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Clinical importance of follicular lesion of undetermined significance (diagnostic category III according to Bethesda System) diagnosed from Fine-Needle Aspiration Biopsy

Kliniczne znaczenie rozpoznania zmiany pęcherzykowej bliżej nieokreślonej (grupa III wg Systemu Bethesda) w biopsji aspiracyjnej cienkoigłowej (BAC)

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Abstract

Introduction: Follicular Lesion of Undetermined Significance (FLUS) belongs to the most controversial category of the Bethesda System. The aim of the study was to specify the risk of malignancy in patients with FLUS diagnosis in the material from the Institute of Oncology in Gliwice. This is the first Polish study specifying the risk of malignant neoplasm presence when Fine-Needle Aspiration Biopsy (FNAB) results in a report of diagnostic category III (DC III).

Material and methods: Three hundred and ninety-five primary DC III diagnoses from FNABs of the thyroid gland performed from 2010 to 2015 were analysed. Correspondence of DC III with diagnoses from repeated FNABs and histopathology reports was evaluated.

Results: From 395 DC III patients, 27 were treated surgically for clinical indications, receiving six diagnoses of cancer. Repeat FNAB was performed in 180 cases, and primary diagnosis was confirmed in 41 cases. In the second FNAB there was one diagnosis of "Papillary Thyroid Carcinoma" and one "Suspicious for Papillary Thyroid Carcinoma". From eight patients treated surgically in these series prior cytological cancer diagnosis was confirmed in two cases. Forty-six patients were subjected to third and subsequent FNABs; in one case the diagnosis was "Suspicious for Malignancy". In the analysed material the risk of cancer in patients with FLUS is 2.78%. Taking into account all 56 subsequent FNABs in which the primary diagnosis was confirmed, the risk decreases to 2.43%.

Conclusions: The diagnosis of FLUS in the absence of clinical indications is not a basis for surgical treatment.

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

Streszczenie

Wstęp: Zmiana pęcherzykowa bliżej nieokreślona (grupa III) należy do najbardziej kontrowersyjnej kategorii systemu Bethesda. Brak jest polskich opracowań określających stopień ryzyka wystąpienia nowotworu złośliwego po rozpoznaniu zmiany z grupy III.

Celem pracy było określenie ryzyka złośliwości po rozpoznaniu zmiany pęcherzykowej bliżej nieokreślonej w materiale Centrum Onkologii w Gliwicach.

Materiał i metody: Analizie poddano 395 rozpoznań z grupy III BAC tarczycy wykonanych w latach 2010–2015. Oceniono zgodność pierwotnego rozpoznania grupy III z rozpoznaniami z kolejnych BAC i wynikami badań histopatologicznych.

Wyniki: Na 395 rozpoznań grupy III zoperowano ze wskazań klinicznych 27 pacjentów i rozpoznano 6 raków. Ponowną BAC wykonano w 180 przypadkach i pierwotne rozpoznanie potwierdzono w 41 przypadkach. Po drugiej BAC 2-krotnie rozpoznano raka brodawkowatego lub jego podejrzenie. U 8 operowanych w tej serii potwierdzono wcześniejsze cytologiczne rozpoznanie raka u 2. Trzecią i kolejne BAC wykonano u 46 pacjentów i w jednym przypadku podejrzewano raka.

Ryzyko raka w zmianie pęcherzykowej bliżej nieokreślonej w analizowanym materiale wynosi 2,78%. Uwzględniając wszystkie powtórnie wykonane 56 BAC, w których potwierdzono pierwotne rozpoznanie grupy III, ryzyko maleje do 2,43%.

