УДК 616.316-076

Бублик Дарья Сергеевна

Врач клинический цитолог, врач КЛД, врач-патологоанатом

ФГБУ «ФНКЦ КМиБ» ФМБА России,

г. Москва, Россия

ЦИТОЛОГИЧЕСКАЯ ДИАГНОСТИКА ВОСПАЛИТЕЛЬНЫХ И РЕАКТИВНЫХ ПРОЦЕССОВ В СЛЮННЫХ ЖЕЛЕЗАХ: ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА С НИЗКОЗЛОКАЧЕСТВЕННЫМИ ОПУХОЛЯМИ

Аннотация: Воспалительные, обструктивные и реактивные процессы слюнных желез могут сопровождаться цитологическими признаками, сходными с проявлениями низкозлокачественных опухолей, что повышает риск ошибочной интерпретации тонкоигольной аспирационной биопсии. Цель работы состоит в систематизации диагностически сложных цитологических сценариев и уточнении последовательности их разграничения с мукоэпидермоидной, ациноклеточной и секреторной карциномами. Выделены морфологические признаки сходства и признаки, повышающие вероятность опухолевого процесса. Предложена последовательность оценки материала с учетом его репрезентативности, фона препарата, эпителиального компонента, клинико-визуализационного соответствия, категорий Milan System и целевых дополнительных исследований.

Ключевые слова: слюнные железы, цитология, сиалоаденит, реактивные изменения, мукоэпидермоидная карцинома, ациноклеточная карцинома, Milan System.

Daria Bublik

Clinical cytologist, clinical laboratory diagnostics physician, pathologist

Federal Scientific and Clinical Center for Medical and Biological Research,

FMBA of Russia,

Moscow, Russia

CYTOLOGICAL DIAGNOSIS OF INFLAMMATORY AND REACTIVE PROCESSES IN SALIVARY GLANDS: DIFFERENTIAL DIAGNOSIS WITH LOW-GRADE MALIGNANT TUMORS

Abstract: Inflammatory, obstructive, and reactive salivary gland processes may show cytologic features overlapping with low-grade malignant tumors and may therefore complicate fine-needle aspiration interpretation. The aim of this study is to systematize diagnostically challenging cytologic scenarios and to refine the sequence for distinguishing them from mucoepidermoid, acinic cell, and secretory carcinomas. Morphological features of overlap and features increasing the likelihood of neoplasia were identified. A stepwise assessment is proposed that considers specimen adequacy, smear background, epithelial component, clinicoradiologic concordance, Milan System categories, and targeted ancillary studies.

Keywords: salivary glands, cytology, sialadenitis, reactive changes, mucoepidermoid carcinoma, acinic cell carcinoma, Milan System.

Fine-needle aspiration (FNA) is used for the preoperative morphological assessment of salivary gland lesions and enables cytological findings to be correlated with the risk of neoplasia and subsequent management. The greatest diagnostic challenges arise in hypocellular, cystic, and inflamed aspirates, as reactive atypia, metaplasia, and degenerative changes may partially overlap with the morphology of low-grade malignant tumors. The second edition of the Milan System for Reporting Salivary Gland Cytopathology assigns an estimated risk of malignancy of 11% to category II, “Non-Neoplastic,” 30% to category III, “Atypia of Undetermined Significance” (AUS), and 35% to category IVB, “Salivary Gland Neoplasm of Uncertain Malignant Potential” (SUMP). In view of these estimates, cytological findings should be correlated with clinical and imaging data [1].

The spectrum of non-neoplastic changes includes acute and chronic sialadenitis, granulomatous inflammation, sialolithiasis and associated obstructive changes, lymphoepithelial sialadenitis, cystic changes, sialadenosis, and reactive changes in acinar and ductal epithelium. Acute inflammation is characterized by a predominance of neutrophils, debris, and degenerating cells. Chronic inflammation more commonly produces a lymphocytic background, with reduced representation of normal acini and small groups of ductal epithelial cells. Obstruction promotes the accumulation of macrophages and mucus, cystic transformation, and squamous, mucinous, or oncocytic metaplasia. Granulomatous inflammation is characterized by epithelioid histiocytes and multinucleated cells. Necrotizing sialometaplasia further expands this spectrum through the combination of ischemic injury, necrosis, and squamous metaplasia; in minor salivary glands, this pattern particularly requires consideration of lesion location and clinical course [2].

The risk of a false-positive cytological diagnosis of neoplasia is determined by a combination of several features:

1) reactive cells may exhibit enlarged nuclei, prominent nucleoli, and moderate variation in cell size;

2) reparative ductal epithelium may form cohesive and three-dimensional groups;

3) metaplasia may result in the appearance of squamous, mucinous, or oncocytic cells;

4) acinar injury may lead to increased cytoplasmic vacuolization and granularity.

Cystic aspirates pose a particular diagnostic challenge, as they may contain abundant mucus, macrophages, and inflammatory cells, while the diagnostically informative epithelial component remains scant.

The presence of an inflammatory background does not, however, confirm the non-neoplastic nature of the lesion, as lymphoid cells, necrosis,

macrophages, and secretions may also be associated with neoplasms, while reactive atypia in an injured gland may be more pronounced than the cellular atypia seen in some low-grade carcinomas. The main sources of error in salivary gland cytology include non-representative aspiration, overinterpretation of metaplasia, underrecognition of a scant monomorphic neoplastic cell population, and interpretation of individual cellular features without consideration of the overall smear background [3].

For practical assessment, non-neoplastic changes can be grouped according to the predominant cytomorphological pattern: inflammatory, obstructive-cystic, metaplastic-reparative, and acinar-reactive. This classification links the mechanism of glandular injury to the expected smear background and to the feature that may create a false impression of neoplasia (see Fig. 1).

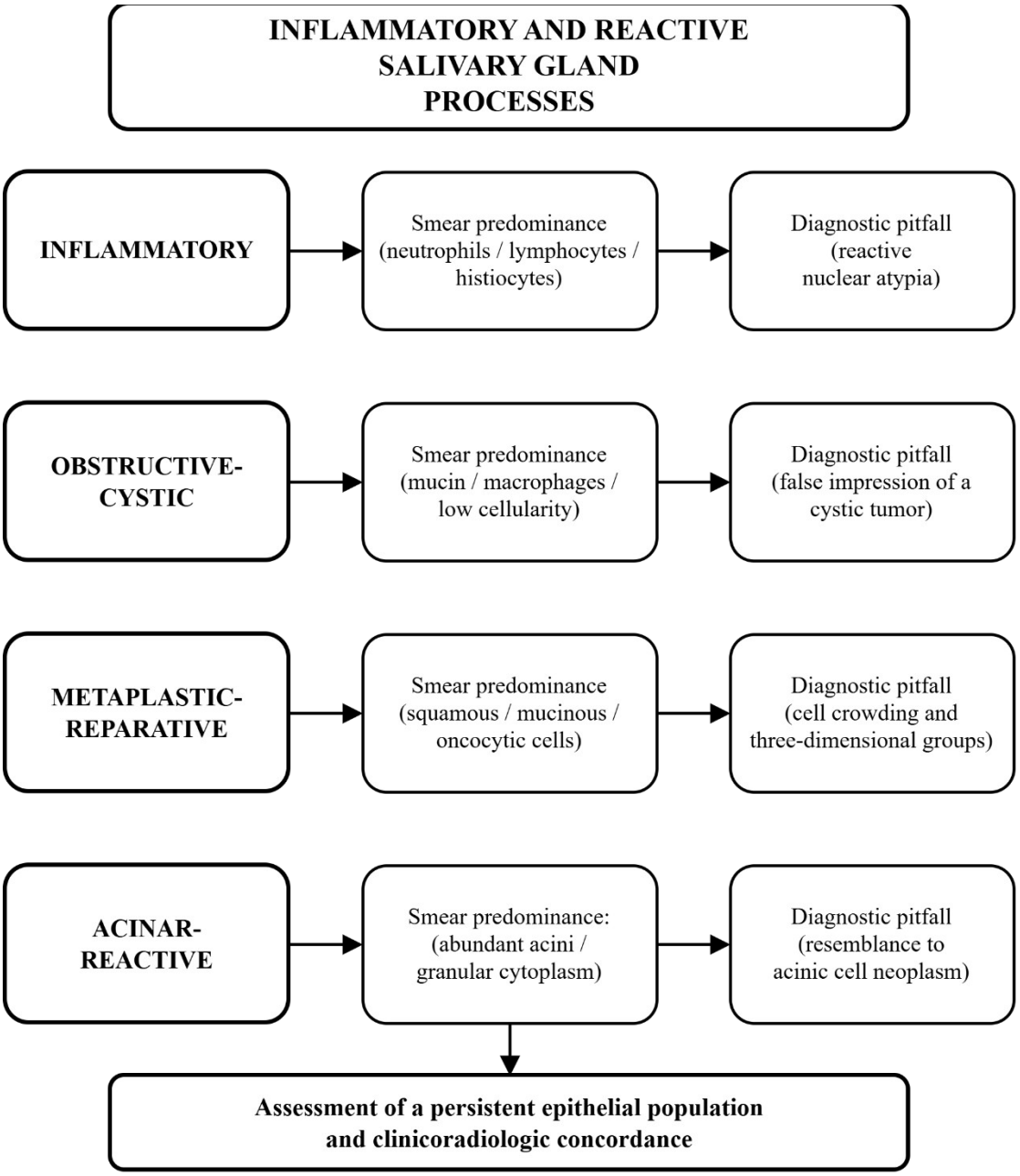

Fig. 1. Classification of cytological patterns of inflammatory and reactive processes in the salivary glands

Among low-grade malignant tumors, particular attention should be paid to mucoepidermoid, acinic cell, and secretory carcinomas, which may show only mild nuclear atypia, while cystic or inflammatory components may sometimes predominate in the aspirate. Therefore, initial recognition should be based on the combined assessment of cellular composition, cell arrangement, and background features, followed by formulation of a focused differential diagnosis [4].

In chronic obstructive sialadenitis with mucinous or squamous metaplasia, the principal neoplastic mimic is low-grade mucoepidermoid carcinoma. The overlap is due to the presence of mucus, a cystic background, and metaplastic cells. A reproducible epithelial population comprising mucous, intermediate, and epidermoid cells favors carcinoma. In entirely or predominantly cystic variants, one of these components may be extremely scant; therefore, abundant mucus in the absence of a convincing neoplastic cell population is insufficient for a definitive diagnosis. When the morphology raises suspicion, MAML2 rearrangement provides additional confirmatory evidence [5].

Distinguishing reactive acinar changes and sialadenosis from acinic cell carcinoma requires assessment of the reproducibility of the cell population. Abundant serous acini with granular cytoplasm may be present in aspirates from normal or reactively altered salivary glands. A neoplastic process is more likely when there is a persistent predominance of a uniform acinar cell population, loss of the normal proportion of acinar and ductal elements, formation of cohesive groups, and granular or vacuolated cytoplasm in the appropriate clinical context. In diagnostically challenging cases, the immunohistochemical markers NR4A3 and DOG1 may be useful; however, the results of any marker should be interpreted in conjunction with the morphological findings.

Secretory carcinoma may mimic a cystic or reactive lesion because of cellular monomorphism, vacuolated cytoplasm, and a secretory background. More concerning features include recurrent three-dimensional, microcystic, or papillary groups, intracellular secretions, and a persistent uniform cell population. ETV6 rearrangement, most commonly resulting in an ETV6::NTRK3 fusion, is characteristic of this tumor. Immunoreactivity for S100, mammaglobin, and pan-TRK may support the diagnostic impression; however, in cases with equivocal morphology, definitive confirmation relies on molecular testing [6].

The main differential diagnostic pairs and the features that allow progression from general morphological overlap to a well-founded suspicion of neoplasia are presented in Table 1.

Table 1. Main differential diagnostic pairs in inflammatory and reactive salivary gland lesions

Process / neoplastic mimic	**Features creating diagnostic overlap**	**Features favoring neoplasia**
Chronic obstructive sialadenitis / low-grade mucoepidermoid carcinoma	mucus, cystic background, squamous and mucinous metaplasia	reproducible population of mucous, intermediate, and epidermoid cells; MAML2
Sialadenosis, reactive acinar changes / acinic cell carcinoma	abundant acinar cells, granular or vacuolated cytoplasm	persistent monomorphic population, disruption of the normal acinar-ductal composition; NR4A3, DOG1
Inflammatory or cystic process / secretory carcinoma	macrophages, vacuolization, secretory background, mild atypia	recurrent three-dimensional, microcystic, or papillary groups; S100, mammaglobin; ETV6

Cytological assessment begins with evaluation of specimen adequacy; a hypocellular sample from a cystic lesion cannot be considered sufficient to account for a persistent solid component. The predominant background is then characterized as neutrophilic, lymphoid, granulomatous, cystic with macrophages, mucinous, secretory, or necrotic, followed by assessment of the epithelial component, including its quantity, reproducibility of cell groups, cytoplasmic features, the nature of nuclear changes, and their relationship to the smear background. In cystic aspirates, it is essential to determine whether the specimen contains material from the wall or solid component of the lesion, as the absence of such cells limits the negative predictive value of the cytological diagnosis.

Clinicocytological correlation completes the morphological assessment:

– Milan category II is appropriate for an adequate specimen without convincing atypia when the cytological findings account for the lesion and are concordant with imaging findings;

– category III, atypia of undetermined significance (AUS), is used for reactive or metaplastic changes that exceed the usual range of a non-neoplastic process but are insufficient to establish a definite neoplasm;

– category IVB, salivary gland neoplasm of uncertain malignant potential (SUMP), is applicable when a definite neoplastic population is present but its benign or malignant potential cannot be reliably determined on cytological material (see Figs. 2 and 3).

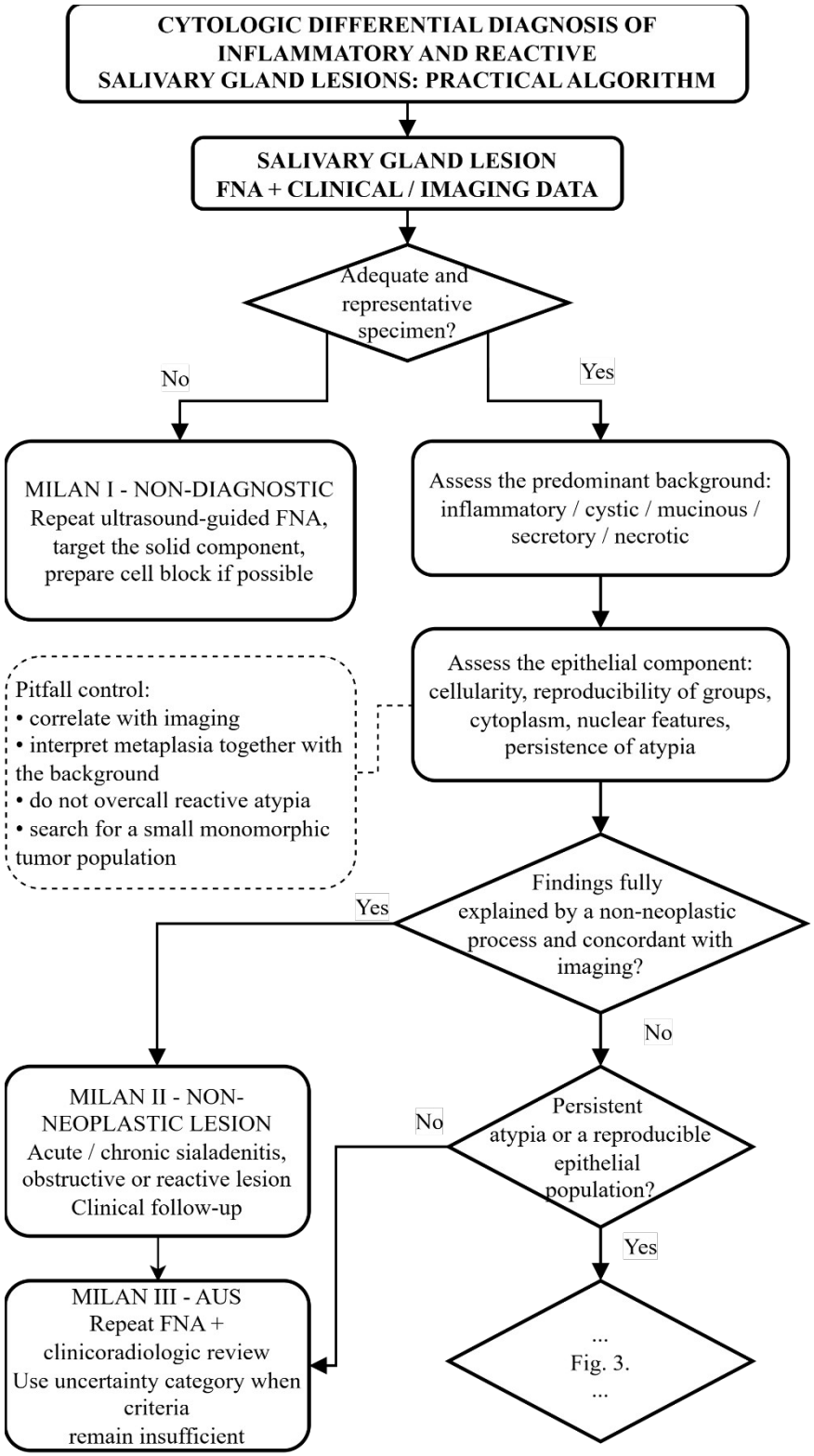

Fig. 2. Algorithm for the cytological differential diagnosis of inflammatory and reactive salivary gland lesions (Part 1)

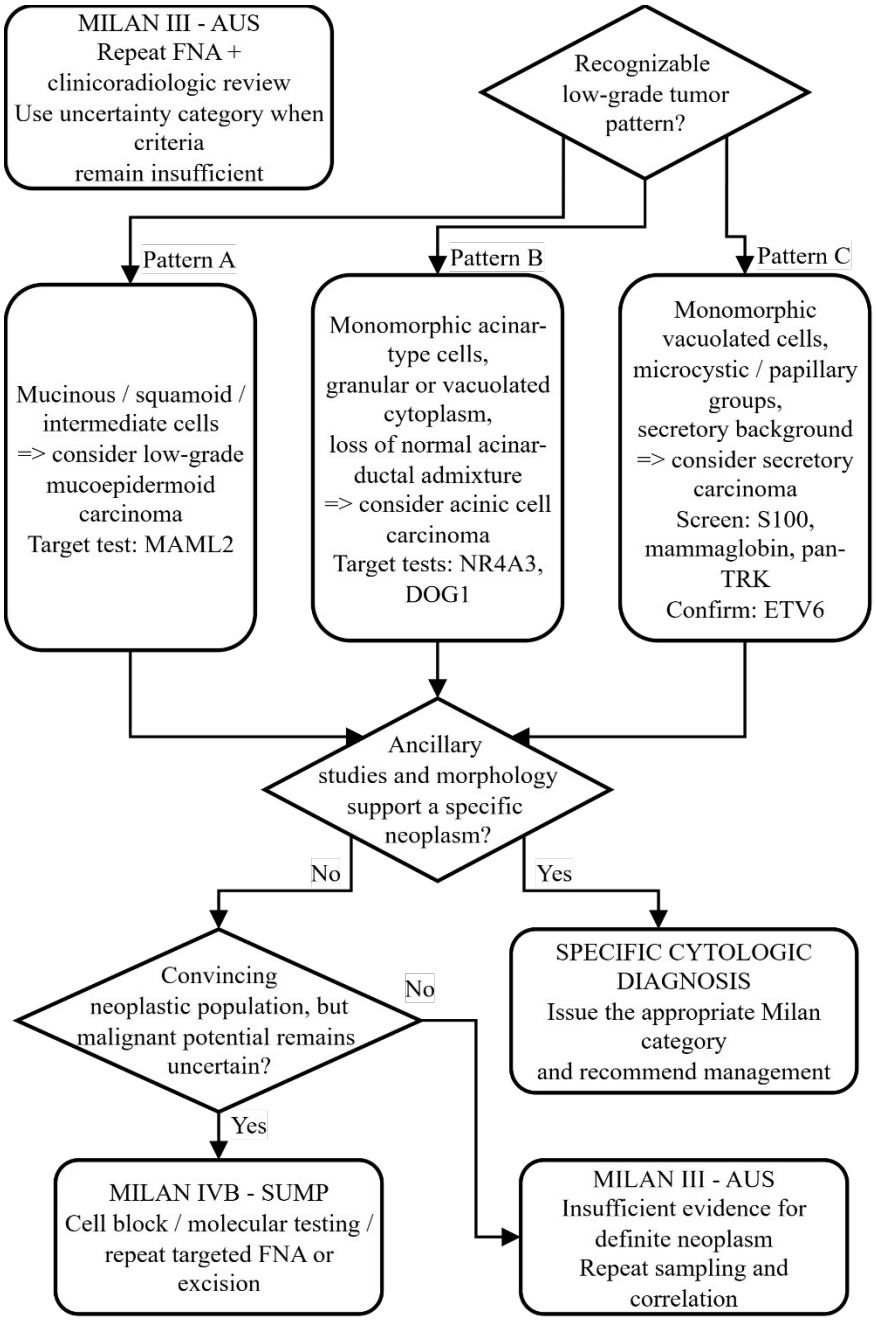

Fig. 3. Algorithm for the cytological differential diagnosis of inflammatory and reactive salivary gland lesions (Part 2)

Ancillary studies are performed after a specific morphological hypothesis has been established. When mucoepidermoid carcinoma is suspected, MAML2 rearrangement is assessed. NR4A3 and DOG1 may be used for acinic cell carcinoma. In suspected secretory carcinoma, the S100, mammaglobin, and pan-TRK immunoprofile helps identify cases for confirmatory ETV6 rearrangement testing. A targeted approach is particularly important in hypocellular aspirates,

as an excessively broad panel of tests can rapidly exhaust the cell block. Molecular testing is most useful for resolving specific differential diagnostic questions [7].

Error minimization depends on the quality of specimen acquisition and a systematic approach to interpretation. In cases of clinicocytological discordance, repeat targeted aspiration of the solid component of the lesion under imaging guidance is warranted; whenever possible, the specimen should be allocated so as to preserve cells for cell block preparation and targeted ancillary studies. Reactive atypia should be assessed for persistence and reproducibility, metaplastic cells in relation to the smear background, and a scant monomorphic population with regard to its reproducibility across different cell groups. The indeterminate categories of the Milan System allow the actual level of diagnostic certainty to be conveyed and help avoid a premature definitive diagnosis.

The analysis shows that a false impression of low-grade neoplasia is often created by obstructive-cystic changes with mucus, squamous and mucinous metaplasia, reactive acinar changes, and a secretory background. Diagnostic reliability increases with a systematic assessment of specimen adequacy, background features, the epithelial population, and its reproducibility. For the three major diagnostic challenges—mucoepidermoid, acinic cell, and secretory carcinomas—ancillary studies should be used to confirm an already established morphological hypothesis.

Thus, the cytological differentiation of inflammatory and reactive salivary gland processes from low-grade malignant tumors requires a stepwise approach. When diagnostic uncertainty persists, targeted immunohistochemical and molecular studies can help determine the most likely diagnosis without unnecessary depletion of the specimen.

References:

1. Rossi E.D., Baloch Z., Barkan G. et al. Second edition of the Milan System for Reporting Salivary Gland Cytopathology: Refining the role of salivary gland FNA // Cancer Cytopathology. – 2024. – Vol. 132. – No. 1. – P. 10–21. – DOI: 10.1002/cncy.22753.
2. Pusztaszeri M., Rossi E.D., Faquin W.C. Update on Salivary Gland Fine-Needle Aspiration and the Milan System for Reporting Salivary Gland Cytopathology // Archives of Pathology & Laboratory Medicine. – 2024. – Vol. 148. – No. 10. – P. 1092–1104. – DOI: 10.5858/arpa.2022-0529-RA.
3. Saoud C., Bailey G.E., Graham A. et al. