

Unified cytological reports determine the clinical management

Unifikacja raportów cytologicznych ułatwia właściwe postępowanie kliniczne

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Medical Studies/Studia Medyczne 2019; 35 (2): 147–152

DOI: <https://doi.org/10.5114/ms.2019.86334>

Key words: cervical cytology, thyroid biopsy, pancreatic biopsy, Bethesda system.

Słowa kluczowe: cytologia szyjki macicy, biopsja tarczycy, biopsja trzustki, system Bethesda.

Abstract

All types of cytological procedures bear a burden of unequivocal reports and confusion with setting a proper clinical procedure. In 1989, The Bethesda System (TBS) was introduced to resolve many concerns in the matter of unclear classification of changes in cervical cytology. The guidelines of TBS were based on the clinical data provided, the quality of the smear assessment, unification of terminology, and updated knowledge about changes underlying cell abnormalities. It is believed that both TBS and thyroid TBS inspired the members of the Papanicolaou Society of Cytology to design and publish a modern approach to pancreatic lesion description. The presented proposal created a strong foundation for clinical management and revealed a serious risk of underdiagnosis. In light of the short time since the launch of this guide, more time is needed to estimate its impact, especially since only a few clinical centres have implemented it to this day.

Streszczenie

Wszystkich typów badań cytologicznych dotyczy problem dwuznacznych wyników, które utrudniają wdrożenie właściwych procedur leczniczych. Aby rozwiązać wiele wątpliwości wynikających z niejasnej klasyfikacji zmian w cytologii szyjki macicy, w 1989 roku stworzono system określony od miejsca powstania jako „Bethesda system”. Jego podstawowe zasady oparto na dostarczonych danych klinicznych, ocenie jakości materiału, ujednoczeniu terminologii, jak również na zaktualizowanej wiedzy o zmianach patologicznych w komórkach. Po zakończonym sukcesem włączeniu go do użytku podobne rozwiązania wdrożono do raportowania biopsji tarczycy. Można podejrzewać, że to zainspirowało członków Papanicolaou Society of Cytology do opublikowania systemu klasyfikacji zmian guzowatych trzustki. Z perspektywy czasu można powiedzieć, że system Bethesda oceny zmian w szyjce macicy i w tarczycy został bardzo chętnie zaakceptowany przez patologów i klinicystów, a przedstawione klasyfikacje stworzyły fundament dla ujednoczonego postępowania klinicznego. Wydaje się, że obiektywna ocena wpływu przedstawionych propozycji na proces diagnostyczny wymaga więcej czasu.

Introduction

Every day, physicians struggle with many unclear cytological reports, which raises a serious concern of incorrect diagnosis, triage, treatment, and also a patient care. There is no doubt that proper categorisation and repeatability of cytological methods is crucial for unification. The implementation of a diagnostic algorithm based on frame construction is willingly accepted and implemented by all professionals, but comparability of self-observations with others is

equally important. Low cost and relatively high adequacy ratio of fine needle aspiration biopsy as well as exfoliating cytology have been broadly used in screening and tumour diagnosis. The last two decades have unveiled a deep necessity of cytological report regulation, not only for better clinical communication but also for repeatable categorisation. Cytological specimen quality and clear separation of benign and malignant lesions with the formulation of a grey-zone of the unequivocal pattern were emphasised to rationalise new rules of categorisation. The efforts of thou-

sands of people involved in this created a milestone for further unification. It is our recent heritage, which should be widely implemented [1].

In the late 1980s, The Bethesda System (TBS) was introduced to unify the terminology of cervical cytology. The name comes from the National Institutes of Health in Bethesda, Maryland, USA where cervical cytopathology workshops were conducted. During this time the three principal rules of the TBS were created: the relevance of information provided by the clinician to the laboratory, the unification and rationality of terminology used, and updated knowledge about the underlying pathway. Moreover, TBS has made a very important step forward in describing specimen quality as a crucial factor of the cytological report. It is extremely important to highlight that low-quality cytological samples should be excluded from examination, or at least its limitations should be clearly emphasised. Intensive research of cervical morphological changes and access to the vast panel of diagnostic tools, such as liquid-based cytology (LBC), computer-assisted imaging, and high-risk HPV test, resulted in the TBS update in 1991 and then once more in 2001. The last modification, which mainly covered LBC approaches in screening, was conducted in 2014 [2–4].

