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Suspicious for follicular neoplasm or follicular neoplasm? The dilemma of a pathologist and a surgeon

Podejrzenie nowotworu pęcherzykowego czy nowotwór pęcherzykowy? Dylemat patologa i chirurga

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Abstract

Introduction: Cytological material obtained from Fine Needle Aspiration Biopsy (FNAB) does not permit us to distinguish between follicular carcinomas, adenomas, and hyperplastic nodules. The limitations of the method are: lack of possibility to assess the presence of tumour capsule, eventual capsular invasion, and angioinvasion. An unequivocal conclusion of whether what we have to deal with is a neoplastic or benign lesion is possible only after histopathological examination. The aim of the study was to confirm justification for using the term "Suspicious for Follicular Neoplasm" (SFN) in cytological diagnostics of thyroid carcinoma.

Material and methods: Three hundred and fifty-two primary SFN FNAB diagnoses (diagnostic category IV [DC IV] — according to Bethesda System) obtained from 2010 to 2015 in the Institute of Oncology in Gliwice were analysed, and their correlation with histopathological diagnoses was verified.

Results: In the Institute of Oncology in Gliwice, 352 primary SFN diagnoses (diagnostic category IV [DC IV] — according to Bethesda System) were established. Surgical treatment was undertaken after first FNAB in six cases, giving confirmation of a neoplasm in five cases, one of which was a follicular carcinoma. Second FNAB performed in 90 patients confirmed DC IV diagnosis in 53 cases. Third FNAB concerned 26 patients, providing another 14 diagnoses of DC IV. 26 out of 352 patients were subjected to surgery, and then histopathological examination confirmed a neoplasm in 19 cases (which comprises 73%), five of which were carcinomas.

Conclusions: High positive predictive value PPV = 73% of SFN diagnosis justifies undertaking surgical treatment in any case of this diagnosis. **(Endokrynol Pol 2016; 67 (1): 17–22)**

Key words: *thyroid cancer; thyroid nodule; fine-needle aspiration biopsy*

Streszczenie

Wstęp: Materiał cytologiczny biopsji aspiracyjnej cienkoigłowej (BAC) tarczycy nie pozwala na zróżnicowanie raków pęcherzykowych, gruczolaków i guzków rozrostowych. Ograniczeniem metody jest brak możliwości określenia obecności torebki guza, jej ewentualnego nacieku oraz angioinwazji. Jednoznaczne rozstrzygnięcie czy mamy do czynienia ze zmianą nowotworową czy łagodną jest możliwe dopiero po badaniu histopatologicznym. Celem pracy było uzasadnienie celowości używania terminu „podejrzenie nowotworu pęcherzykowego" w diagnostyce cytologicznej raka tarczycy.

Materiał i metody: Poddano analizie 352 wyniki BAC tarczycy wykonanych w Instytucie Onkologii (IO) w Gliwicach w latach 2010–2015 i ich korelację z rozpoznaniem histopatologicznym.

Wyniki: W IO rozpoznanie podejrzenie nowotworu pęcherzykowego (grupa IV wg Systemu Bethesda) postawiono pierwotnie w 352 przypadkach. Leczenie operacyjne podjęto po pierwszej BAC w 6 przypadkach uzyskując potwierdzenie nowotworu w 5 przypadkach w tym jednego raka pęcherzykowego. Powtórna BAC przeprowadzona u 90 pacjentów potwierdziła rozpoznanie grupy IV w 53 przypadkach. Trzecią BAC przeprowadzono u 26 chorych, uzyskując kolejnych 14 rozpoznań grupy IV. Leczeniu operacyjnemu poddano 26 pacjentów na 352 rozpoznania nowotworu pęcherzykowego, uzyskując potwierdzenie nowotworu w 19 przypadkach, co stanowi 73% w tym raka 5 razy.

Wnioski: Wysoka dodatnia wartość predykcyjna PPV = 73% rozpoznania „podejrzenie nowotworu pęcherzykowego" uzasadnia podjęcie leczenia operacyjnego w każdym przypadku tego rozpoznania. **(Endokrynol Pol 2016; 67 (1): 17–22)**

Słowa kluczowe: *guzek tarczycy; rak tarczycy; biopsja aspiracyjna cienkoigłowa*

Introduction

Fine Needle Aspiration (FNA) has had a well-established position as an important diagnostic method. In recent years, its usage has undergone some modifications. Its application in breast diagnostics is limited to changes that do not present radiologic features of malignancy, while those that receive BI-RADS 4 or more are managed with core needle biopsy. In the diagnostics of soft tissue tumours it is used with restriction and/or for cell-block preparation. In the workup of thyroid nodules FNA still plays a fundamental role. It is a method

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that allows quick and simple assessment of the risk of malignancy of the biopsied changes, and hence guides clinical management [1].

