ORIGINAL ARTICLE

Comparison of clinicopathological features in patients with noninvasive follicular thyroid neoplasm with papillary-like nuclear features and follicular variant papillary thyroid cancer

Mehmet Celik[1], Buket Y. Bulbul[1], Nuray Can[2], Semra Ayturk[1], Ebru Tastekin[2], Atakan Sezer[3], Funda Ustun[4], Sibel Guldiken[1]

1 Department of Endocrinology and Metabolism, Medical Faculty, Trakya University, Edirne, Turkey
2 Department of Pathology, Medical Faculty, Trakya University, Edirne, Turkey
3 Department of Surgery, Medical Faculty, Trakya University, Edirne, Turkey
4 Department of Nuclear Medicine, Medical Faculty, Trakya University, Edirne, Turkey

KEY WORDS

follicular variant of papillary thyroid carcinoma, noninvasive follicular thyroid neoplasm with papillary-like nuclear features, ultrasonography

ABSTRACT

INTRODUCTION Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a newly defined entity accepted as a tumor precursor.

OBJECTIVES We aimed to examine the features of patients diagnosed with follicular variant papillary thyroid carcinoma (FVPTC), which are classified as NIFTP in the recent classification. This study compares clinical, radiological, histopathological, and molecular features of NIFTP and FVPTC.

PATIENTS AND METHODS A total of 247 patients with FVPTC were retrospectively examined and pathology specimens were reviewed.

RESULTS Patients were divided into 2 groups (NIFTP group: 107 patients; FVPTC group: 140 patients). There was a difference in terms of the percentage of pathologic nodules with irregular borders detected on preoperative neck ultrasonography (NIFTP group: 6.5%, FVPTC group: 15.7%; $P = 0.02$). Central lymph node dissection specimens of 50 patients in the NIFTP group were normal, while 4 of 70 patients (5.7%) in the FVPTC group had lymph node metastasis ($P = 0.14$). In addition, multivariable analysis (binary logistic regression) showed that FVPTC was positively associated only with irregular borders and extrathyroidal extensions ($P = 0.02$ and $P < 0.001$, respectively).

CONCLUSIONS We suggest that patients diagnosed with NIFTP according to the new classification are considered low risk, and margin characteristics of the nodule detected on preoperative ultrasonography may be helpful in the differential diagnosis.

Correspondence to: Mehmet Celik, MD, Department of Endocrinology and Metabolism, Medical Faculty, Trakya University, Edirne, 22030, Turkey, phone: +902842360910, email: drmehmetcelik@hotmail.com
Received: October 27, 2019.
Revision accepted: December 23, 2019.
Published online: January 2, 2020.
Pol Arch Intern Med. 2020; 130 (2): 100-105
doi:10.20452/pamw.15120

INTRODUCTION Recent studies have shown that about 10% to 20% of all thyroid cancers are noninvasive capsulated papillary follicular variant.[1,2] However, there is no consensus on papillary nuclear changes used in the diagnosis of noninvasive capsulated follicular variant of papillary thyroid cancer. Moreover, instead of noninvasive capsulated follicular variant of papillary thyroid cancer, some authors prefer the term noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[3] Although NIFTP is less aggressive, there is an ongoing debate on whether these patients are unnecessarily followed and treated. The role of clinical and laboratory findings of thyroid nodules in the diagnosis of the infiltrative follicular variant of papillary thyroid carcinoma (FVPTC) and NIFTP is still unknown. In this study, we aimed to evaluate the characteristics of our patients with FVPTC who have NIFTP according to the new classification.

PATIENTS AND METHODS **Patient selection** A total of 460 patients with any PTC variant who had been followed between 2010 and 2016 were

WHAT'S NEW?

