Original paper

Morphological and immunohistochemical analysis in encapsulated follicular variant papillary thyroid carcinoma, invasive follicular variant papillary thyroid carcinoma and a new entity: non-invasive follicular thyroid neoplasm with papillary nuclear feature

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Thyroid cancers are the most common endocrine organ cancers. Encapsulated follicular variant papillary thyroid carcinomas (EFVPTC) are quite slow (indolent). Non-invasive follicular thyroid neoplasm with papillary nuclear feature (NIFTP) is a new entity identified as a result of studies in recent years. If the patient instead of EFVPTC develops NIFTP, cancer will not be recognized and the treatment will change.
Three groups, in which CD44, p53, Ki-67, p27, HBME-1, galectin-3, cytokeratin-19, CD56 were used as markers, were evaluated. Nuclear score assessment was also conducted in the NIFTP group. The results were compared with each other.
Significant differences were detected in the intensities and percentages of CK19, HBME-1, CD56, CD44 staining and galectin-3 staining intensity. In group 1, cytokeratin-19, galectin-3, HBME-1 and CD44 expression were not as low as in the other groups, while CD56 staining was detected more frequently. p53, p27 and Ki-67 staining showed no obvious expression differences between the groups.
The NIFTP group showed different IHC results compared to encapsulated invasive FVPTC and common invasive FVPTC. When evaluating whether the IHC expression patterns used in PTCs differ in NIFTP cases, it was found that CD44 could serve as an additional IHC stain that may guide pathologists during the diagnosis.

Key words: p53, Ki67, CD44, NIFTP, thyroid.

Introduction

The thyroid is the organ with the most neoplastic lesions among the endocrine organs. Therefore, the biological behaviour of thyroid nodules is of interest to pathologists [1, 2]. Among thyroid cancers, there is a significant increase in encapsulated follicular variant papillary thyroid carcinomas (EFVPTC). When the invasive and non-invasive forms, the two subtypes of EFVPTC, are examined, it is noteworthy that the non-invasive group has a longer life expectancy, but the diagnostic criteria are quite subjective [1–3].

In a large-scale study by Nikiforov *et al*. [1] in 2016, invasive and non-invasive encapsulated follicular variant papillary thyroid carcinomas were compared. A total of 109 non-invasive and 101 invasive EFVPTC cases were included in this retrospective multidisciplinary study, in which 24 pathologists from different countries participated. No recurrence or metastasis was observed in the long-term

follow-up of the patients in the non-invasive group. It was concluded that the diagnostic process for this group caused overdiagnosis and overtreatment. The patients were diagnosed with cancer unnecessarily; the patients who had lobectomies in the first operation went on to complementary surgery, and there was overtreatment after surgery. For these reasons, it was decided to change the name of non-invasive encapsulated follicular variant papillary thyroid carcinomas to "non-invasive follicular thyroid neoplasm with papillary nuclear feature" (NIFTP) [1–4].

Criteria for the diagnosis of NIFTP (all of the following characteristics must be present) [5]:

1) encapsulation or smooth margin;
2) follicular growth pattern:
   – < 1% papilla,
   – no psammoma bodies,
   – < 30% solid, trabecular or insular growth pattern;
3) papillary thyroid carcinoma nuclear properties (nuclear score should be 2–3);
4) no lymphatic capsular or vascular invasion;
5) no tumour necrosis;
6) mitosis < 3/10 high power field (HPF).

After this study [5], genetic studies conducted in 2017 also confirmed that no papillary structure should be present for the diagnosis of NIFTP. In the case of a minimal papillary structure, papillary carcinoma genetics are determined when genetic studies are performed, whereas in the absence of any papillary structure, the genetics of follicular lesions are determined [6, 7].

In a 2018 study by Thompson *et al*. [3], the aim was to evaluate observer differences when scoring EFVPTC core features and to score NIFTP using the standard scoring system. Thirty thyroid cases were reviewed by the Endocrine Pathology Study Group. There was substantial agreement among observers in reaching the interpretation of the presence or absence of nuclear features to diagnose NIFTP (score 0–1, score 2–3).

Nucleus score:

1) size and shape (nuclear enlargement, overlap, crowding, elongation);
2) nuclear membrane irregularity (irregular contour, groove, pseudoinclusion);
3) characteristic chromatin (clearing, glassy nucleus).