The classification of thyroid cytological diagnoses — the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) — translates the complicated and mysterious language of cytopathological descriptive report into a straight and comprehensive form that eases the dialogue between the pathologist, the surgeon, and the endocrinologist. Moreover, the implementation of BSRTC allows comparison of data concerning the risk of malignancy between institutions and the assessment of the system's effectiveness and capability [2–7] (Table I).

BSRTC was discussed and developed in 2007 by cooperation between pathologists, surgeons, endocrinologists, and radiologists. The inspiration for building a thyroid cytological examination report was the system that operates in gynaecological cytology. The report of thyroid FNA compatible with the recommendations of BSRTC enables the specialties that take part in diagnostic and therapeutic process to communicate clearly [4]. The implementation of the BSRTC to routine use in various countries took place in various intervals. The proposition of Polish guidelines based on the original National Cancer Institute (NCI) BSRTC text with minor modifications was elaborated by The Polish Group of Endocrine Tumours, and presented to the Scientific Committee of the "Thyroid Cancer 2010" Conference, appointed collectively by all scientific societies that organised the conference [7].

"Follicular Neoplasm or Suspicious for Follicular Neoplasm" (FN or SFN) — diagnostic category IV (DC IV) of BSRTC — is a challenging group. We cannot define whether we are dealing with a benign or malignant neoplasm on the basis of cytological examination of a follicular neoplasm [1, 4, 7, 8]. The NCI recommends the use of terms "Follicular Neoplasm" and "Suspicious for Follicular Neoplasm" due to the fact that 25% of these nodules are not neoplasms at all [4]. This category covers changes described before as "Follicular/Oxyphilic Neoplasm" as well as "Follicular/Oxyphilic Tumour". It should not cover changes in which there are nuclear features consistent with papillary carcinoma. The suspicion of oncocytic/oxyphilic neoplasm is aroused when there are at least 75% of oxyphilic cells. It carries a higher risk of malignancy than SFN. According to the NCI, the risk of malignancy for FN and SFN ranges between 15% and 30% [4]. In Poland, the experts set a lower threshold of 5–20%, considering as DC IV only the diagnoses that are consistent with SFN category [7] (Table II). The diagnosis of SFN should be made in cases in which the pathologist predicts the necessity of surgical treatment for obtaining tissue material and establishing a final histopathological (HP) diagnosis [4, 7].

Table I. ***The Bethesda system for reporting thyroid cytopathology [4]***

Tabela I. ***Klasyfikacja cytopatologii tarczycy według systemu Bethesda [4]***

Diagnostic category	Risk of malignancy (%)	Management plan
Non-diagnostic/unsatisfactory	1–4	Repeat FNA with ultrasound guidance
Limited cellularity or a cellular		
Technically compromised		
Cyst fluid only		
Benign	0–3	Clinical follow-up
Adenomatous or colloid nodule		
Chronic lymphocytic thyroiditis		
Other		
Atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS)	5–15	Repeat FNA
Suspicious for a follicular neoplasm/follicular neoplasm	15–30	Surgical lobectomy
Suspicious for malignancy	60–75	Surgical lobectomy or near total thyroidectomy
Papillary carcinoma		
Medullary carcinoma		
Lymphoma		
Metastatic neoplasm		
Other		
Malignant	97–99	Near total thyroidectomy

Table II. ***FNA diagnosis and its risk of malignancy proposed in Polish guidelines (on the basis of [4, 7] with minor modifications)***

Tabela II. ***Wynik biopsji aspiracyjnej cienkoigłowej tarczycy i związane z nim ryzyko złośliwości zaproponowane w Polskich Rekomendacjach (zmodyfikowano na podstawie [4, 7])***

BSRTC category	Risk of malignancy
I — Non-diagnostic	5–10%
II — Benign	< 1%
III — FLUS	5%
IV — SFN	5–20%
V — SM	30–50%
VI — Malignant	95–100%

BSRTC — The Bethesda System for Reporting Thyroid Cytopathology; FLUS — Follicular Lesion of Undetermined Significance; SFN — Suspicious for Follicular Neoplasm; SM — Suspicious for Malignancy

The aim of the study was justification of purposefulness of using the term "Suspicious for Follicular Neoplasm" (SFN) in cytological diagnostics of thyroid carcinoma.