In 2016, a new morphological term, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), was introduced. It corresponds to low-risk tumors known as a noninvasive encapsulated follicular variant of papillary thyroid carcinoma. NIFTP was included in the 2017 Classification of Endocrine Organ Tumors of World Health Organization as "follicular patterned neoplasms with borderline clinical behavior." Initial diagnostic criteria were based only on histopathologic evaluation, and subsequent studies suggested the use of immunomolecular studies for diagnosis of exclusion criteria. In addition, some radiological descriptions have been suggested. In this study, the finding that irregular borders detected on thyroid ultrasonography may be used to differentiate NIFTP and follicular variant papillary thyroid cancer is an important contribution to the literature and ongoing consensus studies on NIFTP.

enrolled in the study. Clinical and laboratory findings of 247 patients with FVPTC were retrospectively examined and pathology specimens were reviewed according to the recent NIFTP criteria.[3] Patients were divided into 2 groups, those with encapsulated FVPTC without capsular invasion (recently called NIFTP) (n = 107) and those with encapsulated FVPTC with capsular invasion (IEFVPTC) (n = 140). Patients who had another variant of thyroid carcinoma or diffuse/multinodular variant of FVPTC, patients with tumors containing more than 1% of true papillae, and partially sampled tumors were excluded in the reevaluation of the slides. The study protocol was approved by the institutional ethics committee of Trakya University (no. TUTF-BAEK 2017/162).

Surgical procedure and follow-up Patients who underwent total thyroidectomy or lobectomy and postoperative radioiodine ablation were classified in accordance with the American Thyroid Association guidelines.[4] The following data were recorder: age, sex, results of thyroid function tests at the time of diagnosis, levels of anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies, preoperative neck ultrasonography findings, postoperative histopathologic features of tumors, thyroglobulin values, repeated radioactive iodine 131 treatment, lymph node and distant metastases and *BRAF-KRAS-NRAS* mutation status.

Clinicopathological criteria Tumors were classified as FVPTC if they exhibited dominant follicular architecture (≤1% true papillae) and nuclear features of PTC (2–3/3 grade according to the alterations in 1) nuclear size and shape: nuclear overlapping, nuclear enlargement, nuclear membrane irregularities, 2) irregular nuclear contours: nuclear elongation, intranuclear pseudoinclusions, nuclear grooves, 3) chromatin characteristics: nuclear chromatin clearing, glassy nuclei, peripheral margination of the chromatin) but were not associated with necrosis, solid/trabecular/cribriform growth patterns, tall cell or columnar cell, or more than 3 mitoses per 10 high-power fields.[3] Follicular variant of papillary thyroid carcinomas completely surrounded by a fibrous capsule or clearly demarcated from the surrounding thyroid tissue were reclassified as NIFTP. Pathology specimens of patients with FVPTC were examined by 2 pathologists according to the present diagnostic criteria. Findings from the study groups were evaluated according to the NIFTP diagnostic criteria by Nikiforov et al[3] (Tables 1 and 2).

***BRAF* mutation analyses** Tissue containing at least 30% of tumor cells was isolated from the sections of tumor tissue. Then, DNA isolation was performed with the nucleic acid isolation kit for paraffine embedded tissues (QIAamp DNA FFPE Tissue Kit 50 QIAGEN Cat. No. 56404, EZ1 DNA Tissue Kit 48 QIAGEN Cat. No. 953034, PAXgene Tissue Containers 10 QIAGEN Cat. No. 765112, PAXgene Tissue DNA Kit 50 QIAGEN Cat. No. 767134; Qiagen, Hilden, Germany). Following the polymerase chain reaction procedures, pyrosequencing analyses were performed on the PyroMarkQ24 (Qiagen) by using sequencing primers: the Seq Primer BRAF 600 or Seq Primer BRAF 464–469 (Qiagen).

Preoperative ultrasonography The recently introduced European Thyroid Imaging Reporting and Data System (EU-TIRADS) classification to determine the risk of malignancy of thyroid nodules was utilized on thyroid ultrasonography. The categories are as follows: EU-TIRADS 1, normal; EU-TIRADS 2, benign; EU-TIRADS 3, low risk; EU-TIRADS 4, moderate risk; EU-TIRADS 5, high risk. We focused particularly on high-risk nodules (EU-TIRADS 5). These include 4 main features: 1) not oval shape (taller than wide), 2) irregular margins (spiculated or lobulated, at least 3 lobulations), 3) microcalcifications (multiple), 4) marked hypoechogenicity (less echoic than the muscles).[5] Thyroid ultrasonographic examinations of all patients were performed by an expert.

