SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 251680, 8 pages
doi:10.4061/2011/251680

Research Article

Subclassification of the "Grey Zone" of Thyroid Cytology; A Retrospective Descriptive Study with Clinical, Cytological, and Histological Correlation

Mariella Bonzanini,[1] Pierluigi Amadori,[2] Luca Morelli,[1] Silvia Fasanella,[1] Riccardo Pertile,[3] Angela Mattiuzzi,[4] Giorgio Marini,[4] Mauro Niccolini,[5] Giuseppe Tirone,[6] Marco Rigamonti,[7] and Paolo Dalla Palma[1]

[1] *Department of Surgical Pathology, S. Chiara Hospital, 38100 Trento, Italy*
[2] *Outpatient Endocrine Surgery, Local Public Health Service, 38100 Trento, Italy*
[3] *Epidemiological Survey, Local Public Health Service, Trento, Italy*
[4] *Department of Radiology, S. Chiara Hospital, 38100 Trento, Italy*
[5] *Department of Radiology, Villa Bianca Hospital, 38100 Trento, Italy*
[6] *Department of Surgery, S. Chiara Hospital, 38100 Trento, Italy*
[7] *Department of Surgery, Cles Hospital, 38100 Trento, Italy*

Correspondence should be addressed to Mariella Bonzanini, mariella.bonzanini@apss.tn.it

Received 15 January 2011; Revised 14 March 2011; Accepted 29 March 2011

Academic Editor: Nelson Wohllk

Undetermined thyroid cytology precludes any definitive distinction between malignant and benign lesions. Recently several classifications have been proposed to split this category into two or more cytological subcategories related to different malignancy risk rates. The current study was performed retrospectively to investigate the results obtained separating "undetermined" cytologic reports into two categories: "follicular lesion" (FL) and "atypia of undetermined significance" (AUS). Biochemical, clinical, and echographic features of each category were also retrospectively analyzed. Altogether, 316 undetermined fine-needle aspirated cytologies (FNACs) were reclassified as 74 FL and 242 AUS. Histological control leads to a diagnosis of carcinomas, adenomas, and nonneoplastic lesions, respectively, in 42.2%, 20%, and 37.8% of AUS and in 8.3%, 69.4%, and 22.2% of FL. Among biochemical, clinical, cytological, and echographic outcomes, altered thyroid autoantibodies, multiple versus single nodule, AUS versus FL, and presence of intranodular vascular flow were statistically significant to differentiate adenoma from carcinoma and from nonneoplastic lesions, whereas no significant differences were found between carcinomas and nonneoplastic lesions for these parameters. The results of this retrospective study show that undetermined FNAC category can further be subclassified in AUS and FL, the former showing higher malignancy rate. Further prospective studies are needed to confirm our results.

1. Introduction

Fine-needle aspiration cytology (FNAC) has become the dominant method in the evaluation of thyroid nodules, being fast, reliable, safe, minimally invasive, cost-effective, and reaching high sensitivity and specificity [1].

FNAC has allowed a dramatic decrease in surgical treatment of patients with thyroid nodular disease [2], enhancing the percentage of malignant operated nodules over 50% [3].

However, even in adequate cellular specimens, the method shows certain limitations and leads to an "undetermined" result in 4–15% of all cases [4, 5], precluding any definitive distinction between malignant and benign lesions.

To assess terminology, description, and interpretation of cytological appearances and transmit them to the clinicians in a clear and reproducible way, several classifications for thyroid cytology report have been proposed [6–10].

All are based on a risk of malignancy scale for adequate specimens."Undetermined" results are mostly composed of atypia of undetermined significance (AUS) and follicular patterned lesions (FL).

According to the recent Bethesda System for Reporting Thyroid Cytopathology (BSRTC), "atypia of undetermined significance/follicular lesion of undetermined significance" (AUS/FLUS) is a heterogeneous category that includes cases with ambiguous cytological findings that appear to be greater than what would be expected of a nonneoplastic process, yet the degree of cellular or architectural atypia is insufficient for an interpretation of "follicular neoplasm" or "suspicious for malignancy" [8].

Therefore, undetermined cytology is a sort of "grey zone" also for the clinicians, whose main goal is a correct therapeutic approach to thyroid lesions, that is, surgery, with its extension, or medical followup. Practically, most of these lesions are surgically removed, in total or subtotal thyroidectomy, although only a minority of them are malignant.

However, true malignancy incidence in undetermined lesions is not definitely known, because not all of them are histologically checked, and the literature reports largely heterogeneous data.

In AUS, malignancy is reported in 25% of operated patients, but it is thought to be closer to 5–10% of the total [8]. Papillary carcinoma is by far the commonest tumour [3, 11, 12].