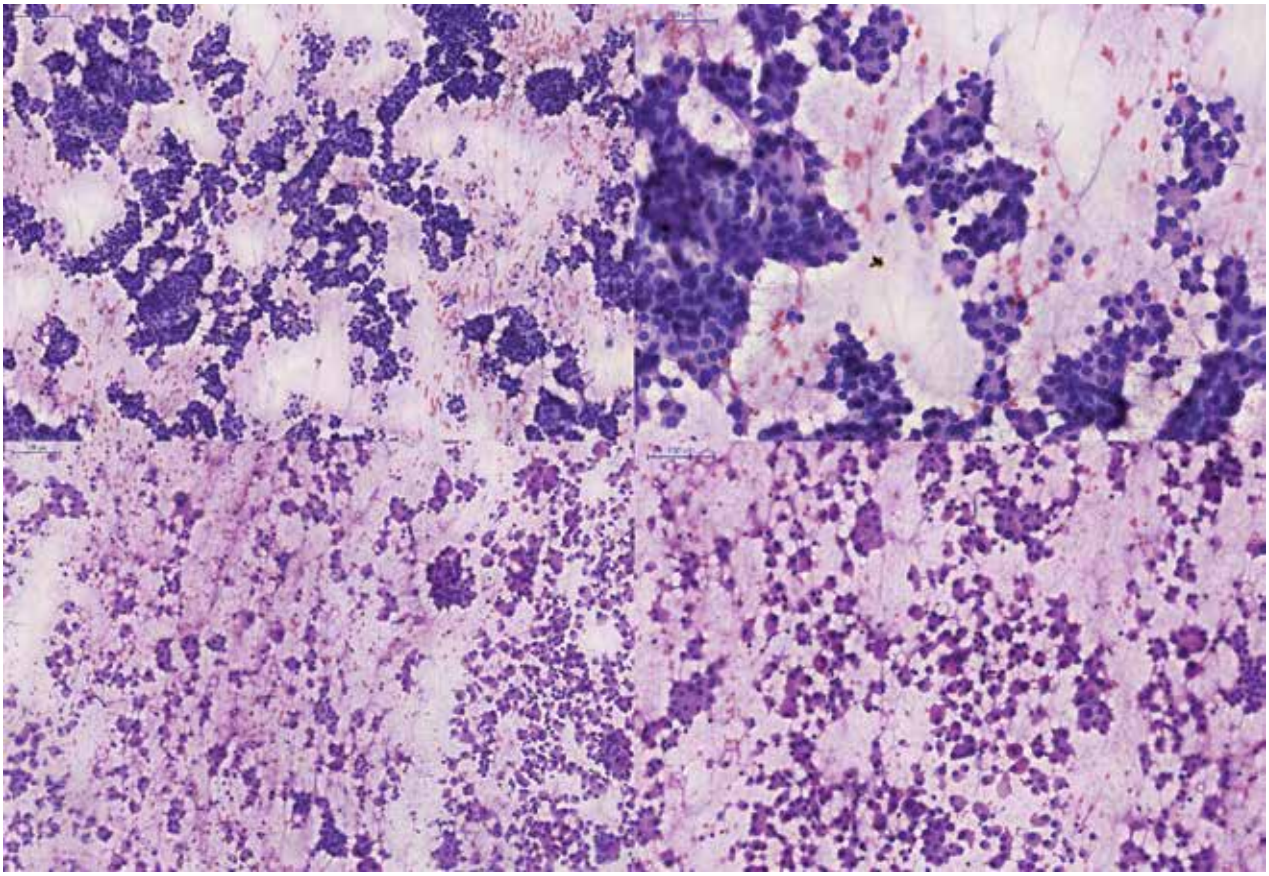

Figure 1. *Representative examples of Bethesda Diagnostic Category IV FNAs. Staining: haematoxylin-eosin*

Rycina 1. *Reprezentatywne przykłady rozmazów z biopsji aspiracyjnej cienkoigłowej tarczycy z kategorii IV klasyfikacji Bethesda. Barwienie: hematoksylina-eozyna*

