Original paper

Correspondence of cytological and histopathological diagnoses in diagnostic category V of the Bethesda system: "suspicious for malignancy"

Agata Stanek-Widera[1], Magdalena Biskup-Frużyńska[1], Mirosław Śnietura[1], Ewa Zembala-Nożyńska[1], Maciej Środa[1], Weronika Szczęsny-Karczewska[2], Dariusz Lange[1]

[1]Department of Tumor Pathology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[2]Chair and Department of Pathology, Medical University of Silesia in Katowice, Poland

The progress in imaging methods enables fine needle aspiration (FNA) biopsy to be performed on smaller and smaller lesions, including malignant ones (papillary microcarcinomas). The follicular variant predominates in this group, with cytological features often not permitting an unbiased interpretation. The aim of the study was to determine the degree of reliability of the "suspicious for malignancy" (SM) diagnosis in material from the Institute of Oncology in Gliwice (IO).
290 primary SM diagnoses were established from 2010 to 2015 in the IO, including the consultations. None of the patients was treated surgically after the first FNA resulting in diagnostic category V (DC V). After the second FNA 80 patients underwent surgery, after the third 58, and after subsequent FNA 10. Together, 148 surgical resections were performed.
Among 148 patients treated surgically, 111 were diagnosed with malignant lesions, which constitutes 75%. Predominantly – in 91 cases – the histopathological outcome was papillary carcinoma. The others were: 16 medullary carcinomas, 2 follicular carcinomas, and 2 poorly differentiated carcinoma cases. Moreover, 8 follicular adenomas and 28 nonneoplastic lesions were found.
The high positive predictive value (PPV = 75%) of SM diagnosis established in the IO testifies to the high reliability of this test. Diagnostic category V in FNA should be an indication for surgical treatment.

Key words: thyroid nodule, thyroid cancer, biopsy, fine-needle.

Introduction

Improved imaging and screening methods have caused a gradual increase in the number of detected thyroid carcinomas worldwide. Increased detection has especially concerned small (< 2 cm) lesions [1, 2, 3, 4, 5]. A greater increase has been observed in southern Europe, the USA and the Republic of Korea, while northern Europe and Japan have noted a moderate increase [1, 2, 3, 6, 7, 8, 9].

Thyroid carcinoma is unlike lung or breast carcinoma, or melanoma, which have bad prognoses and in which it is difficult to achieve a decrease in mortality. Papillary thyroid carcinoma (PTC), which comprises the great majority of malignant changes in the thyroid, has a good prognosis [10]. PTC belongs to the group of neoplasms that are often found on

autopsy (in up to 30% of examinations), because its course is usually asymptomatic and indolent. Over the last 10 years, the progress in imaging methods and serologic and molecular tests has supported fine needle aspiration (FNA), which still is an irreplaceable method of quick workup of thyroid nodules [9, 11]. The first attempts of thyroid lesion diagnostics date back to 1939, when the Tru-Cut (Core Needle) biopsy was tested, but only in 1960 did FNA allow a non-invasive and quick suggestion of diagnosis and assessment of the risk of malignancy which guides patient management [12].

After the implementation of FNA into routine practice, the interpretation of cytological images was gradually improved, translating the pathologists' language into clinical recommendations, until in 2007 a still valid consensus was established. PTC along with other malignant neoplasms and suspected malignancies belong to categories VI and V, respectively, of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) [13]. Depending on our certainty of the diagnosis, either diagnostic category VI (DC VI – malignant) or, in the absence of all cytological features of a malignant neoplasm, suspicion of malignancy (DC V – SM) should be reported [14]. SM defines cytological characteristics allowing formulation of the diagnosis and further management, and determines the risk of malignancy.

Diagnostic category V concerns a cytological image which reveals morphological features of a malignant neoplasm, but not all criteria of this diagnosis are fulfilled. SM is most often related to the follicular variant of PTC (FVPTC). Regarding medullary carcinoma, even if the FNA image is unequivocal, a serum calcitonin test is required. Suspicion of lymphoma should result in repeat FNA and a flow cytometry test. According to the Polish recommendations, the diagnosis of DC V should be confirmed by another cytopathology specialist from a different institution, and the patient should be treated surgically, which often requires additional tests (repeat FNA, intraoperative examination) [13, 14]. An experienced pathologist does not encounter problems diagnosing PTC, but its follicular variant causes difficulties. These thyroid changes cannot be unequivocally diagnosed by cytological examination alone.