Malignancy incidence in FL is even more variously reported than in AUS.

Cancer ratio in all FL lesions (operated and nonoperated) is about 20% in several surveys [3, 11–13], but other authors reported much lesser incidences of 0–7% [14–16].

In this study we have retrospectively split "undetermined" thyroid FNAC into two categories: "follicular lesion" (FL) and "atypia of undetermined significance" (AUS) in order to evaluate

(i) the relative incidences of AUS and FL in thyroid FNA specimens in our district,

(ii) the incidence of malignant lesions in AUS and FL,

(iii) the presence of biochemical, clinical, and echographic features possibly predictive of malignancy related to AUS and FL.

2. Materials and Methods

We reviewed the thyroid FNAC data of our institution from June 2004 to December 2007.

For each FNAC, a specific module was performed, including patient data, clinical and biochemical thyroid status (hypo-, hyper, or euthyroidism), thyroid autoantibodies, and thyroid medication. Moreover, detailed ultrasound features such as size, echogenicity, microcalcifications, boundaries, and color Doppler vascular flow pattern (intra/perinodular) were described for each nodule.

FNACs were mainly performed by four radiologists and one endocrinologist with ultrasound guide, using 25 or 27 gauge needles.

Two-three samplings were performed for each nodule. Papanicolaou and May-Grünwald-Giemsa stains were both used for FNA smears preparations.

2.1. Cytological Classification Criteria. Cytological specimens were evaluated by 3 pathologists, and careful cytological description was reported for each case.

Original cytologic reports were reclassified into 5 categories: inadequate, benign, undetermined, suspicious, and malignant, not knowing the followup.

The undetermined results were divided into two further categories.

(1) FL for samples suggesting follicular neoplasms. In this category were included FNACs with high to moderate cellularity, predominantly or partially microfollicular pattern, scanty or absent colloid, and mild or absent nuclear atypia. Samples consisting almost exclusively/exclusively of Hurthle cells were also included here.

Follicular patterned lesions or Hurthle cells lesions with overt cytological architectural or nuclear atypical features (that is irregular or variably sized follicle, crowding of cells, many single cells, pleomorphic, enlarged nuclei, nuclear grooves, coarse and irregular chromatin, prominent and multiple nucleoli, atypical or numerous mitosis) [17] were reported as suspicious and were not included in this study.

(2) AUS for samples exhibiting cytological atypia or other features raising the possibility of neoplasia, but which were insufficient to enable confident placing into any other category.

This is intended as a broad category encompassing focal features suggestive of papillary carcinoma, cellular atypia hindered by sample preparation artifact, cellular atypia engendered by cystic alteration, repair, and therapy. Atypical lymphoid infiltrate was included [8, 10].

2.2. Histological, Cytological, and Clinical Followup. Corresponding histologic and clinical-cytological followup was reviewed.

The histological diagnosis was made according to the World Health Organization guidelines [18].

The patients who did not undergo thyroid surgery, with benign repeated FNAC, were followed by clinical and periodic thyroid sonographic evaluation, at least once within 2 years from the last FNA. If the thyroid nodule did not undergo any modifications it was considered "bona fide" benign.

2.3. Statistical Analysis. The descriptive analyses included the observed frequencies calculation with the respective percentages for each categorical variable, while median and range were computed for patients' age and diameter of nodules (continuous variables).

Multivariate stepwise logistic regression analysis was performed in order to identify clinical, echographic, and

cytological categories associated with the lesion type (carcinomas versus adenomas, carcinomas versus nonneoplastic lesions, adenomas versus nonneoplastic lesions). In stepwise selection analysis, any significant variables (P value $\leq .05$) are inserted in the model as covariates, but an attempt is made to remove any insignificant variables from the model before adding a new significant variable to the model. Each addition or deletion of a variable to or from a model is listed as a separate step and at each step, a new model is fitted. In this study only the final model is presented. Results are given in terms of odds ratio (OR).

Multivariate analyses were performed with SAS software, version 9.1.3 (SAS Institute Inc., SAS 9.1.3, Cary, NC, USA, 2003).

3. Results

Between June 2004 and December 2007, 2422 FNAs were performed in 1883 patients with thyroid nodule(s). There were 348 men and 1535 women, aged 13–88 years (median 54 years).

Reclassification of the cytological reports yielded 397 (16.4%) nondiagnostic samples, 1554 (64.2%) benign cytology, 84 (3.5%) diagnoses of suspect malignant neoplasia, 71 (2.9%) diagnoses of malignant cytology, and 316 (13%) undetermined cytologic reports. 74 (3%) reports corresponding to follicular lesion were reclassified as FL, and 242 (10%) reports were reclassified as AUS (Figure 1).