Material and methods

A total of 16,656 FNA reports made in the Department of Tumour Pathology of Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch from 2010 to 2015 were analysed and correlated with histopathological outcomes. All FNAs were performed in two-person teams of a pathologist and radiologist, under ultrasound guidance. The material was obtained by 25-gauge needles, and the smears were fixed in 95% alcohol and stained with haematoxylin-eosin (HE, Fig. 1). Usually we perform one FNA for each nodule (two or maximum three when a change does not subject to aspiration). All the evaluations and diagnoses were provided by the pathology specialists. Each test contained a description of the site of the biopsy with the size of the nodule and ultrasound photography. The questionable cases were consulted by another pathologist.

Results

In our institution the diagnosis of SFN — DC IV according to BSRTC was initially established in 352 cases (Fig. 2). Six patients were immediately subjected to operation after first FNA with this diagnosis, receiving the confirmation of a neoplasm in five cases (83% — 5/6): one follicular carcinoma and four follicular adenomas. The sixth patient was diagnosed with a hyperplastic nodule. Repeat (2nd) FNA performed in 90 patients confirmed SFN — DC IV in 53 cases. In this group, 14 patients were treated surgically, which resulted in the diagnoses of 10 neoplasms (71% — 10/14): seven follicular adenomas (including five oxyphilic adenomas) and three cancers: two oxyphilic papillary carcinomas and one follicular carcinoma. Four patients obtained the diagnoses of benign changes: three hyperplastic nodules and one multinodular goiter. The third FNA was performed in 26 patients who had DC IV in first FNA and DC II, DC III or DC IV in second and third FNA. In this group there were four resections performed, only in patients with three consecutive diagnoses of DC IV. The results of histopathological verifications in this group are two benign changes, which comprise 50%: one multinodular goitre and one oxyphilic hyperplastic nodule, and two benign neoplasms — oxyphilic follicular adenomas, which comprise 50%. Ten patients were subjected to

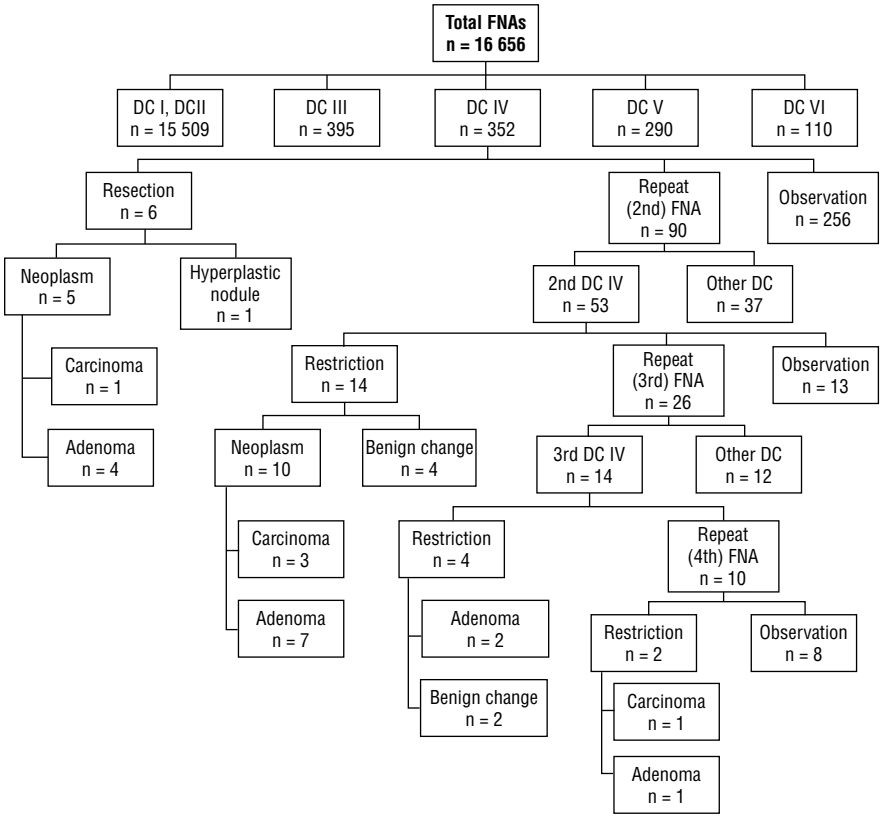

Figure 2. *CONSORT diagram of the study group*
Rycina 2. *Diagram CONSORT analizowanej grupy pacjentów*