Material and methods

16 656 smears from thyroid nodule FNA were evaluated in the Department of Tumor Pathology of Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch between January 2010, when BSRTC was introduced in our institution, and April 2015. All FNAs were performed in 2-person teams of a pathologist and radiologist, under ultrasound guidance. The material was obtained by 25-gauge needles. The smears were fixed in 95% alcohol and stained with hematoxylin-eosin (HE). All patients who were finally subjected to surgical resection had at least 2 FNAs, either both in our institution, or one in an outside institution (with subsequent consultation with our specialists) and another in our department. Each test contained a description of the site of the biopsy with the size of the nodule and ultrasound photography.

Results

In 16 656 FNAs, the initial diagnosis of DC V was made in 290 cases (Fig. 1). All patients were subjected to a repeat FNA, obtaining confirmation of the primary diagnosis of DC V in 217/290 cases (75%). Eighty patients were scheduled for an operation and 35 moved to surveillance. Another (third) FNA was performed in 175 patients, and yet another (fourth) in 81 patients, obtaining confirmation of a primary DC V diagnosis in 67/175 (38%) and 20/81 (25%)

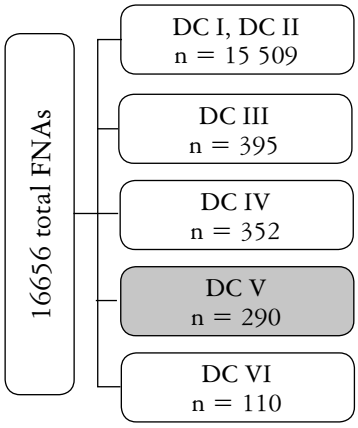

Fig. 1. Proportion of particular diagnostic categories in the study group

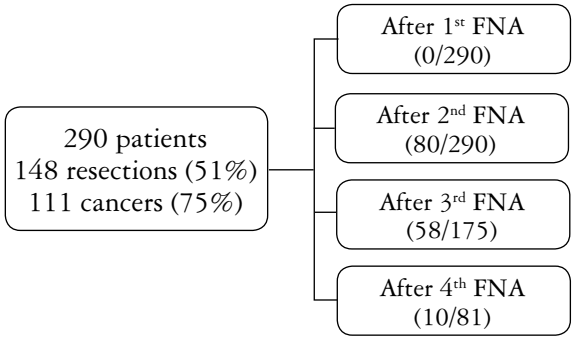

Fig. 2. Number of resections after successive FNAs in the study institution

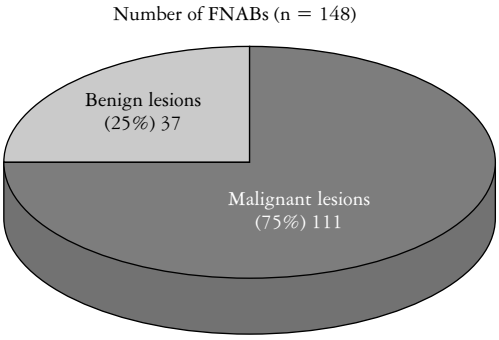

Fig. 3. Histopathological verifications after DC V – malignant vs. benign lesions

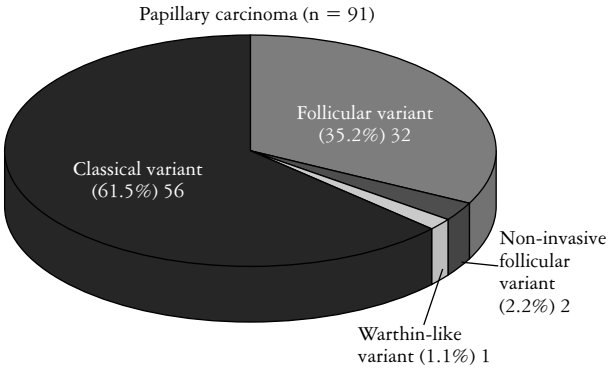

Fig. 4. Histopathological verifications after DC V – variants of papillary carcinoma

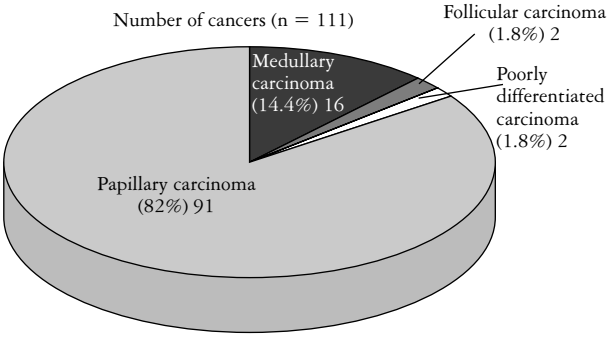

Fig. 5. Histopathological verifications after DC V – proportion of different cancer types

cases, respectively. After the third FNA, 58 patients were treated surgically, and after the fourth, 10.