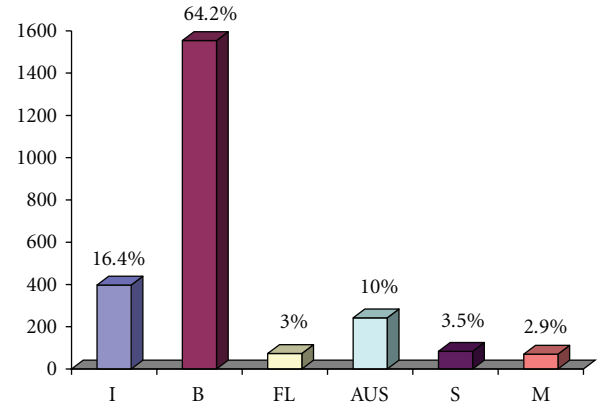

Figure 1: I: inadequate; B: benign; FL: follicular lesion; AUS: atypia of undetermined significance; S: suspicious for malignant neoplasia; M: malignant neoplasia. Distribution of cytological categories after reclassification.

3.1. Histological Followup. The histological diagnosis was available for 81 nodules of the undetermined category: 36 of 74 (48.6%) nodules classified as FL, and 45 of 242 (18.6%) nodules classified as AUS.

There were 22 malignant tumors, 34 follicular adenomas, and 25 nonneoplastic lesions.

Among malignant tumors, 19 were PTC, 15 classic and 4 follicular variant, and 3 were follicular carcinomas.

Follicular adenomas were Hurtle cells type in 13 cases and follicular in 21 cases.

Nonneoplastic lesions have been shown to be nodular hyperplasia in 18 cases, Hashimoto's thyroiditis in 5, granulomatous thyroiditis in 1, and spindled, probably reactive, lesion in 1. Among histologically proven carcinomas, 19 (42.2%) were observed in nodules with preoperative AUS reclassification, whereas 3 (8.3%) were observed in nodules with preoperative FL reclassification.

Adenomas were observed in 25 (69.4%) nodules classified as FL and in 9 (20%) classified as AUS.

Seventeen benign lesions (nodular hyperplasia and thyroiditis) corresponded to cytological reclassification of AUS (37.8%) and 8 to FL (22.2%) (Table 1).

3.2. Clinical Followup. Repetition of FNAC was performed in 73 AUS lesions. Nine resulted inadequate, 46 benign, 10 AUS, 1 FL, 5 suspicious, and 2 malignant.

Repetition of FNAC was performed in 8 FL. In 5 cases the same cytological category was confirmed, whereas in 3 cases the cytological diagnosis was benign.

For 49 lesions with repeated benign FNA (46 AUS and 3 FL), in which the patients did not undergo thyroid surgery, clinical and echographic followup supported the benign nature of the lesion.

3.3. Clinical and Echographic Features. Clinical, echographic features and cytological diagnosis of histologically proven carcinomas and adenomas and of nonneoplastic lesions with histological or clinical followup are reported in Table 2.

No significant statistical differences were found according to age, gender, and thyroid function between carcinomas, adenomas, and nonneoplastic lesions. Moreover, there were no significant differences for clinical, echographic, and cytological reclassification between carcinomas and nonneoplastic lesions. However, altered autoantibodies, multiple nodules versus single nodule, and AUS versus FL cytological category showed a statistically significant difference between carcinomas and adenomas (Table 3). In detail, after conditioning on the other variables entered in the model, the probability of observing a carcinoma was more than 15 times higher when thyroid autoantibodies were altered (OR = 15.43 with a P value = .046), multiple nodules increased the probability of identifying a carcinoma by almost 79 times (OR = 78.94 with a P value = .003), and the presence of AUS cytological category increased the probability of recognizing a carcinoma by more than 21 times (OR = 21.49 with a P value = .023). Total variance explained by these three variables entered in the final model is 56% (R^2 = 0.56) and concordance percentage is 92.9% which means that 93 of every 100 nodules will be well classified using alteration in thyroid autoantibodies, multiple/single nodules, and cytological category as predictors.

Concerning the comparison between nonneoplastic lesions and adenomas, single nodule (versus multiple nodules), follicular lesion (versus AUS), higher diameter, and no vascular flow are all statistically significant features in adenomas compared to nonneoplastic lesions (Table 4). Keeping the other variables constant in the model, the

Table 1: Histologic followup of cases.