The encapsulated non-invasive form of follicular variant papillary thyroid carcinoma, observed in 45,000 patients worldwide annually, has been thought to be a carcinoma for 30 years. Many studies have shown virtually no recurrence of non-invasive tumours, even in patients treated with surgery alone without radioiodine therapy. The new terminology removes the carcinoma label [8]. While the definitions are in place, it is difficult to make a histopathological differential diagnosis between NIFTP and invasive EFVPTC, which makes it difficult to decide on its invasion, and methods to facilitate this diagnosis are being investigated [9].

Immunohistochemical studies are widely used as an auxiliary method in the histopathological diagnosis of thyroid lesions that cause difficulty in differential diagnosis [10, 11]. The most commonly used markers are CK19, HBME-1, galectin-3 and CD56 [12, 13].

Recent studies have focused on immunohistochemical markers to help differentiate benign lesions from malignant lesions and FVPTC from follicular carcinoma/follicular adenoma. CK19, galectin-3, HBME-1, CITED-1, Ret oncoprotein, CD44, CD56, CD57, cyclin D1, p27, p63, E-cadherin, TPO and fibronectin-1 are among them [14–19].

CD56 is the most sensitive immunohistochemical marker after HBME-1 in the differential diagnosis of thyroid lesions. The most specific combination is HBME-1, galectin-3 and CK19 [20].

The cyclin-dependent kinase inhibitor p27 is prognostic for many neoplasms. In a study consisting of three different groups (group 1: well-differentiated papillary or follicular carcinoma, group 2: poorly differentiated papillary or follicular carcinoma, group 3: undifferentiated or anaplastic carcinoma), in which p27 and Ki-67 expression levels were examined, the correlation of p27 with tumour differentiation was determined. As differentiation decreases, p27 expression also decreases [21].

The proliferation index is higher in malignant tumours. Proliferative activity in tumours is determined by mitosis count and immunohistochemical demonstration of proliferation-related nuclear antigens, such as proliferating cell nuclear antigen (PNCA) and Ki67 [22].

CD44 is an integral membrane glycoprotein associated with cell matrix adhesion, lymphocyte activation and migration, as well as tumour growth and metastasis. Severe CD44 expression with a severe plasma membrane pattern was seen in 97% of papillary carcinomas [23].

In this study, we aimed to examine CD44, p53, Ki-67 and p27 immune markers, which are proliferation and oncogenesis markers that are mostly used in the differential diagnosis of malignant and pre-malignant lesions and HBME-1, galectin-3, CK19 and CD56. These are used as auxiliary markers in the identification of papillary carcinoma in FVPTC, invasive EFVPTC and NIFTP cases, to evaluate the results and to obtain important clues for differential diagnosis, as well as to contribute to the literature with significant results.

Material and methods

Local ethics committee approval was obtained for this study. Slides of lesions of the thyroidectomy

surgical materials of male and female patients from the period 2015–2018 were obtained from the archives of the pathology laboratory at Konya Necmettin Erbakan University, Faculty of Medicine, and the lesions were evaluated. A total of 30 cases of newly diagnosed NIFTP and previously diagnosed follicular adenoma/encapsulated follicular lesions were re-evaluated and re-scored by two pathologists. Four out of 30 cases were excluded because they did not meet the diagnostic criteria for NIFTP.

A total of 51 cases were included in the study, and three groups were identified:

- group 1: non-invasive thyroid neoplasm with papillary core features, $n = 26$;
- group 2: invasive follicular variant thyroid papillary carcinoma, $n = 15$;
- group 3: encapsulated invasive follicular variant papillary thyroid carcinoma, $n = 10$.

Immunohistochemical examination

Paraffin blocks of appropriate slides were taken from the block archive. Paraffin blocks of the sections that best reflected the tumour and included the tumour and surrounding thyroid tissue were selected for immunohistochemical study, and at least 10 sections of 5 microns thick were taken from each case on positively charged slides. The sections were immunohistochemically stained using a Ventana (VENTANA, Bench Mark XT) automatic staining device for CK19 (A53-B/A2.26, Thermo), galectin-3 (9c4, BioSB), HBME-1 (Mesothelioma Ab-1, Thermo), CD56 (123C3-D5, Thermo), Ki-67 (Rabbit Pab, Thermo), p27 (Rabbit Pab, Thermo), p53 (D07, Biogenex) and CD44 (6-3C11, Thermo) staining. An Ultraview Universal DAB Detection Kit (Catalogue no: 04015630972173, LOT NO: E04506, Ventana Medical Systems, USA) was used as the secondary antibody. After the slides had been sealed with a coverslip with the help of Entellan, all materials were evaluated by two pathologists under an Olympus light microscope (Olympus BX51, Japan). The staining results were reported as percentages and by intensity and were statistically compared with each other.