Altogether, 148 patients were operated on (Fig.2), establishing 111 diagnoses of malignant neoplasms, 29 benign non-neoplastic changes and 8 benign neoplasms (Fig. 3). In the group of cancers there were 91 PTCs (56 classical, 32 follicular, 2 non-invasive follicular variant of PTC (NI-FVPTC) and 1 Warthin-like PTC (Fig. 4), 16 medullary carcinomas, 2 follicular carcinomas, and 2 poorly differentiated carcinomas (Fig. 5).

Moreover, 8 adenomas were found, and in the group of benign lesions there were 29 cases of: multinodular goiter, hyperplastic nodules, colloid nodules and inflammatory changes.

Finally we analyzed FNA slides of DC V cases available in our department's archive (27 of 37 diagnoses) in which the postoperative HP report did not confirm malignancy with 27 randomly chosen (in order to create groups similar in size) cases in which the postoperative report gave the diagnosis of papillary carcinoma. The analysis concerned six major features that are the basis of cytological diagnosis of papillary carcinoma. Results of the analysis are summarized in Table I.

To facilitate communication, the group of 27 randomly chosen papillary carcinoma cases confirmed in HP examination was named as group I and the group of 27 benign neoplasms/benign lesions reported in postoperative HP examination was named as group II.

In group I, 6 cases (4 PC, classical variant and 2 PC, follicular variant) had all 6 major features, while in group II three cases (2 hyperplastic nodules and 1 multinodular goiter) presented all 6 features (Table II).

Discussion

The main task of BSRTC was categorization of the diagnoses and determination of the risk of malignancy (RM) for each diagnostic category. BSRTC assesses the RM for "suspicious for malignancy" group at the level of 60-75% (Table III) [13]. Literature data concerning this topic are varied. A large study based on 25 publications that were divided into two groups, pre-Bethesda and post-Bethesda, recorded the RM for DC V at 67.8% and 79%, respectively. It was a metaanalysis of 102 076 FNA results [15].

Renshaw *et al.*, on the material of 7089 FNAs, presented 131 DC V (123 cases of suspicion of PTC and 8 of suspicion of lymphoma). Seventy-five patients were subjected to surgery; the obtained RM was 97%. For 123 suspected PTCs, 59% (73/123) were histologically verified, and the diagnosis of cancer was confirmed in 99% (72/73) [16].

A large series of 8 studies was pooled by Bongiovanni *et al.* [17]. They obtained the DC V RM at the level of 75% in the group of 25 445 FNAs. Nayar *et al.* obtained 97 SM (2%) from 5194 FNAs, 83 patients had surgical treatment (85.5%), and the reported RM was 53% (44/97) [18].

In a smaller analysis, Mondal *et al.* obtained 14 DC V from 1020 FNA, operating 12 patients. The diagnosis of a malignant change was confirmed in 75% [19].

A similar group was analyzed by Tepeoglu *et al.* 1021 FNAs, 36 DC V (3.5%), RM at 91.4% [20].

An even smaller study by McElroy *et al.* showed 97 FNAs with 2% of DC V, and the risk of malignancy was 100%.