	AUS (242 cases)		FL (74 cases)	
	45	18.6%	36	48.6%
Benign	26	57.8%	33	91.6%
Follicular adenoma	5	19.2%	16	48.5%
Hurtle cell adenoma	4	15.4%	9	27.3%
Nodular hyperplasia	11	43.3%	7	21.2%
Hashimoto thyroiditis	4	15.4%	1	3%
De Quervain thyroiditis	1	3.8%	—	—
Reactive nodule	1	3.8%	—	—
Malignant	19	42.2%	3	8,4%
Papillary carcinoma classic type	14	73.7%	1	33.3%
Follicular variant of papillary carcinoma	3	15.8%	1	33.3%
Follicular carcinoma	2	10.5%	1	33.3%

AUS: atypia of undetermined significance; FL: follicular lesion.

Table 2: Clinical, biochemical, and echographic features of 130 thyroid nodules with histological (81 cases) or benign repeated cytology with clinical-echographic followup (49 cases).

	Carcinoma		Adenoma		Nodular hyperplasia/thyroiditis	
	22	16.9%	33	25.4%	75	57.7%
Clinical and biochemical features						
Age (years)	Range 25–75 Median 53		Range 18–81 Median 49		Range 27–72 Median 51	
Female	18	80.8%	26	78.8%	68	90.7%
Male	4	19.2%	7	21.2%	7	9.3%
AbHTG and/or AbTPO	7	31.8%	4	12.1%	27	36.0%
Hypothyroidism	1	4.5%	—	—	3	4.0%
Hyperthyroidism	1	4.5%	1	3.0%	2	2.7%
Single nodule	8	36.4%	25	75.8%	24	32.0%
Unknown	—		1	3.0%	3	4.0%
Diameter (mm)	Range 6–48 Median 18		Range 7–54 Median 23		Range 8–50 Median 15	
Palpable	14	63.6%	22	66.7%	35	46.7%
Echographic features						
Solid	20	90.9%	26	78.8%	54	72.0%
Hypoechoic	14	70.0%	20	76.9%	37	68.5%
Hyperechoic	2	10%	1	3.8%	10	18.5%
Isoechoic	4	20%	5	19.2%	7	13.0%
Microcalcifications	5	25%	5	19.2%	3	5.6%
Vascular flow	4	20%	14	53.8	11	20.4%
Irregular margins	3	15%	2	7.7%	3	5.6%
Unknown	—		2	6.1%	3	4.0%
Mixed	2	9.1%	5	15.1%	16	21.3%
Cystic	—	—	—	—	2	2.7%
Cytologic category						
AUS	19	86.4%	9	27.3%	65	86.7%
FL	3	13.6%	24	72.7%	10	13.3%

AUS: atypia of undetermined significance; FL: follicular lesion.

Table 3: Multivariate logistic analysis of the probability of identifying a carcinoma versus an adenoma by clinical, echographic features and cytologic category.

	Parameters entered in the model	OR	*P* value	Concordance percentage	*R*2
All nodules ($n = 54$)	Ab altered (yes versus no)	15.43	**.046**	92.9%	0.56
	Multiple versus single nodule	78.94	**.003**		
	Cytologic Category (AUS versus FL)	21.49	**.023**		
Only solid nodules ($n = 45$)	Multiple versus single nodule	29.53	**.005**	85.9%	0.48
	Cytologic Category (AUS versus FL)	12.50	**.044**		

AUS: atypia of undetermined significance; FL: follicular lesion.

Table 4: Multivariate logistic analysis of the probability of identifying a benign nodule (NH and thyroiditis) versus an adenoma by clinical, echographic features and cytologic category.

	Parameters entered in the model	OR	*P* value	Concordance percentage	R^2
All nodules ($n = 108$)	Multiple versus single nodule	14.47	**.002**	81.3%	0.38
	Cytologic Category (AUS versus FL)	11.96	**.000**		
	Diameter (mm)	0.94	**.043**		
Only solid nodules ($n = 80$)	Multiple versus single nodule	10.93	**.006**	80.8%	0.37
	Cytologic Category (AUS versus FL)	8.48	**.005**		
	Vascular flow (yes versus No)	0.14	**.035**		

AUS: atypia of undetermined significance; FL: follicular lesion.

probability of identifying a benign lesion increased by 14.5 times in case of multiple nodules (OR = 14.47 with a *P* value = .002) and by 12 times with an AUS cytological category (OR = 11.96 with a *P* value $\leq$ .0001). Finally, for each mm. of increase in the nodule diameter, the logistic regression model predicted a 6% decrease in the probability of observing a nonneoplastic lesion rather than an adenoma (OR = 0.94 and *P* value = .043). Concordance percentage of the model is 81.3% and R^2 is 0.38.