Cytoplasmic membranous staining for CK19, cytoplasmic and nuclear staining for galectin-3, membranous staining for HBME-1, CD56 and CD44, and nuclear staining for p53, p27 and Ki-67 were considered positive. The number of positively stained cells was determined by counting 1,000 cells at 40× magnification in the areas with the highest staining in the tumoral area, and the prevalence of staining was evaluated as % for all antibodies. The staining density was evaluated as follows:

- (-): no staining;
- (+): poor staining;
- (++): moderate staining;
- (+++): strong staining.

Statistical analysis

The data obtained in the study were analysed using SPSS Statistics for Windows 2.0. Descriptive statistics and frequency tables were prepared for all variables. Median, minimum and maximum values were given for numeric variables. Cross-tables showing the relative status of the categorical variables were prepared. Since the observation values of the variables were sequential and discrete, they were tested with the help of non-parametric statistical analyses. The Kruskal-Wallis test was used for multi-group comparisons, and the Mann-Whitney U test with Bonferroni correction was used for pair-group comparisons. A p-value of < 0.05 was considered statistically significant in all analyses.

Results

When evaluated in terms of distribution according to age and gender, the minimum age at diagnosis was 19, the maximum age was 75, and the mean age was 48.3 in a total of 51 patients in all groups. Of the 51 cases, 40 were female (78.4%), and 11 were male (21.6%). This result was found to be compatible with the literature [24].

Eight of the 10 cases were female (80%), and two were male (20%). When the groups were compared statistically, male patients were more common in group 1 than in the other groups (group 1: 30%, group 2: 6%, group 3: 20%) (Table I).

The distribution of immunohistochemical staining according to the groups is given in the tables in detail (Tables II and III).

Table I. Gender and age distribution between groups

	Gender		Age		
	Female	Male	Minimum	Maximum	Mean
Group 1 (NIFTP) ($n = 26$)	18 (69.2%)	8 (30.8%)	19	66	46.8
Group 2 (IFVPTC) ($n = 15$)	14 (93.3%)	1 (6.7%)	26	65	43.3
Group 3 (EIFVPTC) ($n = 10$)	8 (80%)	2 (20%)	45	74	59.9

NIFTP – non-invasive follicular thyroid neoplasm with papillary-like nuclear features, IFVPTC – invasive follicular variant papillary thyroid carcinoma, EIFVPTC – encapsulated invasive follicular variant papillary thyroid carcinoma

Table II. Immunohistochemical staining intensity table

	Group 1 NIFTP (n = 26)				Group 2 Invasive FVPTC (n = 15)				Group 3 Encapsulated invasive FVPTC (n = 10)			
	Staining intensity				Staining intensity				Staining intensity			
	0	(+)	(++)	+++	0	(+)	(++)	+++	0	(+)	(++)	+++
CK19	1 3%	6 23%	11 42%	8 30%	0 0%	0 0%	1 6%	14 93%	0 0%	2 20%	3 30%	5 50%
Gal-3	22 84%	3 11	1 3%	0 0%	0 0%	9 60%	5 33%	1 6%	0 0%	6 60%	4 40%	0 0%
HBME-1	8 30%	11 42%	6 23%	1 3%	0 0%	2 13%	9 60%	4 26%	0 0%	3 30%	4 40%	3 30%
CD56	4 15%	14 53%	7 26%	1 3%	11 73%	4 26%	0 0%	0 0%	5 50%	4 40%	1 10%	0 0%
CD44	0 0%	2 7%	8 30%	16 61%	0 0%	0 0%	2 13%	13 86%	0 0%	0 0%	0 0%	10 100%
p53	1 3%	24 92%	1 3%	0 0%	0 0%	15 100%	0 0%	0 0%	0 0%	7 70%	3 30%	0 0%
p27	0 0%	12 46%	13 50%	1 3%	0 0%	8 53%	6 40%	1 6%	0 0%	6 60%	1 10%	3 30%