Statistical analysis Statistical analysis was performed by the SPSS version 20.0 (IBM, Armonk, New York, United States) and MedCalc version 12.7.7 (MedCalc Software, Ostend, Belgium) statistical software. The *t* test was used for the comparison of numeric independent factor (age) between the study groups. Categorical independent factors were compared by the χ^2 test. Statistical analyses were performed with descriptive statistics, the Pearson χ^2 test, Fisher exact tests, and Yates (Continuity Correction) χ^2 test. Multivariable logistic regression model was utilized using ultrasonographic findings (hypoechoic appearance, internal vascularization, microcalcification, and irregular border) adjusted for age and sex. A *P* value less than 0.05 was accepted as significant.

RESULTS There were no differences between the groups in terms of age, sex, thyroid function tests and the presence of lymphocytic thyroiditis. The mean (SD) follow-up period was 27 (17) months in the NIFTP group and 30 (20) months

Table 1 Diagnostic criteria for noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Encapsulation or clear demarcation[a]
Follicular growth pattern[b] with 1) <1% papillae; 2) no psammoma bodies; 3) 30% solid/trabecular/insular growth pattern
No tumor necrosis
No vascular or capsular invasion[c]
Nuclear grade 2–3
No high mitotic activity[d]

a Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue

b Including microfollicular, normofollicular, or macrofollicular architecture with abundant colloid

c Requires adequate microscopic examination of the tumor capsule interface

d High mitotic activity defined as at least 3 mitoses per 10 high-power fields (magnification ×400)

Table 2 Nuclear features of noninvasive follicular thyroid neoplasm with papillary-like nuclei

Size and shape
Enlargement
Elongation
Overlapping
Membrane irregularities
Irregular contours
Grooves
Pseudoinclusions
Chromatin characteristics
Chromatin clearing
Margination of chromatin to membrane
Glassy nuclei

A 3-number scoring system was developed, each nuclear feature was scored as 0 or 1, giving a total score of 0–3.

in the IEFVPTC group. Central lymph node dissection revealed normal lymph nodes in 50 patients in the NIFTP group, while 4 of 70 patients (5.7%) in the IEFVPTC group were found to have lymph node metastasis (P = 0.14). There were no significant differences between the groups in terms of the presence of *BRAF* mutation (P = 0.08). One patient in the IEFVPTC group had distant metastasis. Extrathyroidal extension was significantly more common in those with IEFVPTC (Table 3). A second dose of radioactive iodine 131 was necessary in 2 patients from the IEFVPTC group, and it was not needed in the NIFTP group.

The number of patients who had central lymph node metastasis was 50 and 74 in NIFTP and IEFVPTC groups, respectively. There were no differences between these patients in terms of age, sex, and follow-up period. There were no differences in terms of the results of preoperative thyroid nodule fine needle aspiration biopsy. However, there was a tendency for atypia of undetermined significance and malignancy in the IEFVPTC group and for follicular neoplasm in the NIFTP group (Table 4). Preoperative neck ultrasonography revealed irregular border in 6.5% of pathologic nodules from the NIFTP group, and in 15.7% from the IEFVPTC group (P = 0.02) (Table 5). Lymph node metastasis was excluded from the analysis because lymph node dissection was not performed in all patients. Additionally, multivariable analysis (binary logistic regression) showed that follicular variant papillary thyroid cancer was positively associated only with irregular border and extrathyroidal extension (P = 0.02 and P <0.001, respectively) (Table 6).