Taking into account only solid nodules ($n = 80$), the diameter was no more statistically significant, but another variable entered in the model, that is, vascular flow: the presence of vascular flow decreased the probability of observing a nonneoplastic lesion by 86% (OR = 0.14 and *P* value = .035).

4. Conclusions

Although FNAC has been used with success in the diagnosis of papillary, medullary, and anaplastic thyroid carcinomas, it is difficult to assess its value in follicular lesions. The main problem is the distinction between benign lesions, such as follicular adenoma or nodular adenomatous goiter, and follicular carcinoma or follicular variant of papillary carcinoma (FVPTC).

Therefore, histological evaluation is necessary to demonstrate capsular/vascular invasion for follicular carcinoma and the subtle nuclear aspects in FVPTC [11].

Classifications, practically overlapping as for benign and malignant definitions, show some substantial differences managing undetermined lesions.

Follicular lesions are managed in two main different ways depending on the classification.

The Bethesda System distinguishes 3 subcategories: "follicular neoplasm or suspicious for a follicular neoplasm" refers to a cellular aspirate comprised of follicular cells, most of which are arranged in an altered architectural pattern characterized by significant cell crowding and/or microfollicle formation; "follicular neoplasm, Hurthle cell type/suspicious for follicular neoplasm, Hurthle cell type" refers to a cellular aspirate consisting exclusively (or nearly exclusively) of Hurthle cells.

Follicular patterned aspirates that do not otherwise fulfil the aforementioned criteria are set together with AUS (AUS/FLUS).

However, a significant difference in malignancy incidence seems not to appear from the document [8].

The recently published "Guidance on the reporting of thyroid cytology specimens" of English Royal College of Pathologist (RCP) names "neoplasm possible" (Thy3) the undetermined category and separates samples suggesting follicular neoplasms (Thy3f-f for follicular) from samples which exhibit cytological atypia or other features which raise the possibility of neoplasia but which are insufficient to enable confident placing into any other category (Thy3a-a for atypia).

Operative indications emerging from BSRTC recommend FNAC repetition for AUS/FLUS (with subsequent surgery if AUS/FLUS, or worse category, are found) [8], whereas RCP recommends an individualized and multidisciplinary assessment for each patient [10].

As for AUS, its incidence among thyroid cytological specimens is variably reported, ranging from 2% to 6%, although some heterogeneity in its definition makes it difficult to draw consistent conclusions [3, 5, 11, 12]. The Bethesda System for Reporting Thyroid Cytopathology recommends to use this

category as a last resort and limit its use to approximately 7% [8].

In our institution, thyroid FNAC classification similar to that of The Royal College of Pathologists [9, 10] has been actually chosen, where the presence/absence of nuclear atypia is the key of the undetermined lesions subclassification in AUS and FL.

In the present study, data obtained on this basis indicate that AUS is associated with higher malignancy rates than FL.

Low malignancy incidence in FL emerging from our study contradicts the usually accepted rates of about 20% reported by some studies [3, 5, 13, 14, 19, 20] but it is in agreement with others.

Two Italian studies found no cancers in all operated nodules with cytological diagnosis of FL [15, 21].

DeMay, at histological examination, found only 2 cancers (none follicular) among 138 FL [16].

Such a discrepancy may reflect inconsistent patterns in cytological criteria of classification.

One of the heaviest factors influencing this discrepancy is cellular atypia, particularly its definition and association with follicular patterned lesions.

The role of atypia as an independent risk factor for malignancy has been matter of interest and debate. Although some authors report no correlation between atypia and malignancy [5, 22, 23], other studies show, conversely, that atypia alone or in association with a follicular patterned FNAC can be linked to a higher risk of malignancy [12, 14, 16, 20, 24, 25].

Interestingly, most literature showing high malignancy rates in FL, actually reports substantial reduction when lesions with atypia are excluded [12, 14, 19].

Moreover, among the malignancies histologically proven in FL, FVPTC appears to be the commonest one, whereas follicular carcinoma and Hurthle cell carcinomas seem to be much rarer than usually reported both in FL and, generally, among all thyroid cancers [13–16].

It is well known that the cytological diagnosis of FVPTC is challenging, due to a paucity or lack of well-defined nuclear features of papillary carcinoma, leading, in samples containing few cellular groups, to a diagnosis of AUS or FL [13].

However, an accurate evaluation of focal cytological features and the architectural pattern has been shown to allow a correct diagnosis of malignancy or suspect for malignancy [26, 27], but adequate smears and skilled pathologists are necessary, and this could play some role in outcome differences.

Multivariate analysis of our data allows to draw some other relevant conclusions.

Among the cytological undetermined lesions of thyroid, adenomas seem to be the more correctly classifiable on the basis of cytological, immunological, and ultrasound data.

