results for thyroid nodules 10 mm or larger. Eur Radiol. 2016;26(12):4442-4448.

47. Rossi M, Lupo S, Rossi R, et al. Proposal for a novel management of indeterminate thyroid nodules on the basis of cytopathological sub-classes. Endocrine. 2017;57(1):98-107.

48. Vargas-Salas S, Martinez JR, Urra S, et al. Genetic testing for indeterminate thyroid cytology: review and meta-analysis. Endocr Relat Cancer. 2018;25(3):R163-R177.

49. Schnadig VJ. Overdiagnosis of thyroid cancer: is this not an ethical issue for pathologists as well as radiologists and clinicians? Arch Pathol Lab Med. 2018;142(9):1018-1020.

50. Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of “follicular neoplasm”: a gray zone in thyroid fine-needle aspiration cytology. Diagn Cytopathol. 2002;26(1):41-44.

How to cite this article: Li F, Pan D, Wu Y, et al. Ultrasound characteristics of thyroid nodules facilitate interpretation of the malignant risk of Bethesda system III/IV thyroid nodules and inform therapeutic schedule. Diagnostic Cytopathology. 2019;47:881–889. https://doi.org/10.1002/dc.24248