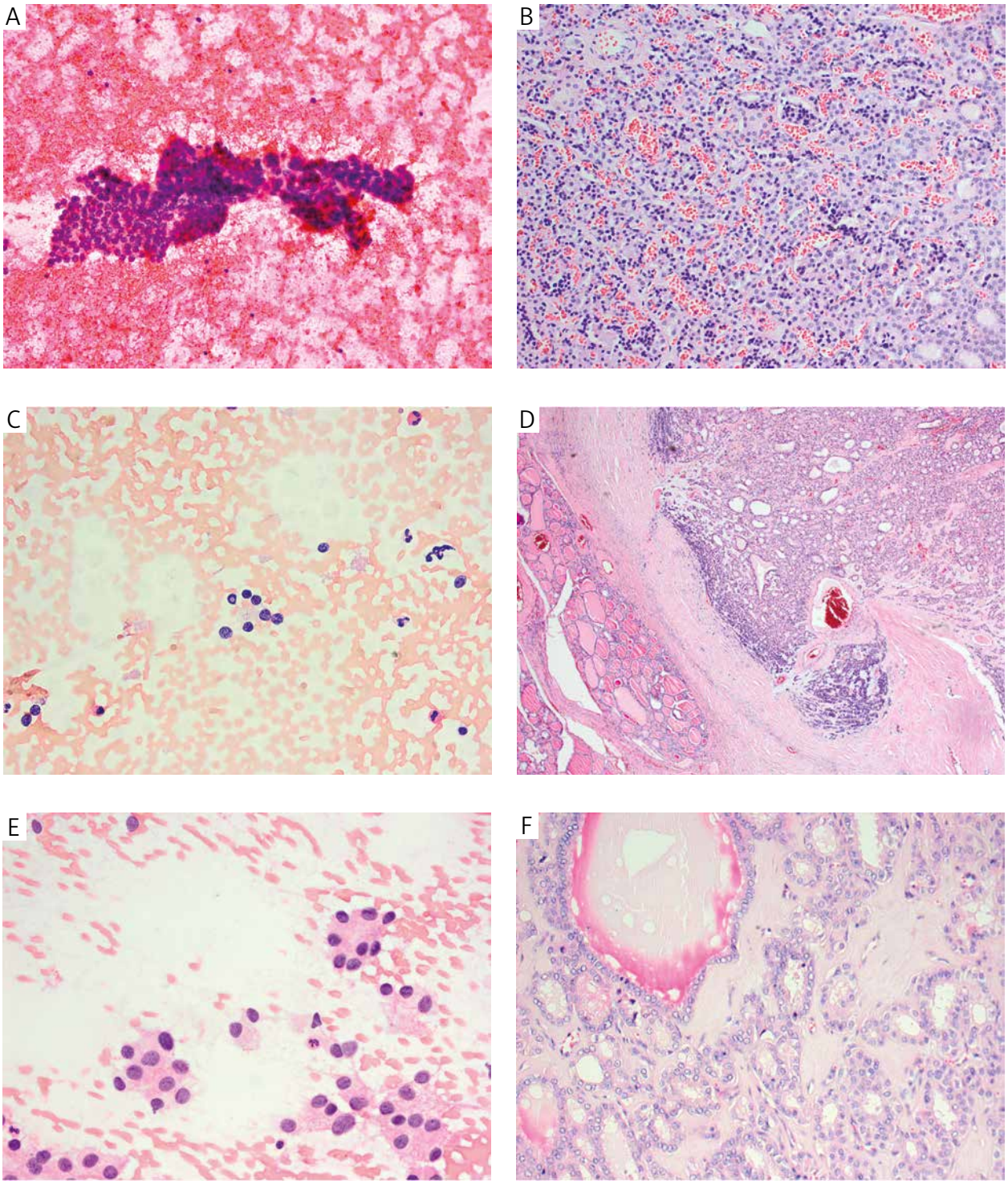

Fig. 6. Discordant FNA vs. HP results. A, C, E) FNA: suspicious for papillary carcinoma (DC V); B) HP: hyperplastic nodule; D) HP: follicular adenoma; F) HP: benign lesion (staining: HE)

The discrepancies between the studies probably result from the size of the cohorts, but irrespectively of the size of the group, the risk of malignancy is considered high.

The "suspicious for papillary carcinoma" diagnosis is established in the absence of all PTC cytological criteria, but when we report "papillary carcinoma" in FNA, it is confirmed in histopathological verification in an overwhelming majority of cases [15].

The analysis of cytological features in smears from thyroid nodules shown in Table II illustrates the difficulty in cytological diagnostics of thyroid lesions and the necessity of existence of DC V. We studied 6 major cytological features that allow the diagnosis