Firstly, most of FL specimens lead to a histological diagnosis of adenoma.

Secondly, thyroid autoantibodies appear to be more common in non-neoplastic lesions and in carcinomas than in adenomas. As for carcinomas, this is not surprising. Coexistence of chronic lymphocytic thyroiditis and PTC has been reported, at variable frequencies, although it remains unclear whether these two thyroid disorders share a common aetiology or thyroiditis represents a host tumor immune response [28–30].

Moreover, Kim et al. recently reported positive serum antithyroglobulin antibodies as an independent predictor for thyroid malignancy in thyroid nodules, regardless of the presence of autoimmune thyroiditis [31].

Our results, although limited to thyroid cancers discovered in undetermined cytology, seem to be in agreement with this observation.

Conversely, the overlapping incidences of thyroid autoantibodies in carcinomas and in non-neoplastic lesions in the present study could almost partially be due to the fact that, in the latter, both autoimmune thyroiditis and nodular hyperplasia were enclosed.

In conclusion, our outcomes suggest higher malignancy risk in cytological undetermined thyroid lesions with atypia than without atypia.

The very low incidence of thyroid cancer found in FL refers to the same perplexity about an unavoidable surgical treatment, arisen by other authors with similar results [15, 16, 21].

Although all patients with FL should be considered for surgical resection, they should be also informed about the low malignancy risk of their condition and other aspects, such as underlying medical conditions and age of the patients, presence/absence of thyroid autoantibodies, growth rate of the nodule, which could be taken in account for the decision.

Conversely, a more relevant indication to surgery could be advisable for AUS.

In this lesion, FNAC repetition seems also appropriate. Our data confirm that about half of these aspirates are reclassified as benign, as already reported in the literature [3, 12].

Being based on the review of previous cytological data, our study shares the same limitations of the retrospective studies, not allowing a prospective, two-arm followup of operated versus nonoperated cases. Therefore our findings should be evaluated in this light. Anyway, we clearly documented clinical and cytological findings in subclassified undetermined cytologic category in 81 nodules histologically checked and in 49 nodules with repeated FNAC and clinical and echographic followup.

Two years ago our results led to the employment, in our department, of a cytological classification similar to that of the RCP. A larger, prospective study design has been planned for the risk assessment in each cytological category.

In recent years, molecular tests have been shown to be useful in the diagnosis of thyroid neoplasms. Point mutations in BRAF and RAS genes and gene rearrangements involving PAX8/PPARγ and RET/PTC have been found in approximately 70% of thyroid neoplasia [32].

The B-RAF V600E mutation has been shown as diagnostic marker for PTC, and there have been many reports on its diagnostic usefulness in refining the cytological diagnosis of

this tumor [33–37]. But, unfortunately BRAF analysis is of limited value in preoperative diagnosis of FVPTC [38].

Moreover, several studies indicate that molecular testing of thyroid nodules for a panel of mutations can enhance the accuracy of undetermined FNAC [39, 40], but at present no single marker seems to be accurate enough to distinguish thyroid carcinoma from its benign mimics to be introduced in the routine [41].

Finally, our results support the indication to distinguish undetermined thyroid cytological samples with follicular patterned feature without atypia from the undetermined samples with atypical cells and to relate the FNAC results with clinical and echographic findings.

Conflict of Interests

There is no financial interest in or arrangement with a company whose product was used in a study. In addition, there is no financial interest in or arrangement with a competing company, and there are no other direct or indirect financial connections or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated—including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships, or direct academic competition.

References

[1] M. W. Ashcraft and A. J. Van Herle, "Management of thyroid nodules. I: history and physical examination, blood tests, X-ray tests, and ultrasonography," *Head and Neck Surgery*, vol. 3, no. 3, pp. 216–230, 1981.

[2] H. Gharib and J. R. Goellner, "Fine-needle aspiration biopsy of the thyroid: an appraisal," *Annals of Internal Medicine*, vol. 118, no. 4, pp. 282–289, 1993.

[3] L. Yassa, E. S. Cibas, C. B. Benson et al., "Long-term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation," *Cancer*, vol. 111, no. 6, pp. 508–516, 2007.

[4] Z. W. Baloch, M. J. Sack, G. H. Hu, V. A. Livolsi, and P. K. Gupta, "Fine-needle aspiration of thyroid: an institutional experience," *Thyroid*, vol. 8, no. 7, pp. 565–569, 1998.

[5] J. Yang, V. Schnadig, R. Logrono, and P. G. Wasserman, "Fine-needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations," *Cancer*, vol. 111, no. 5, pp. 306–315, 2007.