Wnioski: Rozpoznanie zmiany pęcherzykowej bliżej nieokreślonej przy braku wskazań klinicznych nie jest podstawą do wszczęcia postępowania chirurgicznego. **(Endokrynol Pol 2016; 67 (1): 12–16)**

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

Introduction

The progress of ultrasonographic techniques and methods of interpretation of Fine-Needle Aspiration (FNA) cytology caused an increase in the value of this test in routine diagnostics of thyroid nodules. The implementation of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) as a standard in FNA evaluation improved clinical management (Table I). FNA is an accessible, cost-effective, quick and safe method, and the diagnostic success depends on the performance and right interpretation. The categorisation of cytological

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Table I. *The Bethesda System for Reporting Thyroid Cytopathology: Implied risk of malignancy and recommended clinical management [2]*

Tabela I. Klasyfikacja cytopatologii tarczycy według systemu Bethesda [2]

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

The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

diagnoses in six groups allowed improvement in the communication and specifying of the right clinical management [1–6].

Diagnostic category III (DC III): atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) has been the most controversial category of the BSRTC. It is a category of exclusion, which should be used exceptionally — in up to 7% of cytological reports [7]. The images from this group usually do not fulfill the criteria of other groups and require correlation with clinical presentation along with repeat FNA. The expected risk of malignancy in this class ranges between 5 and 15% [2, 7]. The creation of this category reduces the malignancy risk and the number of unnecessary surgical interventions in favour of repeat FNA and correlations of cytological, clinical, and ultrasonographic presentation [7, 8].

BSRTC was introduced for the evaluation of cytological smears from thyroid FNA in 2010 in Poland, hence the creation of DC III improved the dialogue between the surgeon, the endocrinologist, and the pathologist, and what is most important, precisely defined the clinical management.

The six-tier scale established by the Polish Workgroup is accurately characterised and contains some minor alterations to the one proposed by the NCIS. In "our" scale there is an exact description of DC III: "The aspirate should be rather cell-rich, with marked domination of small structures (groups, nests, rosettes) on the colloid background. Such elements as macrophages, lymphocytes, or plasma cells are admissible. This category is not an indication for surgical treatment and the biopsy should be repeated." The Polish Workgroup excluded the criterion of cellular atypia from our definition [9]. We believe this minor modification carries important clinical implications, which are reflected in our analysis.

The aim of the study was to specify the risk of malignancy in patients with FLUS diagnosis in the material from the Institute of Oncology in Gliwice.

Material and methods

16,656 reports of thyroid FNA were generated in the Department of Tumour Pathology of Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch from January 2010 to April 2015. All FNAs were performed in two-person teams including a pathologist and a radiologist, under ultrasound guidance. The material was obtained by 25-gauge needles, and direct smears were alcohol-fixed and stained with haematoxylin-eosin. All of the evaluations and reports 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. Our analysis concerns 395 diagnoses of DC III that were rendered from January 2010 to April 2015.

Results

We analysed 16,656 FNA, from which DC III was reported in 395 cases (Fig. 1 and 2). After initial diagnosis of DC III, 180 (45.5%) patients underwent repeat FNA, 27 (6.8%) patients were operated on, and 188 (47.6%) did not undergo additional sampling or surgery at the study institution and were moved to surveillance. Twenty-seven thyroidectomies after initial DC III yielded six cancers and 21 benign changes. In 180 cases repeat FNA was performed, from which the diagnosis of DC I or DC II was established 109 times (60.5%); 41 (22.7%) patients again obtained DC III (36 were put under observation after that, five had another [third] FNA). The remaining 30 patients had DC IV, DC V, or