Also, the National Cancer Institute, Bethesda, Maryland hosted a conference devoted to thyroid fine needle aspiration biopsy in 2007. During the workshop, a frame to the interpretation of cytological reports and better clinical communication were established and described. As a mirrored image of the original TBS, the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) was launched. It was the first time that quality criteria concerning fine needle biopsy cellularity and smear quality were described in detail. Therefore, all reporting categories launched were bound with the recommendations of patient management. Over 10 years of experience has proven that the implemented third group has been very helpful in this regard, as well as in avoiding unnecessary surgeries [5–9].

Cytopathologists have gathered together, and in cooperation with the Papanicolaou Society of Cytopathology have presented the fruit of their experience in pancreatic cytopathology. A practical guide was published in 2015. Pitman *et al.*, inspired by the canonical numerical Papanicolaou classification, decided to set a six-tiered system, which is quite similar to the BSRTC (Table 1) [10–13].

Looking at Table 1, we can observe the similarity of the three classifications described above. The shelf-like construction provides a smooth flow of clinical-pathological communication and better patient care. Although they concern completely different organs, the clinical procedures are similar when the same level of categorisation is assumed.

The successful wide acceptance of both TBS and BSRTC had to have common reasons. Similarly to TBS, the generic BSRTC and Papanicolaou Society of Cytopathology system for reporting pancreaticobiliary cytopathology clearly separates benign, unequivocal, suspected of malignancy, and finally malignant categories. The understanding of the motives driving these changes should guide the future management.

Cervical cytology

The low level of cervical Pap screening accuracy led to the assessment of smear quality and then categorisation of unequivocal cases by ASC-US (atypical squamous cells of undetermined significance), AG-US (atypical glandular cells of undetermined significance), and ASC-H (cannot exclude HSIL) formulation. Moreover, for a better division of low- and high-grade lesions, the two-tiered frame-division on LSIL and HSIL (low/high-grade squamous intraepithelial lesion) was implemented. The TBS enforced strict rules of specimen quality evaluation, which allow precise cytological reporting. The procedure was designed to qualify only those diagnostic specimens that provide the most accurate results. Therefore, clinicians or screening providers who use the results for further diagnosis or treatment have clear outlines of the procedures.

The TBS has replaced three-tiered ‘dysplasia’ and ‘carcinoma in situ’ with the two-tiered system, namely LSIL and HSIL, which made the results more repeatable and accurate.

Additionally, that division is crucial for triage, especially in the context of colposcopy referral. Currently, high-risk human papilloma virus (HPV) evaluation is becoming standard and could completely replace cervical smears, so some serious changes in the TBS can be expected [14, 15].

Grey-zone categories implemented in TBS, such as ASC-US, ASC-H, and AG-US, reach a new significance if we can dissolve that unequivocal cytological pattern. The launch of the LBC has improved the accuracy ratio of HSIL and decreased the ASC-US ratio. Moreover, to fix that problem the p16/Ki67 test and hrHPV genotyping were also employed [16–21]. Finally, well-designed categorisation with the assistance of cutting-edge solutions allows a very high level of accuracy. Recent Polish research applying strict TBS rules and modern solutions depicts HSIL detection with an accuracy ratio of almost 90%. There were some correlations noted between positive p16/Ki-67 and positive Pap test ($p < 0.001$; 66% sensitivity (95% CI: 51.2–78.8%), 87.8% specificity (95% CI: 75.2–95.4%), 76.8% accuracy (95% CI: 67.2–84.7%), and OR = 13.9 (95% CI: 4.9–39.2)), especially HSIL and HPV16 ($p < 0.001$; sensitivity (95% CI) 64.0, specificity (95% CI) 98.4, accuracy (95% CI) 88.6, OR (95% CI) 109.3) [20]. Of note, these data were similar to those ob-