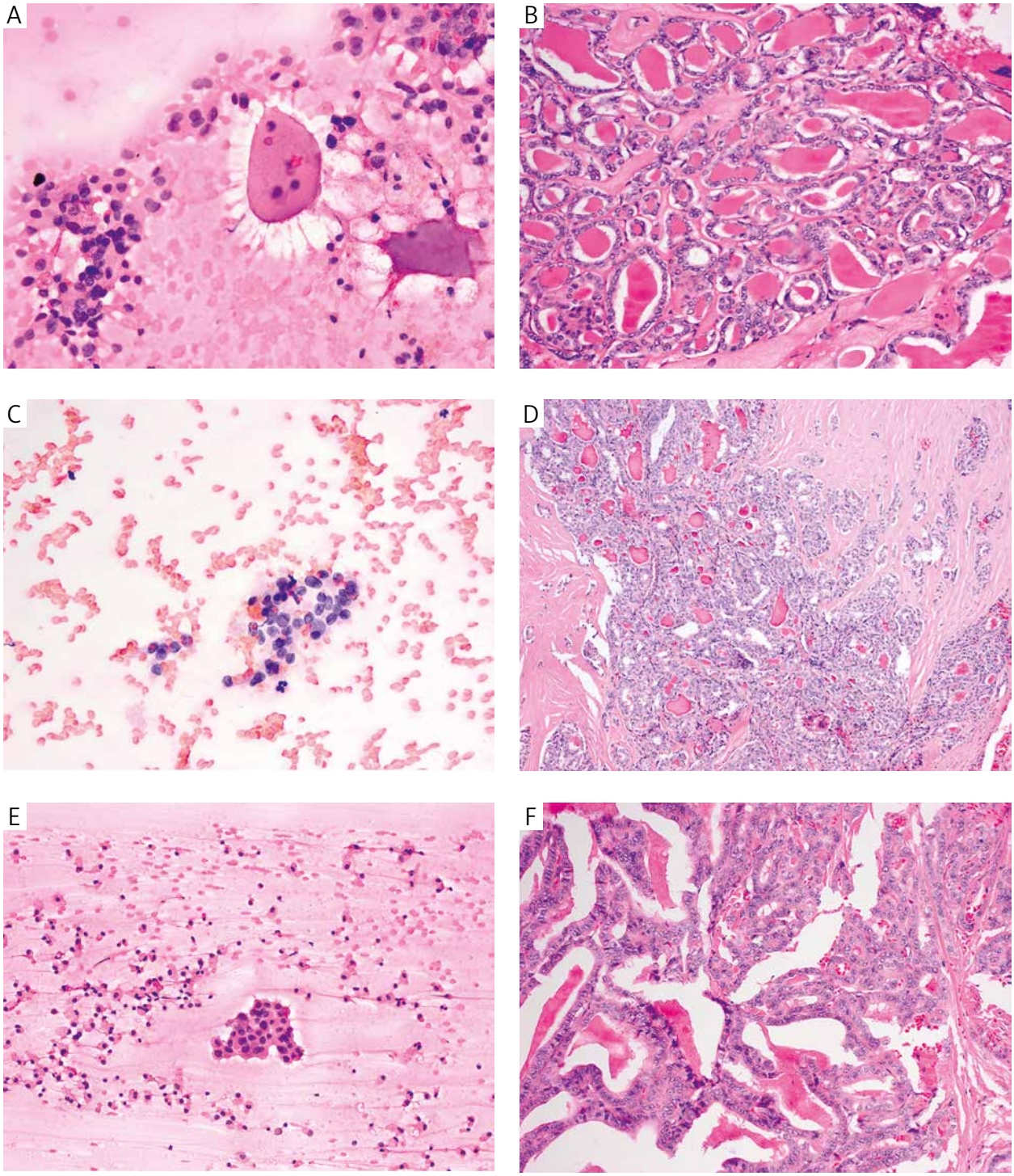

Fig. 7. FNA and HP results – confirmation of the diagnosis. A, C, E) FNA: suspicious for papillary carcinoma (DC V); B, D, F) HP: papillary carcinoma (follicular variant) (staining: HE)

of papillary carcinoma from the FNA smear. Moreover, our evaluation covered six secondary features (smear adequacy, cellularity, sheets/follicles forming, eosinophilic cytoplasm), absence of which may impede an unequivocal diagnosis despite the presence of major features.

We cannot make a diagnosis of papillary carcinoma (only raise a suspicion) when there are few characteristic cytological features or when they are strongly expressed but the quality of the smear is poor.

Literature analyzing cytohistological correlations point out the differences resulting from adequacy and quality of smears and the variety of material caused by occurrence of various histological variants of papillary thyroid carcinoma and histoarchitectural features of benign lesions, which explain the difficulties

Table I. Analysis of cytological features of DC V cases: 27 histopathologically confirmed papillary carcinomas and 27 histopathologically diagnosed benign neoplasms/benign lesions

FNA – cytological features	HP – papillary carcinoma		HP – benign neoplasm / benign lesion	
	number	%	number	%
Pseudoinclusions	12/27	44	6/27	22
Grooves	20/27	74	14/27	52
Nuclear clearing	26/27	96	22/27	81
Nucleoli	12/27	44	19/27	70
Enlargement	27/27	100	23/27	85
Overlapping	18/27	67	12/27	44

related to cytological diagnostics of papillary thyroid carcinoma.

Polish experts determined the RM for DC V between 30% and 50% [14]. In our material in 290 SM (in 16 656 FNAs), which comprises 1.7%, we found 111 malignant changes in 148 operated patients, which equals 75%.

Slightly divergent data were collected by Ho *et al.* In the analysis of 541 FNAs they found that 4.2% were in DC V (4/96), operated on 2 patients (50%) and did not find any malignant lesions in the postoperative material [21].

The SM category accurately expresses diagnostic doubts resulting from a cytological image of nodules which do not present the full set of features characteristic for a malignant neoplasm. Whether the analysis concerns a few thousands [15] or one thousand FNAs [19], the results obtained by researchers working in different parts of the world and staining their specimens with different methods, are quite similar (Papanicolaou stain [18, 19, 22, 23, 24, 25, 26, 27, 28, 29], Giemsa and Papanicolaou stain [19, 20, 30] and Giemsa stain [20, 31, 32]).