DISCUSSION This study aimed to review clinical and pathologic evaluation of noninvasive EFVPTC, which is classified as a malignancy despite its indolent nature. In a study by Rosario,[6] who evaluated preoperative thyroid ultrasonography findings, data of 120 patients from the NIFTP group and 54 patients from the EFVPTC group were compared showing that suspicious nodule findings were more common in the EFVPTC group. However, since the number of patients with suspicious nodule was 6 (5%) in the NIFTP group and 8 (14.8%) in the EFVPTC group, further studies including more patients are required. In our study, nodules with irregular borders detected by ultrasonography were more common in the FVPTC group than in the NIFTP group (P = 0.02) (Table 5). In a mini meta-analysis by Maletta et al,[7] Bethesda categories of preoperative fine-needle aspiration biopsies were changed after the reevaluation of the diagnosis of NIFTP and malignancy risk. The risk of malignancy was found to change by up to 66%, especially in Bethesda category IV. In our study, preoperative fine-needle aspiration biopsy, especially of patients with NIFTP, showed Bethesda category IV to be more common. Therefore, we suggest that prospective fine-needle aspiration biopsy molecular assessment may be valuable in the diagnostic workup of NIFTP. In the literature, only 2 (0.6%) of 352 well-documented noninvasive FVPTC cases had recurrence. In one of these, excision was incomplete, while noninvasive characteristic of tumor was disputable in the other. In general, data suggest that this lesion rarely has negative results in the absence of invasion.[8-14] In our study, none of the patients with NIFTP developed recurrence during the follow-up period. In the study by Nikiforov et al,[15] which was important in building a consensus on the main histopathologic features of NIFTP, noninvasive FVPTC (n = 109) and invasive FVPTC (n = 101) were compared. Most of patients with noninvasive encapsulated follicular variant of papillary thyroid carcinoma were lobectomized and none had radioactive iodine treatment treatment. The decision of radioactive treatment was made considering the American Thyroid Association criteria.[4] These criteria are: macroscopic tumoral invasion to perithyroidal soft tissues, incomplete tumor resection, distant metastasis (M1 according to the TNM system), postoperative significant

Table 3 Clinical, demographic, histopathologic, and genetic characteristics of the study groups

Variable		Group 1 NIFTP (n = 107)	Group 2 FVPTC (n = 140)	*P* value
Age, y, mean (SD)		51.7 (11.5)	50.5 (11.9)	0.67[a]
Sex	Female	81 (75.7)	116 (82.9)	0.16[b]
	Male	26 (24.3)	24 (17.1)	
Anti-TG (+)		23 (26.4)	36 (32.4)	0.36[b]
Anti-TPO (+)		26 (32.1)	42 (40.4)	0.24[b]
Tumor size	<10 mm	58 (54.2)	87 (62.1)	0.20[b]
	≥10 mm	49 (45.8)	53 (37.9)	
Focality	Unifocal	53 (49.5)	72 (51.4)	0.76[b]
	Multifocal	54 (50.5)	68 (48.6)	
Perineural invasion (+)		–	3 (2.2)	0.25[c]
Lymphovascular invasion (+)		–	5 (3.6)	0.07[c]
Pathologic lymphocytic thyroiditis (+)		36 (40.9)	52 (59.1)	0.56[b]
CK-19 (+)		62 (77.5)	79 (76.7)	0.89[b]
Galectin (+)		57 (70.4)	85 (78.7)	0.19[b]
Lymph node metastasis		–	4 (5.7)	0.1[4]b
Extrathyroidal extension		–	26 (18.6)	<0.001[b]
BRAF mutation	Total	3 (3.8)	12 (12.2)	0.08[d]
	BRAF^{V600E}	1 (0.9)	11 (7.8)	
	BRAF^{V600K}	1 (0.9)	1 (0.7)	
	BRAF^{G469A}	1 (0.9)	0	
Distant organ metastasis		–	1 (0.7)	0.56[c]

Data are presented as number (percentage) of patients unless otherwise indicated.

a *t* test

b Pearson χ^2 test

c Fisher exact test

d χ^2 with Yates continuity correction

Abbreviations: +, positive; Anti-TG, anti-thyroglobulin; Anti-TPO, anti-thyroid peroxidase; CK-19, cytokeratin 19; FVPTC, follicular variant papillary thyroid carcinoma; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Table 4 Preoperative thyroid fine-needle aspiration biopsy results

Variable	NIFTP	FVPTC	*P* value
Insufficient	8 (8.2)	8 (7.1)	0.09
Benign	4 (4.1)	4 (3.6)	
Undetermined atypia	16 (16.5)	24 (21.4)	
Follicular neoplasm	60 (61.9)	52 (46.4)	
Suspicious malignancy	9 (9.3)	24 (21.4)	

Data are presented as number (percentage). Statistical significance was tested by the Pearson χ^2 test.