NIFTP – non-invasive follicular thyroid neoplasm with papillary-like nuclear features, FVPTC – follicular variant papillary thyroid carcinoma, CK19 – cytokeratin 19, Gal-3 – galectin-3

Table III. Average staining numbers and percentages

	Case number	CK19	Gal-3	HBME-1	CD56	CD44	p53	p27	Ki-67
NIFTP	26	25	4	18	22	26	25	26	
		96.1%	15.3%	69.2%	84.6%	100%	96.1%	100%	3.6%
IFVPTC	15	15	15	15	4	15	15	15	
		100%	100%	100%	26.6%	100%	100%	100%	5.0%
EIFVPTC	10	10	10	10	5	10	10	10	
		100%	100%	100%	50%	100%	100%	100%	5.1%

NIFTP – non-invasive follicular thyroid neoplasm with papillary-like nuclear features, IFVPTC – invasive follicular variant papillary thyroid carcinoma, EIFVPTK – encapsulated invasive follicular variant papillary thyroid carcinoma, CK19 – cytokeratin 19, Gal-3 – galectin-3

CK19

When the groups were compared statistically, a significant difference was found between group 1 and group 2 and between group 2 and group 3 in terms of expression rates and intensities (staining rate $p < 0.001$, staining intensity $p = 0.001$). However, no statistically significant difference was found between group 1 and group 3 in terms of staining percentage and intensity ($p = 0.129$). Group 1 had significantly lower CK19 expression than the other two groups. While complete negativity was not observed in the other groups, there was a complete loss of expression in one case in group 1. When group 2 and group 3 were compared immunohistochemically, a difference was found in CK19 staining intensity. The invasive group had a higher rate of strong staining.

Galectin-3

In galectin-3 staining, a significant difference was detected in the staining intensity between group 1 and group 2 ($p < 0.001$). Likewise, a difference in staining intensity was detected between groups 1 and 3 ($p < 0.001$). No significant difference was detected between group 2 and group 3 ($p = 0.892$). Group 1 had less galectin-3 positivity than the other groups.

HBME-1

There was a difference between group 1 and group 2 in both staining percentage and staining intensity in HBME-1 staining ($p < 0.001$, $p = 0.001$). Likewise, there was a difference in both the percentage of staining and the intensity of staining between group 1 and

group 3 in HBME-1 staining ($p = 0.018, p = 0.009$). When the expression rates and intensities were compared between groups 2 and 3, no significant difference was found ($p = 0.115$, $p = 1.000$). In NIFTP cases, the frequency of negative results was higer, while positive cases were less comon than the other groups in terms of HBME-1 staining. However, strong positivity was detected in a small number of cases.

CD56

A significant difference was found between group 1 and group 2 in terms of expression rates and intensities ($p = 0.013$, $p < 0.001$). There was no difference between group 1 and group 3 and between group 2 and group 3 ($p = 0.033, p = 0.126, p = 0.556, p = 0.238$). Expression loss was not 100% in the NIFTP group. Positivity was detected in one case. While negativity and 1 (+) weight were predominant in the other groups, 2 (++) results were significantly higher in the NIFTP group.

CD44

A significant difference was detected in the percentage of CD44 staining between group 1 and group 2 ($p = 0.003$). There was no statistically significant difference in CD44 staining percentage and intensity between group 1 and group 3, or between group 2 and group 3 ($p = 0.94$, $p = 0.177$). While group 2 and group 3 tended to stain with high intensity, the tendency for low intensity staining was higher in the NIFTP group compared to the other groups.

p53

There was no statistically significant difference between group 1, group 2 and group 3 in terms of expression rates and intensities ($p = 0.726, p = 0.160, p = 0.305$).

When the core scoring and immunostaining of the NIFTP group were compared, it was found that only p53 staining decreased as the core score increased (there was an inverse correlation). Therefore, it was concluded that NIFTP had different core scoring and immunohistochemical staining panels than invasive FVPTC and encapsulated invasive FVPTC, but only in p53 staining.

p27

No statistically significant difference was found between group 1, group 2 and group 3 in terms of expression rates and intensities ($p = 0.975, p = 0.825$).

Ki-67

No statistically significant difference was found between group 1, group 2 and group 3 in terms of expression rates and intensities ($p = 0.326$).

The histopathological appearances of group 1 (NIFTP) cases are shown in Figure 1.