The report of "suspicious for papillary carcinoma" is most common in this category, but it is the diagnosis of FVPTC that arouses most controversy.

FVPTC comprises 85% of PTCs. Characteristically, the tumor cells are arranged almost entirely in a follicular pattern with the nuclear features identical to those of PTC (nuclear pallor, intranuclear inclusions and grooves) [33].

It is not difficult to diagnose FVPTC on a HP examination, and we can support the report with immunohistochemistry. However, when interpreting the cytology image we can only raise a suspicion of this variant and possibly carry out a molecular test, but its value is limited [33]. The diagnosis of the right variant of PTC is clinically essential; moreover, the encapsulated FVPTC has a very good prognosis, and the metastases almost never occur in this variant. Of course, in the literature and clinical practice we encounter possibilities of indirect pre-operative identification of an encapsulated or diffuse FVPTC. Because of the tumor biology, molecular tests are useful, but even the combination of a molecular test and FNA does not give 100% compliance with the HP report. Generally, the encapsulated FVPTC is thought to have a similar biology as the classic PTC, but the NI-FVPTC has an indolent clinical course comparable to follicular adenoma [33]. More and more lesions like this have been detected, partly thanks to the improvement of the quality of imaging methods. Commonly, the detection of small, non-invasive, indolent tumors increases, which results in raised morbidity with a stable level of mortality. The NI-FVPTC has been recently widely discussed in the literature.

Table II. The number of cytological features characteristic for papillary carcinoma (pseudoinclusions, grooves, nucleoli, nuclear clearing, overlapping, nuclear enlargement) present in analyzed smears in 27 cases of papillary carcinoma (group I) and 27 cases of benign neoplasms/ benign lesions (group II) verified in HP

Number of cytological features present in smears	Group I (n = 27)	Group II (n = 27)
6/6	6	3
5/6	5	7
4/6	8	7
3/6	7	3
2/6	1	2
1/6	0	5

Faquin *et al.* introduced a reclassification based on BSRTC [9]. They evaluated the risk of malignancy on their post-operative material, excluding lesions with NI-FVPTC characteristics from the group of cancers. Their study was conducted on the basis of a conference that took place in March 2015. The Endocrine Pathology Society proposed a formal reclassification, treating NI-FVPTC as a benign neoplasm [34]. The researchers analyzed 5 studies from 5 institutions,

Table III. The Bethesda System for Reporting Thyroid Cytopathology [13]

Diagnostic category	Risk of malignancy (%)	Usual management
Nondiagnostic or unsatisfactory	1-4	repeat FNA with ultrasound guidance
Benign	0-3	clinical follow-up
Atypia of undetermined significance or follicular lesion of undetermined significance	5-15	repeat FNA
Follicular neoplasm or suspicious for a follicular neoplasm	15-30	surgical lobectomy
Suspicious for malignancy	60-75	near-total thyroidectomy or surgical lobectomy
Malignant	97-99	near-total thyroidectomy

reclassifying 6943 FNAs, concluding in accordance that changing the NI-FVPTC status from malignant to benign neoplasm results in a decrease of RM in all categories of BSRTC, with the most remarkable decline in DC V [9, 35, 36]. Moreover, they concluded that after reclassification due to the decrease in RM there should be an indication for lobectomy instead of a thyroidectomy in many cases [9].

When we carried out such a reclassification in our analysis, the risk of malignancy decreased from 75% to 73% for DC V (in our material there were 2 cases of NI-FVPTC).

A benign lesion that might be misinterpreted as PTC due to its cytological image is hyalinizing trabecular tumor (HTT). It is a benign neoplasm with nuclear features as in PTC – nuclear grooves and inclusions are common [37]. There is a possibility of misdiagnosing it as PTC because HTT is a rare finding. A diagnostic tip might be a multitude of nuclear pseudoinclusions (which are not so numerous in PTC) and a definitely larger amount of material. The correct diagnosis is achievable after the surgical intervention. This tumor usually has a rather characteristic image, but most often requires immunohistochemical confirmation (at least MIB-1 expression should be evaluated – membranous reaction). A molecular test might also be useful (this tumor does not carry the BRAF mutation, specific for PTC) [37, 38, 39, 40].

At the end of the list of changes that could be reported as SM in FNA are medullary carcinoma, lymphoma and metastases to the thyroid gland.

In each of these lesions the image might not be characteristic; hence diagnosing as SM is entirely reasonable. In our analysis 16 medullary carcinomas were found in the post-operative material, which comprised 14% (16/111) of all malignancies. It is generally accepted that the frequency of medullary carcinoma among thyroid cancers ranges between 5% and 10% [41]. In all cases in which we suspect a medullary carcinoma, the serum calcitonin (CT) level should be measured.