Abbreviations: see Table 3

serum thyroglobulin level elevation suspicious for distant metastasis, pathological lymph node metastasis of 3 cm or greater in longest diameter (N1 according to the TNM system), follicular thyroid cancer with disseminated vascular invasion (>4 foci).[4] In their study, Szczepanek-Parulska et al[16] mentioned that the serum thyroglobulin level was the most important factor suggesting poor response to radioiodine treatment in the patients with differentiated thyroid cancer. They suggested that it should be considered for treatment, follow-up, and also to predict the prognosis. In our study, serum thyroglobulin levels measured during follow-up did not increase in patients with NIFTP. In this comparison, no *BRAF*^{V600E} mutation, distant metastasis, and mortality were seen during follow-up period of patients with NIEFPTC. On the other hand, in the IEFVPTC group, which mostly included patients who undergone total thyroidectomy and radioactive iodine treatment, mortality occurred in 7 patients (5 related to distant metastasis and 2 to the disease itself). This study suggested that noninvasive encapsulated follicular variant of papillary thyroid carcinoma has a less aggressive course and these cases should be categorized as NIFTP. In contrast to the study by Nikiforov et al,[15] one of our cases with NIFTP was found to have *BRAF*^{V600E} mutation, a poor prognostic factor, while distant and lymph node metastases were similarly rare when compared with the ECFVPTC group (Table 3). Cho et al[17] suggested that the evaluation of patients who undergone standard lymph node dissection is more important in the prognostic evaluation of those with NIFTP. In the study by Cho et al,[17] patients who underwent standard central lymph node dissection were divided into 2 groups, based on histopathological findings: those with 1% of papillae or less (n = 105) and those with no papillae. Among these, the rate of *BRAF*^{V600E} mutation and lymph node metastasis was 10% and 3%, respectively, in the group with 1% papillae or less, while in the group with no papillae, none of the patients had *BRAF*^{V600E} mutation and 3% had lymph node micrometastasis. As a result, it was stated that further prospective studies are required to accept NIFTP as a neoplasm. In the literature, patients with indeterminate thyroid nodule fine-needle aspiration cytology results have been evaluated by 7-gene mutation and rearrangement (*BRAF*, *RAS*, *RET* / *PTC*, *PAX8* / *PPARc*).[18] It has been suggested that these tests could not safely exclude malignancy. The use of a 167 gene expression classifier (GEC) has been proposed as a rule-out test due to relatively high sensitivity (92%) and net present value (93%), as reported in a prospective multicenter study.[19] In addition, relatively low specificity of 167 GEC test (48%–53%) has shown that it could not establish malignancy criteria for indeterminate nodules. Alexander et al[20] reported that the prevalence of 167 GEC benign readings varied among institutions and reached up to 29%, which was not significant. Borowczyk et al[21] in their meta-analysis evaluated GEC and ThyroSeq v2 methods performed on thyroid nodule fine-needle aspiration biopsy samples with indeterminate pathology. They reported that 167 gene GEC method was helpful in excluding malignancy in patients with indeterminate thyroid

Table 5 Nodule characteristics on preoperative thyroid ultrasonography

Variable	NIFTP	FVPTC	*P* value
Hypoechoic	65 (61.3)	92 (67.2)	0.34
Internal vascularization	17 (16)	15 (10.9)	0.24
Nodule length > nodule width	20 (18.9)	31 (22.8)	0.45
Microcalcification	18 (17)	28 (20.4)	0.49
Irregular border	7 (6.5)	22 (15.7)	0.02

Data are presented as number (percentage). Statistical significance was tested by the χ^2 test.