fourth FNA. In this group there were two patients that had four consecutive DC IV diagnoses, and these two were subjected to surgery, which resulted in diagnoses of one oxyphilic papillary carcinoma and one follicular adenoma. The remaining eight patients (three with quadruple DC IV and the remainder that were given the diagnoses of DC IV, DC II, or DC I, alternately) did not undergo surgical procedure. Altogether, there were 26 resections for 352 DC IV (7%), providing 19 diagnoses of neoplastic changes, which comprise 73%. Malignancy was reported in five patients, which comprise 19% of verified cases.

Discussion

Achieving the right diagnosis should not cause any problems if the material is of high quality: properly obtained, fixed, and stained. This process is essential for a comprehensive analysis of cytological specimens. Another key element is an experienced pathologist who deals with thyroid cytology on a daily basis. In our institution there were 16,656 FNAs performed in the last five years, giving the DC IV result in 352 initial examinations, which comprise 2.11%. Most of our patients had multiple FNAs, but repeat FNAs did not always confirm the initial diagnosis.

The literature data are varied. First of all, the elaborations that we encountered concern smaller study groups. Mondal et al. achieved 43 DC IV in 1020 FNAs, which comprise 4.2% [9]. Nayar et al. in their study based on 5194 cases assessed the quantity of DC IV at 4.7% [6]. Wu et al. showed a slightly higher percentage of DC IV, namely 8.4%, in a group of 1382 [5]. Theoharis et al. received more DC IV, 378 for 3207 FNAs (11.7%) [10]. Srbova et al. in their analysis of 1310 FNA presented 220 DC IV (16.8%) [11]. A very high percentage (40%) was shown by Faquin et al. in a small group of 857 FNAs [12]. Radically different results were obtained by McElroy et al., who documented 1% of DC IV in 97 analysed FNAs in 2006, and after a review in 2012 the rate changed to 7% [13].

According to BSRTC recommendations, the diagnosis of SFN — DC IV should result in lobectomy [4]. Our attitude, as well as the surgeons', is rather conservative. There is a tendency to believe that DC IV does not carry a high risk of malignancy, and aggressive therapy is not necessary. After 1st DC IV diagnosis at the study institution there were only six resections performed, giving the diagnosis of a neoplasm in 83% (5/6) cases. Repeat FNA had a 58% efficacy in confirming the initial diagnosis of DC IV (53/90).

Ho et al. in their study tentatively divided the DC III (AUS/FLUS) into subgroups, naming the last one as "AUS/FLUS — cannot exclude follicular neoplasm". On HP verification they obtained 24.4% of benign changes, and as much as 56.4% of malignant changes [1]. Harvey et al. compared the results of FNA before and after the implementation of BSRTC on groups of similar size (3302 and 3432), obtaining 309 and 79 of DC IV, respectively. 70% from the 1st and 33% from the 2nd group were histopathologically verified, receiving the diagnoses of malignancy in 26% and 7%, respectively [14]. Moreover, they submitted an analysis of 11 studies comparing the number of surgical resections in DC IV category. The differences in the analysed cohorts are remarkable, the numbers range from 14% to 45% of operations. In our review altogether we achieved the diagnosis of 19 neoplasms, which comprise 73% (19/26 surgeries). In our material the risk of malignancy is 1.4% (5/352), and the risk of neoplasia is 5.4% (19/352).

BSRTC determines the risk of malignancy in detail [4–6]. An essential feature of DC IV is that correct classification of cytological image does not suggest the HP diagnosis. In this category, the premise is that the HP outcome is unknown. Only thorough HP evaluation one can assess the capsular and/or vascular invasion, which is the key feature of follicular carcinoma. The NCI estimates that 15–30% of changes with the diagnosis of FN or SFN would eventually be a cancer. In Poland, at implementation of BSRTC the rate has been assessed at 5–20% (for SFN only) by our experts [4, 7].

High risk of malignancy was described by Tepeoglu et al., at the level of 35% [8]. Similarly high results were presented by Yang et al. — 32.2% [15], Theoharis et al. — 34% [10], and Broome et al. — 36% [16]. Mondal reported a malignancy rate of 30.6% in the analysis of 1020 FNA [9]. A lower rate was achieved by Srbova et al., who obtained a risk of malignancy of 23.6%, and a risk of neoplasia of 55% [11].