[6] H. H. Wang, "Reporting thyroid fine-needle aspiration: literature review and a proposal," *Diagnostic Cytopathology*, vol. 34, no. 1, pp. 67–76, 2006.

[7] "Papanicolau Society of cytopathology recommandetionsfor thyroid fine-needle aspiration," 2010, http://www.pathology.org/guidelines.html.

[8] S. Z. Ali and E. S. Cibas, *The Bethesda System for Reporting Thyroid Cytopathology. Definitions, Criteria and Explanatory Notes*, Springer, New York, NY, USA, 2010.

[9] British Thyroid Association Royal College of Physicians, "Guidelines for the management of thyroid cancer," in *Report of the Thyroid Cancer Guidelines Update Group*, P. Perros, Ed., Royal College of Physicians, London, UK, 2nd edition, 2007.

[10] The Royal College of Pathologists, "Guidance on the reporting of thyroid cytology specimens," London: RCP 2009, http://www.rcpath.org/resources/pdf/g089guidanceonthereportingofthyroidcytologyfinal.pdf.

[11] Y. Shi, X. Ding, M. Klein et al., "Thyroid fine-needle aspiration with atypia of undetermined significance: a necessary or optional category?" *Cancer Cytopathology*, vol. 117, no. 5, pp. 298–304, 2009.

[12] R. E. Goldstein, J. L. Netterville, B. Burkey, and J. E. Johnson, "Implications of follicular neoplasms, atypia, and lesions suspicious for malignancy diagnosed by fine-needle aspiration of thyroid nodules," *Annals of Surgery*, vol. 235, no. 5, pp. 656–664, 2002.

[13] W. C. Faquin and Z. W. Baloch, "Fine-Needle aspiration of follicular patterned lesions of the thyroid: diagnosis, management, and follow-up according to National Cancer Institute (NCI) recommendations," *Diagnostic Cytopathology*, vol. 38, pp. 731–739, 2010.

[14] N. Dabelić, N. Matesa, D. Matesa-Anić, and Z. Kusić, "Malignancy risk assessment in adenomatoid nodules and suspicious follicular lesions of the thyroid obtained by fine needle aspiration cytology," *Collegium Antropologicum*, vol. 34, pp. 349–354, 2010.

[15] L. Foppiani, M. Tancredi, G. L. Ansaldo et al., "Absence of histological malignancy in a patient cohort with follicular lesions on fine-needle aspiration," *Journal of Endocrinological Investigation*, vol. 26, no. 1, pp. 29–34, 2003.

[16] R. M. DeMay, "Follicular lesions of the thyroid: W(h)ither follicular carcinoma?" *American Journal of Clinical Pathology*, vol. 114, no. 5, pp. 681–683, 2000.

[17] R. M. De May, "Thyroid," in *The Art and Science of Cytopathology*, pp. 724–729, ASCP Press, Chigago, Ill, USA, 1996.

[18] C. Hedinger, *Histological Typing of Thyroid Tumours*, Springer, Berlin, Germany, 2nd edition, 1988.

[19] R. Mihai, A. J. C. Parker, D. Roskell, and G. P. Sadler, "One in four patients with follicular thyroid cytology (THY3) has a thyroid carcinoma," *Thyroid*, vol. 19, no. 1, pp. 33–37, 2009.

[20] G. Bahar, D. Braslavsky, T. Shpitzer et al., "The cytological and clinical value of the thyroid "follicular lesion"," *American Journal of Otolaryngology*, vol. 24, no. 4, pp. 217–220, 2003.

[21] D. Piromalli, G. Martelli, I. Del Prato, P. Collini, and S. Pilotti, "The role of fine needle aspiration in the diagnosis of thyroid nodules: analysis of 795 consecutive cases," *Journal of Surgical Oncology*, vol. 50, no. 4, pp. 247–250, 1992.

[22] T. S. Greaves, M. Olvera, B. D. Florentine et al., "Follicular lesions of thyroid: a 5-year fine-needle aspiration experience," *Cancer*, vol. 90, no. 6, pp. 335–341, 2000.

[23] C. R. McHenry, S. R. Thomas, S. J. Slusarczyk, and A. Khiyami, "Follicular or Hurthle cell neoplasm of the thyroid: can clinical factors be used to predict carcinoma and determine extent of thyroidectomy?" *Surgery*, vol. 126, no. 4, pp. 798–804, 1999.

[24] A. Carpi, E. Ferrari, M. G. Toni, A. Sagripanti, A. Nicolini, and G. Di Coscio, "Needle aspiration techniques in preoperative selection of patients with thyroid nodules: a long-term study," *Journal of Clinical Oncology*, vol. 14, no. 5, pp. 1704–1712, 1996.