Data are missing in the following number of patients: hypoechoic, n = 4; internal vascularization, n = 4; nodule length > nodule width, n = 5; microcalcification, n = 4

Abbreviations: see Table 3

Table 6 Multivariable logistic regression adjusted odds ratios for follicular variant papillary thyroid cancer

Variable	Odds ratio	95% CI	*P* value
Age >50 y	0.952	0.567–1.599	0.85
Female sex	1.441	0.767–2.707	0.25
Hypoechoic appearance	1.288	0.753–2.203	0.35
Internal vascularization	0.689	0.323–1.473	0.35
Microcalcification	1.249	0.633–2.465	0.52
Irregular border	2.706	1.109–6.601	0.02
Extrathyroidal extension	3.333	1.449–3.448	<0.001

nodule cytology, while examination by ThyroSeq v2 was more specific and accurate with significantly acceptable sensitivity. Borowczyk et al[22] aimed to evaluate the genetic background of indeterminate thyroid nodules and determine potential genetic pathways playing a role in follicular thyroid cancer. In that study, the 50-gene Ion AmpliSeq Cancer Hotspot Panel v2 was used to perform next-generation sequencing. They concluded that the heterogenicity of genetic background of indeterminate thyroid nodules corresponds with the histopathologic diversity and the role of kinase insert domain receptor as a malignancy biomarker should be verified. Erba et al[23] evaluated diagnostic peptide targeting cholecystokin-2/gastrin receptors in patients with medullary thyroid cancer. As a result, they reported that cholecystokin-2/gastrin receptor may become a novel and more effective target in diagnosis, early detection, and treatment of metastatic medullary thyroid cancer. In summary, at present, we do not have any optimal molecular test that could exclude malignancy in case of indeterminate cytology, and long-term data are needed to demonstrate the clinical efficacy of targeting cholecystokin-2/gastrin receptors in patients with medullary thyroid cancer.

In conclusion, patients diagnosed with NIFTP after a careful histopathologic examination developed no recurrence during the first 3 years. However, one of the patients with NIFTP was found to have *BRAF*^{V600E} mutation as a poor prognostic factor. Further prospective studies are required for differential diagnosis of NIFTP especially in the patients who underwent preoperative fine-needle aspiration biopsy. In addition, further prospective studies are necessary for prognostic evaluation of patients with NIFTP.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT MC, BYB and SG conceived the study design. MC, BYB, NC, SA, ET, AS, FU, SG were involved in data collection. SG, MC, and SA performed the statistical analysis. ET and NC conducted the genetic examination. MC, AS and FU interpreted data and prepared the manuscript draft. SG, MC, BYB and SA critically reviewed the final version of the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

HOW TO CITE Celik M, Bulbul BY, Can N, et al. Comparison of clinicopathological features in patients with noninvasive follicular thyroid neoplasm with papillary-like nuclear features and follicular variant papillary thyroid cancer. Pol Arch Intern Med. 2020; 130: 100-105. doi:10.20452/pamw.15120

REFERENCES

1 Jung CK, Little MP, Lubin JH, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. J Clin Endocrinol Metab. 2014; 99: E276-E285.

2 Lupi C, Giannini R, Ugolini C, et al. Association of BRAF V600E mutation with poor clinicopathological outcomes in 500 consecutive cases of papillary thyroid carcinoma. J Clin Endocrinol Metab. 2007; 92: 4085-4090.

3 Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol. 2016; 2: 1023-1029.

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

5 Russ G, Bonnema SJ, Erdogan MF, et al. European Thyroid Association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. Eur Thyroid J. 2017; 6: 225-237.

6 Rosario PW. Ultrasonography and cytology as predictors of noninvasive follicular thyroid (NIFTP) neoplasm with papillary-like nuclear features: importance of the differential diagnosis with the invasive encapsulated follicular variant of papillary thyroid cancer. Clin Endocrinol (Oxf). 2017; 87: 635-636.

7 Maletta F, Volante M, Papotti M. Experience on NIFTP cytology, with a mini meta-analysis of the literature. J Basic Clin Med. 2017; 6: 1.

8 Vivero M, Kraft S, Barletta JA. Risk stratification of follicular variant of papillary thyroid carcinoma. Thyroid. 2013; 23: 273-279.

9 Piana S, Frasoldati A, Di Felice E, et al. Encapsulated well-differentiated follicular-patterned thyroid carcinomas do not play a significant role in the fatality rates from thyroid carcinoma. Am J Surg Pathol. 2010; 34: 868-872.

10 Liu Z, Zhou G, Nakamura M, et al. Encapsulated follicular thyroid tumor with equivocal nuclear changes, so-called well-differentiated tumor of uncertain malignant potential: a morphological, immunohistochemical, and molecular appraisal. Cancer Sci. 2011; 102: 288-294.

11 Rosario PW, Penna GC, Calsolari MR. Noninvasive encapsulated follicular variant of papillary thyroid carcinoma: is lobectomy sufficient for tumours ≥1 cm? Clin Endocrinol (Oxf). 2014; 81: 630-632.

12 Howitt BE, Paulson VA, Barletta JA. Absence of BRAF V600E in non-infiltrative, non-invasive follicular variant of papillary thyroid carcinoma. Histopathology. 2015; 67: 579-582.

13 Ganly I, Wang L, Tuttle RM, et al. Invasion rather than nuclear features correlates with outcome in encapsulated follicular tumors: further evidence for the reclassification of the encapsulated papillary thyroid carcinoma follicular variant. Hum Pathol. 2015; 46: 657-664.

14 Baloch ZW, LiVolsi VA. Encapsulated follicular variant of papillary thyroid carcinoma with bone metastases. Mod Pathol. 2000; 13: 861-865.

15 Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm

shift to reduce overtreatment of indolent tumors. JAMA oncology. 2016; 2: 1023-1029.

16 Szczepanek-Parulska E, Wojewoda-Korbelak M, Borowczyk M, et al. Predictive factors determining incomplete response to radioiodine therapy in patients with differentiated thyroid cancer. Q J Nucl Med Mol Imaging. 2018 Sep 13. [Epub ahead of print].

17 Cho U, Mete O, Kim MH, et al. Molecular correlates and rate of lymph node metastasis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features and invasive follicular variant papillary thyroid carcinoma: the impact of rigid criteria to distinguish non-invasive follicular thyroid neoplasm with papillary-like nuclear features. Modern Pathology. 2017; 30: 810-825.

18 Nikiforov YE, Ohori NP, Hodak SP, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. J Clin Endocrinol Metab. 2011; 96: 3390-3397.

19 Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. 2012; 367: 705-715.

20 Alexander EK, Schorr M, Klopper J, et al. Multicenter clinical experience with the Afirma gene expression classifier. J Clin Endocrinol Metab. 2014; 99: 119-125.

21 Borowczyk M, Szczepanek-Parulska E, Olejarz M, et al. Evaluation of 167 gene expression classifier (GEC) and ThyroSeq v2 diagnostic accuracy in the preoperative assessment of indeterminate thyroid nodules: bivariate/HROC meta-analysis. Endocr Pathol. 2019; 30: 8-15.

22 Borowczyk M, Szczepanek-Parulska E, Dębicki S, et al. The genetic heterogeneity of indeterminate thyroid nodules assessed preoperatively with next generation sequencing reflects the diversity of the final histopathological diagnoses. Pol Arch Intern Med. 2019; 129: 761-769.

23 Erba PA, Maecke H, Mikolajczak R, et al. A novel CCK2/gastrin receptor-localizing radiolabeled peptide probe for personalized diagnosis and therapy of patients with progressive or metastatic medullary thyroid carcinoma: a multicenter phase I GRAN-T-MTC study. Pol Arch Intern Med. 2018; 28: 791-795.