An unquestionably lower risk was demonstrated by Nayar et al. In their study based on 5194 cases the estimated risk of malignancy was 14%, and the risk of neoplasia — 75% [6]. Slightly higher rates were recorded by Wu et al.: 1382 FNAs, risk of malignancy at the level of 22% and the risk of neoplasia of 67% [5].

Faquin et al. (875 FNA) assessed the risk of malignancy at 25%, and the risk of neoplasia at 43% [12]. Theoharis documented the risk of malignancy at the level of 43% (on a group of 3207 FNAs) [10].

The risk of neoplasia, and especially the risk of malignancy, presented by the researchers is greatly varied [2, 17, 18]. These major discrepancies may result from the number of analysed cases, from 97 FNAs [13] to more than 16 thousand (16,656 in our study). The conclusions drawn from a study based on a small group are always encumbered with a greater likelihood of error. The experience of cytopathologists is another factor that may affect the results; the accuracy of the evaluation diminishes the number of incorrect diagnoses. The verifications in our study group were provided by a team of experienced pathologists who remained constant in the period covered by this study.

It is difficult to state whether the type of staining has an influence on the result. NCI does not impose any specific method of fixation or staining of the aspirates. In Poland, 99% of pathology departments use HE staining. Owing to this fact, we encounter no problems if any re-consultation is needed. Our experience with one institution that stains with the Giemsa method indicates that such images are confusing for pathologists educated on HE staining. The interpretive difficulties cause the need for repeat FNA to eliminate diagnostic doubts.

Theoharis et al. based their analysis on a group of 5897 FNA; most of the material was stained with Papanicolau stain; part of the analysed cases were outside consultations stained with Papanicolau and HE [18]. Ho et al. [1] verified aspirates stained with Papanicolau and Giemsa, and Topeoglu studied specimens stained with Giemsa and HE, performing from 4 to 20 smears [8]. Part of the reviews are based on specimens stained with Giemsa and Papanicolau [8, 9, 19]. These studies often come from different medical centres, and the stains vary because of the need to collect a sufficiently large cohort. An overwhelming majority of researchers use Papanicolau stain [5, 6, 10, 14, 18, 20–28].

A smaller number of studies are based on specimens stained with Giemsa [8, 20, 29]. We did not encounter a study in which the aspirates were stained only with HE.

We always prepare two specimens from one FNA, second and eventually third FNA is conducted only if we obtain very scanty material in first biopsy. This increases the chance for a correct diagnosis. Producing more specimens is unnecessary in our opinion, but the smearing glass slide is worth examining. Sometimes when the material is cell-rich and there is a lot of blood, the small amount that rests on the second slide is more adequate for assessment. We found studies in which there was only one specimen prepared, and the smearing slide was discarded. Srbova et al. performed from 2 to 10 smears stained with Giemsa [11]. Ohori et al. and Hyeaon et al. performed 2–4 FNAs [21, 30]. Our experience shows that high-quality diagnostic material can be obtained by one or, when we encounter problems in aspiration, two biopsies, to reduce the damage that is caused in the thyroid nodule, which impedes the assessment of capsular invasion (infiltration or artefact?).

Analysing the publications, we noticed considerable differences regarding the qualification of the nodule to the FNA. Our institution is a comprehensive cancer centre and we perform FNA on all nodules, not only the ones with specific size or radiologic features of malignancy [26, 27].

The large amount of thyroid FNAs performed in our institution, the wide experience of the pathologist as well as radiologists, the possibility of consultation (there are 11 specialists working in our department, dealing, among others, with thyroid FNA), and the opportunity to verify the cytological diagnoses (we perform the intraoperative examinations and we obtain abundant post-operative material) lead to the high accuracy of our diagnoses. This entitles us to make the bold statement that the diagnoses of the category "Suspicious for Follicular Neoplasm" are established precisely, and the patient's management — if it is undertaken — is appropriate. Directing the patient to excision after receiving the diagnosis of this category is clearly indicated as the only way to determine the final diagnosis.

Conclusions

The high positive predictive value (PPV = 73%) of "Suspicious for Follicular Neoplasm" report justifies undertaking surgical treatment in any case of this diagnosis.

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