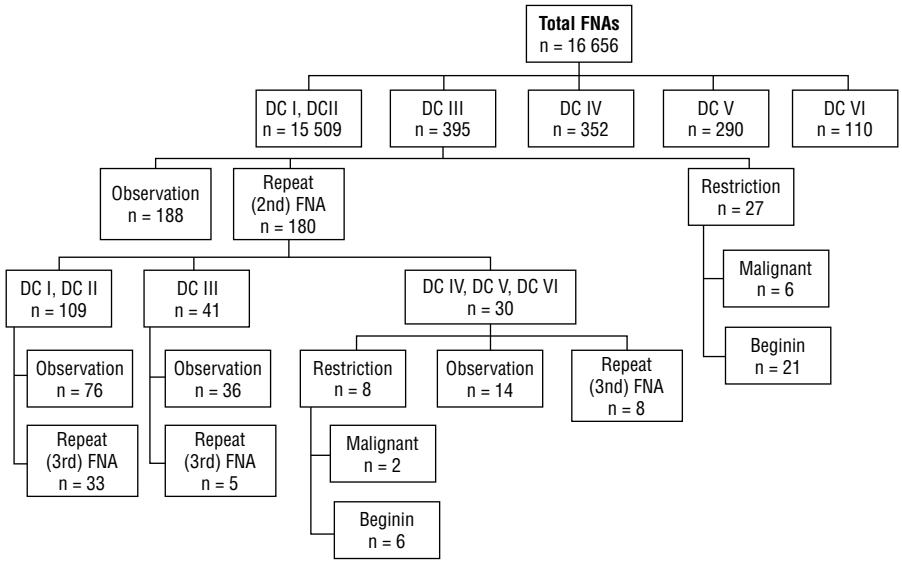

Figure 1. *CONSORT diagram of the study group*
Rycina 1. *Diagram CONSORT analizowanej grupy pacjentów*

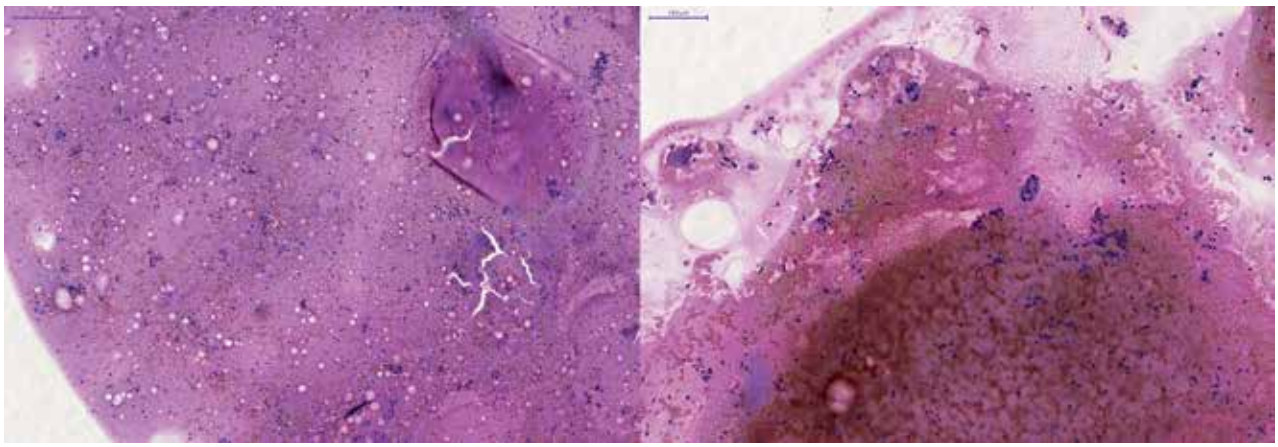

Figure 2. *Representative examples of Bethesda Diagnostic Category III FNAs. Staining: haematoxylin-eosin*
Rycina 2. *Reprezentatywne przykłady rozmazów z biopsji aspiracyjnej cienkoigłowej tarczycy z kategorii III klasyfikacji Bethesda. Barwienie: hematoksylina-eozyna*

DC VI, from which eight were treated surgically (two cancers, six benign changes), and 14 were subjected to observation. Altogether, third FNA was performed in 46 cases, giving DC III (10×), DC IV, V, VI (3×), and DC I or II (33×). Four and more FNAs were performed in 10 (in 395) patients (4× DC III, 1× DC V, 5× DC I or II), and all these patients were being further observed. In summary, from 395 FNAs with DC III, 34 patients underwent surgery (27 after first diagnosis of DC III and eight after second biopsy diagnosis of DC IV, V, or VI) obtaining the histopathological reports of six cancers after first biopsy with DC III diagnosis, and two cancers after second biopsy with the diagnosis of category of higher acuity than DC III.