The research of Bugalho *et al.* included the analysis of 91 cases of medullary carcinoma. Retrospectively, on the basis of the HP reports they analyzed the sensitivity of FNA and serum CT level tests. They concluded that the serum CT level is a more sensitive method for detecting medullary carcinoma than FNA [41].

The diagnosis of a lymphoma in thyroid FNA is difficult, but (luckily) rare. In our material we did not obtain any lymphoma classified as DC V in FNA. In every case, repeat FNA and a flow cytometry test should be conducted [13, 14].

In the literature analysis we found a study that compared the efficiency of a core needle biopsy and FNA. The researchers proved that a core needle biopsy might be useful for evaluation of thyroid lesions that are suspicious for malignancy, but with exclusion of follicular lesions. Assuming that FNA has acceptable reliability to distinguish between benign and malignant lesions, it is regarded as the gold standard in thyroid nodules workup [41].

Conclusions

A high positive predictive value (PPV = 75%) of SM diagnosis established in the Department of Tumor Pathology of Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch, testifies to the high reliability of this test. DC V in FNA should be an indication for surgical treatment.

The authors declare no conflict of interest.

References

1. Vaccarella S, Dal Maso L, Laversanne M, et al. The impact of diagnostic changes on the rise in thyroid cancer incidence: a population-based study in selected high-resource countries. Thyroid Off J Am Thyroid Assoc 2015; 25: 1127-1136.
2. Brito JP, Morris JC, Montori VM. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. BMJ 2013; 347: f4706.

3. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"– screening and overdiagnosis. N Engl J Med 2014; 371: 1765-1767.
4. Ratour J, Polivka M, Dahan H, et al. Diagnosis of follicular lesions of undetermined significance in fine-needle aspirations of thyroid nodules. J Thyroid Res 2013; 2013: 250347.
5. Bohacek L, Milas M, Mitchell J, et al. Diagnostic accuracy of surgeon-performed ultrasound-guided fine-needle aspiration of thyroid nodules. Ann Surg Oncol 2012; 19: 45-51.
6. La Vecchia C, Malvezzi M, Bosetti C, et al. Thyroid cancer mortality and incidence: a global overview. Int J Cancer J Int Cancer 2015; 136: 2187-2195.
7. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014; 140: 317-322.
8. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer 2009; 115: 3801-3807.
9. Faquin WC, Wong LQ, Afrogheh AH, et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in The Bethesda System for Reporting Thyroid Cytopathology. Cancer Cytopathol 2016; 124: 181-187.
10. Davies L, Morris LGT, Haymart M, et al., AACE Endocrine Surgery Scientific Committee American Association Of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: The increasing incidence of thyroid cancer. Endocr Pract 2015; 21: 686-696.
11. Ali SZ. Thyroid cytopathology: Bethesda and beyond. Acta Cytol 2011; 55: 4-12.
12. Dean DS, Gharib H. Fine-needle aspiration biopsy of the thyroid gland. In: De Groot LJ, Beck-Peccoz P, Chrousos G, et al. (eds.). Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000.
13. Cibas ES, Ali SZ., NCI Thyroid FNA state of the science Conference The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol 2009; 132: 658-665.
14. Jarząb B, Sporny S, Lange D, et al., Polish Endocrinology Society, Polish Thyroid Society, Polish Pathologic Society et al. Diagnosis and treatment of thyroid cancer – Polish guidelines. Endokrynol Pol 2010; 61: 518-568.
15. Olson MT, Boonyaarunnate T, Altinboga AA, et al. "Suspicious for papillary thyroid carcinoma" before and after The Bethesda System for Reporting Thyroid Cytopathology: impact of standardized terminology. Acta Cytol 2014; 58: 15-22.
16. Renshaw AA. Should "atypical follicular cells" in thyroid fine-needle aspirates be subclassified? Cancer Cytopathol 2010; 118: 186-189.
17. Bongiovanni M, Spitale A, Faquin WC, et al. The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. Acta Cytol 2012; 56: 333-339.
18. Nayar R, Ivanovic M. The indeterminate thyroid fine-needle aspiration: experience from an academic center using terminology similar to that proposed in the 2007 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. Cancer 2009; 117: 195-202.
19. Mondal SK, Sinha S, Basak B, et al. The Bethesda system for reporting thyroid fine needle aspirates: A cytologic study with histologic follow-up. J Cytol Indian Acad Cytol 2013; 30: 94-99.
20. Tepeoğlu M, Bilezikçi B, Bayraktar SG. A histological assessment of the Bethesda system for reporting thyroid cytopathology (2010) abnormal categories: a series of 219 consecutive cases. Cytopathology 2014; 25: 39-44.
21. Ho AS, Sarti EE, Jain KS, et al. Malignancy rate in thyroid nodules classified as Bethesda category III (AUS/FLUS). Thyroid 2014; 24: 832-839.
22. Vanderlaan PA, Krane JF, Cibas ES. The frequency of "atypia of undetermined significance" interpretations for thyroid fine-needle aspirations is negatively correlated with histologically proven malignant outcomes. Acta Cytol 2011; 55: 512-517.
23. VanderLaan PA, Marqusee E, Krane JF. Clinical outcome for atypia of undetermined significance in thyroid fine-needle aspirations: should repeated fna be the preferred initial approach? Am J Clin Pathol 2011; 135: 770-775.
24. Smith M, Pantanowitz L, Khalbuss WE, et al. Indeterminate pediatric thyroid fine needle aspirations: a study of 68 cases. Acta Cytol 2013; 57: 341-348.
25. Al-Abbadi MA, Shareef SQ, Ali JA, et al. Application of the Bethesda System for Reporting Thyroid Cytopathology in the Eastern Province of Saudi Arabia: phase I pilot retrospective analysis. Acta Cytol 2013; 57: 481-488.
26. Olson MT, Clark DP, Erozan YS, et al. Spectrum of risk of malignancy in subcategories of "atypia of undetermined significance". Acta Cytol 2011; 55: 518-525.
27. Harvey AM, Mody DR, Amrikachi M. Thyroid fine-needle aspiration reporting rates and outcomes before and after Bethesda implementation within a combined academic and community hospital system. Arch Pathol Lab Med 2013; 137: 1664-1668.
28. Theoharis C, Adeniran AJ, Roman S, et al. The impact of implementing The Bethesda System for reporting of thyroid FNA at an academic center. Diagn Cytopathol 2013; 41: 858-863.
29. Jo VY, Stelow EB, Dustin SM, et al. Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda System for Reporting Thyroid Cytopathology. Am J Clin Pathol 2010; 134: 450-456.
30. Bongiovanni M, Crippa S, Baloch Z, et al. Comparison of 5-tiered and 6-tiered diagnostic systems for the reporting of thyroid cytopathology: a multi-institutional study. Cancer Cytopathol 2012; 120: 117-125.
31. Srbova L, Gabalec F, Ryska A, et al. Results of retrospective classification of thyroid FNAs according to the Bethesda system: would this have improved accuracy? Cytopathology 2015; 26: 231-237.
32. Dincer N, Balci S, Yazgan A, et al. Follow-up of atypia and follicular lesions of undetermined significance in thyroid fine needle aspiration cytology. Cytopathology 2013; 24: 385-390.
33. Chen H, Izevbaye I, Chen F, et al. Recent advances in follicular variant of papillary thyroid carcinoma. NAJ Med Sci 2012; 5: 212-216.
34. Strickland KC, Howitt BE, Marqusee E, et al. The Impact of noninvasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnostic categories. Thyroid 2015; 25: 987-992.
35. Giordano TJ, Beaudenon-Huibregtse S, Shinde R, et al. Molecular testing for oncogenic gene mutations in thyroid lesions: a case-control validation study in 413 postsurgical specimens. Hum Pathol 2014; 45: 1339-1347.
36. Damiani D, Suciu V, Vielh P. Cytopathology of follicular cell nodules.. Endocr Pathol 2015; 26: 286-290.
37. Baloch ZW, LiVolsi VA. Cytologic and architectural mimics of papillary thyroid carcinoma. Diagnostic challenges in fine-needle aspiration and surgical pathology specimens. Am J Clin Pathol 2006; 125 Suppl: S135-S144.
38. Cheung CC, Boerner SL, MacMillan CM, et al. Hyalinizing trabecular tumor of the thyroid: a variant of papillary carcinoma proved by molecular genetics. Am J Surg Pathol 2000; 24: 1622-1626.
39. Boerner SL, Asa SL. Hyalinizing trabecular tumor of the thyroid gland: much ado about nothing? Am J Clin Pathol 2004; 122: 495-496.

40. Papotti M, Volante M, Giuliano A, et al. RET/PTC activation in hyalinizing trabecular tumors of the thyroid. Am J Surg Pathol 2000; 24: 1615-1621.
41. Bugalho MJM, Santos JR, Sobrinho L. Preoperative diagnosis of medullary thyroid carcinoma: fine needle aspiration cytology as compared with serum calcitonin measurement. J Surg Oncol 2005; 91: 56-60.

Address for correspondence

Miroslaw Śnietura MD, PhD
Tumor Pathology Department
Institute of Oncology, Wybrzeże Armii Krajowej 15
44-101 Gliwice, Poland
tel. +48 32 278 94 00
fax: +48 32 278 94 15
e-mail: mirek@snietura.net