Table 1. Comparison of three implemented algorithms to divide all possible cytological findings

	Cervical TBS	Thyroid TBS	Pancreatobiliary cytopathology
Specimen adequacy (specimen quality assessment)	Satisfactory for evaluation or not	Group 1 Non-diagnostic or unsatisfactory	Non-diagnostic
Negative for malignancy	<ul style="list-style-type: none"> a. Infection b. Squamous metaplasia c. Keratotic changes d. Tubal metaplasia e. Atrophy f. Pregnancy-associated changes g. Radiation h. IUD – associated changes 	Group 2 Benign	Negative for malignancy: <ul style="list-style-type: none"> a. Benign pancreatic tissue (in an appropriate clinical setting) b. Acute pancreatitis c. Chronic pancreatitis d. Autoimmune pancreatitis e. Pseudocyst f. Lymphoepithelial cyst g. Splenule/accessory spleen
Epithelial cell abnormalities	<ul style="list-style-type: none"> 1. Atypical squamous cells of undetermined significance (ASCUS), cannot exclude HSIL (ASC-H) Atypical glandular cells of undetermined significance (AGUS) 1. Squamous intraepithelial lesion: <ul style="list-style-type: none"> a. LSIL b. HSIL 	Group 3 Atypia of undetermined significance or follicular lesion of undetermined significance AUS, FLUS	Atypical cells (undetermined significance)
		Group 4 Follicular neoplasm or suspicious for follicular neoplasm	Neoplastic: <ul style="list-style-type: none"> a. Serous cystadenoma b. Neuroendocrine microadenoma c. Lymphangioma d. Well-differentiated neuroendocrine tumour e. Intraductal papillary mucinous neoplasm, all grades of dysplasia f. Mucinous cystic neoplasm, all grades of dysplasia g. Solid-pseudopapillary neoplasm
		Group 5 Suspicious for malignancy	Suspicious for malignancy
		Group 6 Malignant	Positive or malignant: <ul style="list-style-type: none"> a. Ductal adenocarcinoma of the pancreas and its variants b. Cholangiocarcinoma c. Acinar cell carcinoma d. Poorly differentiated (small and large cell) neuroendocrine carcinoma e. Pancreatoblastoma f. Lymphoma g. Metastatic malignancy
	Malignant		
	<ul style="list-style-type: none"> a. Squamous cell carcinoma (SCC) b. Adenocarcinoma c. Other 		

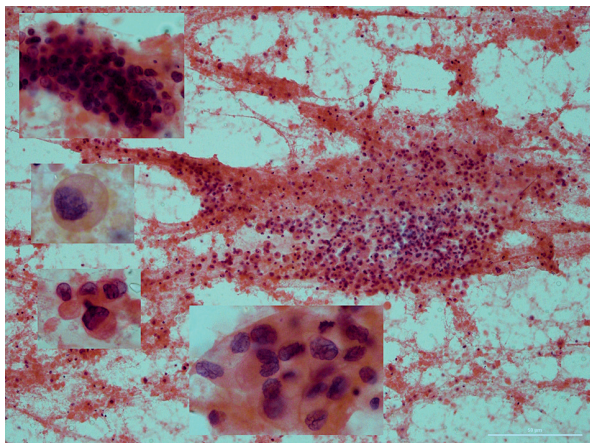


Figure 1. A biopsy taken from a solid cystic pancreatic lesion of a 55-year-old man. In haemorrhagic and necrotic background singular, and groups of, highly atypical cells resembling cancer cells can be seen. The case was categorised as indeterminate atypia and was caused by onset of acute pancreatitis

tained in the other large-cohort studies, which proves their repeatability and high efficiency [17–19]. The accuracy value varies significantly, with 30% efficiency of the traditional Pap smear performed in the past.