Discussion

The Bethesda System allows qualification of FNA diagnoses to six categories, which eases subsequent clinical management. It supports providing a brief diagnosis (as the description of the cytological image might be too expanded and illegible), hence defining the level of risk assigned to each of the six categories. The suggested frequency of DC III reporting is about 7%, and the expected risk of malignancy assigned for DC III is in the range of 5–15%. The most important feature of DC III is the definition of patients' management. The Bethesda System in principle recommends repeat FNA if there are no other clinical implications.

In 16,656 examined FNAs we obtained 395 FLUS, which comprises 2.3%. The percentage of DC III considerably varies between the studies. Kholova et al. presented a meta-analysis of 20 retrospective and six prospective studies. The percentage of DC III is variable, ranging from 0.8% to 27%. It was observed that the most numerous groups that were analysed (7–8000 FNAs) obtained the percentage of 2–3% [10]. Harvey et al. in their analysis achieved a ratio of 2.3% (79/3432), similar to ours [8]. Broome et al. stated in their study that the number of DC III diagnoses in their institution comprised 10%; moreover, they demonstrated how this percentage altered in particular years: 7.4%, 11.8%, 11.5%, 8.3% in 2009–2012, respectively [11]. In the literature there are some studies available which show a definitely higher percentage of DC III. The research of Jo et al. revealed 15.5% AUS (61/393) [12]. Similar results were displayed in a prospective study based on a small study group (11 AUS/225 FNA), in which the observation was continued only for two years [13].

FNA evaluation requires long experience and wide cytological knowledge. The possibility of consultation between the competent pathologists regarding aspirates examination is essential. Most of the shown analyses concern the work of cytopathologists or pathologists that deal with cytological diagnostics of the thyroid on a daily basis [1, 4, 10, 11]. The authors of one of the large studies base the initial diagnostics on the work of screeners. However, the published data do not differ from other analyses [8].

The Bethesda System imposes a certain scheme of procedure and sets the clinical indications: DC III diagnosis is to be followed by repeat FNA.

In our study, after obtaining DC III in 395 patients 180 (45.5%) had repeat FNA (215 patients were either operated on or put under observation). In the study by Srbova et al. we encountered similar numbers: 57% of repeat FNA [14]. One hundred and eighty-nine patients did not undergo invasive procedures, which may mean that they resigned from repeat FNAs and were subjected to observation only, or were moved to other medical centres. The remaining 180 patients followed the recommendations strictly.

Other researchers indicated that repeat FNA after initial DC III was performed in 6.8% [7] and 33% [11] of cases, and a meta-analysis of 10 studies demonstrated an average performance of repeat FNA ranging from 9.39% to 20.5% [10]. In the study repeat FNA was performed 26 times, which comprises 46.4% [15]. These data are considerably divergent, but that probably depends on different socio-economic conditions. Broome et al. mentioned that the factor that directly influenced the number of repeat FNAs, and hence the number of surgical interventions was the patient's decision [11]. Patients that do not accept the "wait and watch" approach can choose thyroidectomy. In our medical centre, following the National Health Fund recommendations and taking into consideration that the queues for oncological treatment are long, the waiting time for an operation for patients with double DC III diagnosis is at least six months. Taking this into account, the recommendation of repeat FNA after first diagnosis of DC III is usually followed. Our patients do not have the possibility to choose either "watchful waiting" strategy and a repeat FNA after six months or a more radical procedure, which is less stressful for them.