[25] A. S. Kelman, A. Rathan, J. Leibowitz, D. E. Burstein, and R. S. Haber, "Thyroid cytology and the risk of malignancy in thyroid nodules: importance of nuclear atypia in indeterminate specimens," *Thyroid*, vol. 11, no. 3, pp. 271–277, 2001.

[26] S. Logani, P. K. Gupta, V. A. LiVolsi, S. Mandel, and Z. W. Baloch, "Thyroid nodules with FNA cytology suspicious for follicular variant of papillary thyroid carcinoma: follow-up

and management," *Diagnostic Cytopathology*, vol. 23, no. 6, pp. 380–385, 2000.

[27] I. A. El Hag and S. M. Kollur, "Benign follicular thyroid lesions versus follicular variant of papillary carcinoma: differentiation by architectural pattern," *Cytopathology*, vol. 15, no. 4, pp. 200–205, 2004.

[28] K. C. Loh, F. S. Greenspan, F. Dong, T. R. Miller, and P. P. B. Yeo, "Influence of lymphocytic thyroiditis on the prognostic outcome of patients with papillary thyroid carcinoma," *Journal of Clinical Endocrinology and Metabolism*, vol. 84, no. 2, pp. 458–463, 1999.

[29] E. Kebebew, P. A. Treseler, P. H. G. Ituarte, and O. H. Clark, "Coexisting chronic lymphocytic thyroiditis and papillary thyroid cancer revisited," *World Journal of Surgery*, vol. 25, no. 5, pp. 632–637, 2001.

[30] S. Arif, A. Blanes, and S. J. Diaz-Cano, "Hashimoto's thyroiditis shares features with early papillary thyroid carcinoma," *Histopathology*, vol. 41, no. 4, pp. 357–362, 2002.

[31] E. S. Kim, D. J. Lim, K. H. Baek et al., "Thyroglobulin antibody is associated with increased cancer risk in thyroid nodules," *Thyroid*, vol. 20, pp. 885–891, 2010.

[32] Y. E. Nikiforov, "Thyroid carcinoma: molecular pathways and therapeutic targets," *Modern Pathology*, vol. 21, supplement 2, pp. S37–S43, 2008.

[33] G. Salvatore, R. Giannini, P. Faviana et al., "Analysis of BRAF point mutation and RET/PTC rearrangement refines the fine-needle aspiration diagnosis of papillary thyroid carcinoma," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 10, pp. 5175–5180, 2004.

[34] K. W. Chung, S. K. Yang, G. K. Lee et al., "Detection of BRAF mutation on fine needle aspiration specimens of thyroid nodule refines cyto-pathology diagnosis, especially in BRAF mutation-prevalent area," *Clinical Endocrinology*, vol. 65, no. 5, pp. 660–666, 2006.

[35] M. R. Sapio, D. Posca, A. Raggioli et al., "Detection of RET/PTC, TRK and BRAF mutations in preoperative diagnosis of thyroid nodules with indeterminate cytological findings," *Clinical Endocrinology*, vol. 66, no. 5, pp. 678–683, 2007.

[36] G. Troncone, I. Cozzolino, M. Fedele, U. Malapelle, and L. Palombini, "Preparation of thyroid FNA material for routine cytology and BRAF testing: a validation study," *Diagnostic Cytopathology*, vol. 38, no. 3, pp. 172–176, 2010.

[37] S. Girlando, L. V. Cuorvo, M. Bonzanini et al., "High prevalence of B-RAF mutation in papillary carcinoma of the thyroid in North-East Italy," *International Journal of Surgical Pathology*, vol. 18, no. 3, pp. 173–176, 2010.

[38] A. Proietti, R. Giannini, C. Ugolini et al., "BRAF status of follicular variant of papillary thyroid carcinoma and its relationship to its clinical and cytological features," *Thyroid*, vol. 20, pp. 1263–1270, 2010.

[39] Y. E. Nikiforov, D. L. Steward, T. M. Robinson-Smith et al., "Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 6, pp. 2092–2098, 2009.

[40] N. P. Ohori, M. N. Nikiforova, K. E. Schoedel et al., "Contribution of molecular testing to thyroid fine-needle aspiration cytology of "follicular lesion of undetermined significance/atypia of undetermined significance"," *Cancer Cytopathology*, vol. 118, no. 1, pp. 17–23, 2010.

[41] B. C. G. Freitas and J. M. Cerutti, "Genetic markers differentiating follicular thyroid carcinoma from benign lesions," *Molecular and Cellular Endocrinology*, vol. 321, no. 1, pp. 77–85, 2010.