Thyroid cytology

A comparison of thyroid biopsy reports from before and after the BSRTC age shows a significant difference in frequency of cases between benign and those suspicious for malignancy. During the last 10 years some specific studies touching on selected aspects of the BSRTC have been published. As an example, Krauss *et al.* in a meta-analysis of malignancy risk in TBS showed relevant results of growing cancer risk in classes III–V [22]. Other research pointed out the overuse of AUS/FLUS (atypia of undetermined significance or follicular lesion of undetermined significance) due to the lack of clear diagnostic criteria and remarkable pathologists subjectivism [23]. Therewithal, it is worth noting that the ratio of ‘suspicious for papillary thyroid carcinoma’ led to higher diagnostic accuracy in the post-TBSRTC period than in the pre-BSRTC one [24]. Recently, a comprehensive paper by Jarzab *et al.* [25], as a Polish think tank, recommended that effective diagnosis and treatment of a thyroid cancer should be a multicentre experience. Their own 10-year observation related to BSRTC implementation was presented as well as a strict algorithm for patient management and for the biopsy procedure itself. The paper pointed out how to resolve the most common concerns, such as AUS/FLUS (third group) and “follicular neoplasm” (fourth group). All of the recommendations presented based on the BSRTC proved the significant value of categorisation in patient treatment

[25]. To summarise, a thesis could be stated that strict regulation and maintaining a high quality of biopsy provides a high accuracy ratio in detecting thyroid cancer and helps to avoid unnecessary surgeries.

Pancreatic cytology

The Papanicolaou Society guidelines are less studied than TBS or BSRTC for an obvious reason: they are simply newer. According to Perez-Machado, a second look at the analysis of pancreatic smears after the publication of a new guide has changed the primary diagnosis. Former 30.9% negative samples were replaced with 23.9%, and 18.7% of atypical samples were split into other, new categories and gained a completely new meaning [25]. This terminology covers the most frequent pancreatic entities and is the first step towards a unified nomenclature. An important and very practical aspect of this system is a recognition of the established need to reach the cytological diagnosis in the context of the radiological findings as well as the importance of incorporating into our reports the biochemical analysis of cystic fluids, immunoprofile, and molecular analysis [26]. In the past, studies of unequivocal cases of pancreatic biopsy were reported in which the term “atypical cells in inflammatory background” was used. That problem occurs in both endoscopic ultrasonography fine needle aspiration (EUS/FNA) and percutaneous fine needle aspiration (PCFNA) biopsies and usually results from necrosis, cystic degeneration, or sometimes massive inflammation in the vicinity of a drainage tube into the compressed common biliary duct [27–29]. From a time-perspective, the molecular solutions and immunocytochemistry barely support correct diagnosis and proper patient management. Additionally, diagnosis of cystic lesions should be backed up by NRAS, GNAS testing. Biliary tract brush cytology has been somewhat abandoned because of its low-level diagnostic ratio. This simple non-traumatic method could provide a more accurate diagnosis than directed focal biopsy because the entire surface is sampled and dedicated fixative solutions might be accompanied by immunohistochemistry and molecular assays. It is still underappreciated, although it could be a helpful tool for cancer diagnosis and for biliary tract screening among patients with chronic biliary tract gallstones.

Even though pancreatobiliary cytological nomenclature varies between centres, it is clear that there is an urgent need for consensus, to provide good clinicopathological communication and comparable research results. That is why we should speak the same language and why unification is crucial.

Conclusions

The presented approaches, used to describe cytological reports, demonstrate a similar frame construc-

tion, and they were willingly accepted and implemented in daily practice by clinicians. It seems that they provided a good solution to minimise the risk of cancer under-diagnosis. Given the availability of high-quality specimens and possible molecular support, these methods, which reduce trauma for the patient, have gained new diagnostic value.

Conflict of interest

The authors declare no conflict of interest.

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