In our analysis, after first DC III diagnosis 27 (6.8%) patients were subjected to surgical treatment because of urgent clinical indications (enlarged and/or suspicious lymph nodes, active neoplastic disease or family history of cancer). In the world, many resections are performed after initial DC III diagnosis. The authors of many articles explained that the reason is the concern about the patients and bending to their will when they do not want to wait, be observed, and subjected to repeat FNA after the initial diagnosis of an unequivocal change. Ho et al. in the analysis of 541 DC III diagnoses reported surgical removal in 350/541 (64.7%) cases [7]. Harvey et al. showed 25% (18/72) of excisions [8].

Even if for the sake of patient the number of surgical procedures is high, the percentage of operations before and after the implementation of the Bethesda System has diminished significantly. Joy et al. compared two groups of patients: one categorised before the creation of Bethesda System (BS) and another, similar in number, in which the diagnoses were compatible with the recommendations of the BS. The researchers noticed that the implementation of DC III caused a reduction in the number of thyroidectomies [15].

The limitation of unnecessary surgical interventions is at the opposite pole of the problem of assessing the risk of malignancy after DC III diagnosis. In our institution operations after initial DC III diagnosis concerned 27/395 (6.8%) patients. They were performed because of urgent clinical indications when the cytological diagnosis (DC III) did not correspond with the suspicious clinical picture. There were 6/27 (22%) malignant changes operated after first DC III diagnosis; altogether cancers comprised 6/395 (1.5%).

Altogether we reported 8/395 (2.02%) cancers after two FNAs. Subsequent FNAs did not give the diagnoses of cancer (46 patients had three FNAs, 10 had four or more FNAs).

Ho et al. in the analysis of 541 DC III cases described 350/541 (64.7%) operations. More than half of their patients were operated on "offhand". They received 135 diagnoses of malignancies (38.6%), and after subsequent FNA with DC III 12 patients had surgical

treatment, obtaining four diagnoses of malignancies [7]. Meta-analysis based on 26 studies showed 34% risk of malignancy [10]. Wu et al. reported 7% risk of malignancy [5].

It appears that risk of malignancy shown as this, regardless of so much data, is unclear for DC III, because the divergence of the results presented by the researchers is quite remarkable and depends on many factors, such as the size of the group, strict following of the recommendations of the Bethesda System, and the clinical consequences.

We have to admit that we operate on far fewer patients, but not only due to the long queues for the surgical treatment. It appears that DC III — FLUS adapted by us by elimination of the cytological specimens containing atypical cells became more uniform and more effective in reducing the risk of malignancy for this category. The recommended risk of malignancy for a nodule with this diagnosis in Poland was not supposed to exceed 5% in the assumptions made by the Polish Workgroup [9]. After first FNA with DC III diagnosis we operated on 27 patients receiving reports of six cancers, after second BAC we obtained two diagnoses of malignancies. In eight cases operated on in this series previous cytological diagnosis of cancer was histopathologically confirmed in two patients. Third and subsequent FNA was performed in 46 patients, and in one case there was a suspicion of malignancy, but there were no operations performed.

In our material the risk of malignancy in Follicular Lesion of Undetermined Significance is 2.78%. Taking into account all repeated 56 FNAs with confirmation of primary DC III diagnosis, the risk diminishes to 2.43%. Broome et al. showed higher risk of malignancy (9.2%) in this category [11], Chen et al. reported 19% [15], Ho et al. presented 38.6% after first FNA on a group of 8862 patients [7].

The researchers praise the clarity of the Bethesda System and its simple transfer to clinical recommendations, resulting in the limitation of the number of unnecessary surgical interventions. We cannot ignore major differences in the assessment of malignancy risk and considerable divergences in applying the recommendations of the Bethesda System. Our definition of DC III without the group of atypical changes appears to be clearer and hence carries lower risk of malignancy and a smaller percentage of surgical interventions.

Conclusions

In the analysed material, the risk of cancer in patients with FLUS is 2.78%. Taking into account all 56 subsequent FNABs in which the primary diagnosis was confirmed, the risk decreases to 2.43%.

The diagnosis of FLUS in the absence of clinical indications is not a basis for surgical treatment.

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