Immunohistochemical staining intensities in group 1 (NIFTP) cases are shown in Figures 2 and 3.

Discussion

The most common cancers are thyroid cancers due to their slow progression. When the invasive and non-invasive forms, which are the two subtypes of EFVPTC, are examined, it is noteworthy that the non-invasive group has a longer life expectancy. In large-scale studies among these groups, a new entity and a very low-risk group, non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has emerged. NIFTP is considered a precancerous cancer, not an exact carcinoma, and only resection is said to be sufficient. Treatment and follow-up opportunities for patients diagnosed with NIFTP are quite successful [1, 3, 25].

In the study conducted by Rossi *et al*. [25] in 2019, in addition to the above information, it was stated that there are still unanswered issues, such as how to manage lesions smaller than 1 cm, lesions larger than 4 cm and oncocytic lesions. It was also stressed that, in many NIFTP cases, the most typical genetic change is RAS mutation, similar to that found in follicular adenoma and follicular carcinomas.

Haematoxylin and eosin (HE) examination is the most effective method in determining the behaviour of thyroid nodules and making a definitive diagnosis of the lesions [26].

In our study, we investigated the staining characteristics of CK19, galectin-3, HBME-1, CD56, CD44, p53, p27 and Ki-67 immunostaining in NIFTP, invasive FVPTC and encapsulated invasive FVPTC and whether there was a difference between the groups.

In a study by Taştekin *et al*. [27] in 2019, immunohistochemical CD56, CD57, HBME-1, galectin-3, CK19 and p63 were studied in thyroid benign/malignant lesions and in the differential diagnosis of NIFTP. In conclusion, as in our study, CD56 showed high expression in benign lesions, but it did not exclude the diagnosis of follicular carcinoma. CD57 expression was higher from NIFTP in malignant follicular lesions. Interestingly, it was found that p63 was highly expressed in FVPTCs, and this may be promising in terms of predicting invasiveness in follicular lesions.

In a study by Sadiq *et al*. [28] in 2021, immunohistochemical HBME-1 and CK19 were examined in thyroid lesions of NIFTP and other follicular patterns. In this study, the expression levels of these immunohistochemical markers were found to be statistically significant in differentiating NIFTP from follicular adenoma and adenomatoid nodule (multinodular goitre). No significant difference was found in HBME-1

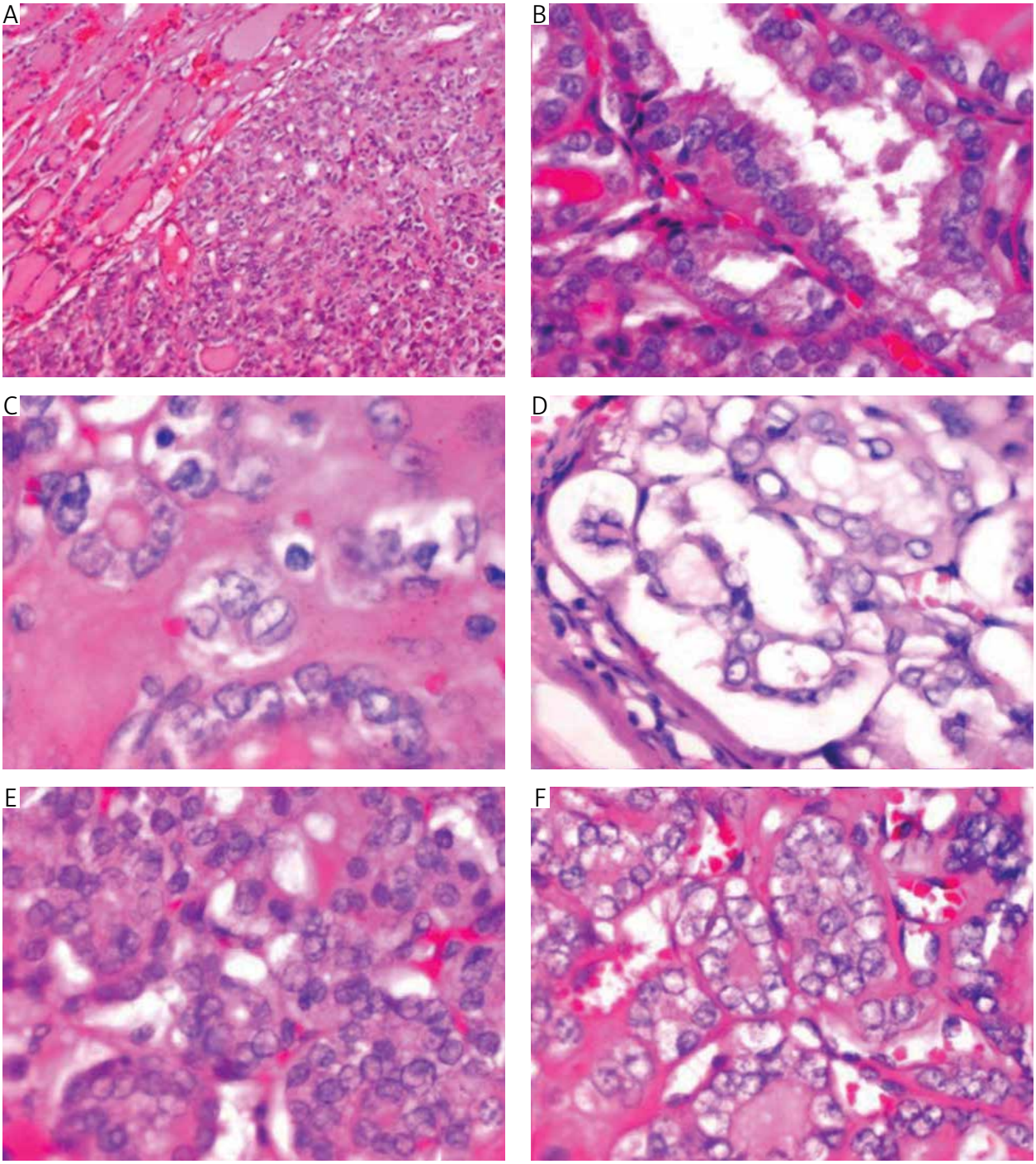

Fig. 1. Papillary nuclear features (haematoxylin and eosin stain). **A**) Nuclear enlargement (×100), **B**) peripheral nucleolus (×400), **C**) groove (×400), **D**) glassy nucleus (×400), **E**) nuclear overlapping (×400), **F**) nuclear clearing (×400)

staining to differentiate NIFTP from classical/follicular variant PTC. The simultaneous expression of HBME-1 and CK19 was sensitive in diagnosing lesions with PTC-like nuclear features. As a result, there was no increase in sensitivity and specificity in the diagnosis of NIFTP/PTC/FVPTC with the co-administration of HBME-1 and CK19, as in our study.

In a study by Elsers *et al*. [29] in 2021, diagnostic changes in thyroid lesions in the follicular pattern were examined. In the groups in which HBME-1, CK19, galectin-3 and CD56 were studied, galectin-3 was the most specific (90.3%) marker for carcinoma, and HBME-1 and galectin-3 were the most sensitive (75%) markers in the diagnosis of malignant lesions.

In a study by Hirokawa *et al*. [30] in 2024, an NIFTP case with a nuclear score of three revealed nodal metastasis 2.5 years after resection, and the carcinoma cells were immunohistochemically positive for BRAF.

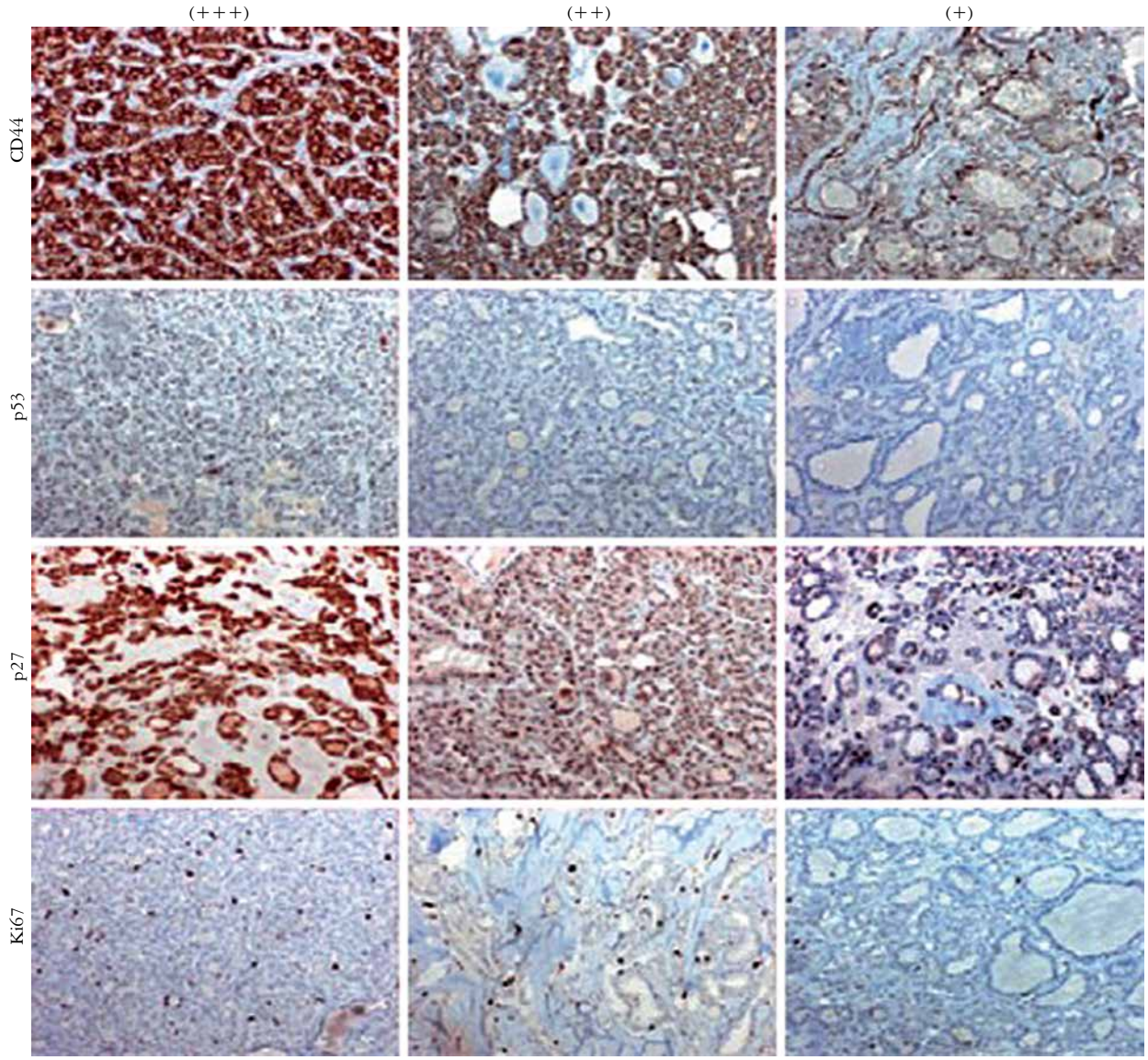

Fig. 2. Group 1 (non-invasive follicular thyroid neoplasm with papillary nuclear feature – NIFTP) cases (×200). Intensities of immunohistochemical CD44, p53, p27 and Ki67 staining

Follicular thyroid adenomas or NIFTPs with a nuclear score of two did not metastasize. In our study, nodal metastasis was observed in the NIFTP group.

Conclusions

Diagnosis of thyroid follicular lesions is one of the difficult areas of pathology, and no matter how much attention is paid to the histopathological features, there is a need for auxiliary tools to reach a definitive diagnosis today. Immunohistochemistry is one of the most important methods used in this regard. As a result of our study, it can be seen that some immune markers which are currently used in daily routines can help in identification. It will be possible to obtain clearer data with larger-scale future studies in which the genetic data of the cases are added.

NIFTP should be considered with a high probability in encapsulated follicular cases with papillary nuclear features with a low CK19 staining pattern since CK19 expression in the NIFTP group had lower rates and intensities in our study compared to the malignant group. Both positivity and negativity can be seen in dyes used as PTC markers, such as galectin-3 and HBME-1. It should be noted that not every positive case is definitely PTC but may also be NIFTP. Since CD56 has both positivity and negativity, careful nuclear scoring should be done by considering the diagnosis of NIFTP before making a diagnosis of follicular adenoma in encapsulated lesions with a high nuclear score and follicular pattern. In addition, in our study, no increase in sensitivity and specificity was detected in the diagnosis of NIFTP/EIFVPTC/IFVPTC with the co-administration of CD44, p53, Ki-67 and p27.

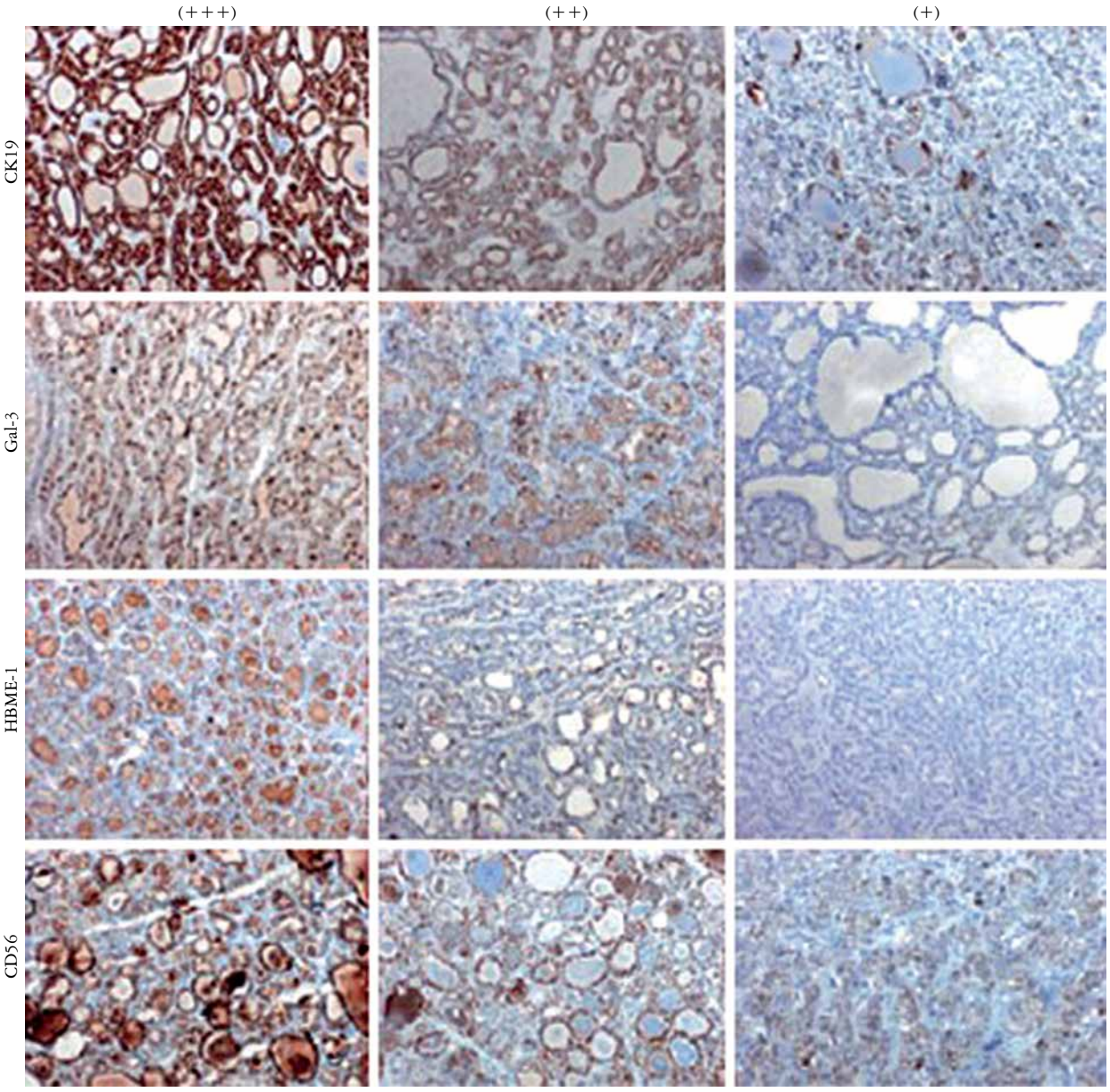

Fig. 3. Group 1 (non-invasive follicular thyroid neoplasm with papillary nuclear feature – NIFTP) cases (×200). Intensities of immunohistochemical cytokeratin-19 (CK19), galectin-3 (Gal-3), HBME-1 and CD56 staining

Disclosures

1. Institutional review board statement: Ethical approval for the study was obtained from the Pharmaceutical and Non-medical Device Research Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine (decision number: 2017/869, date:14.04.2017)
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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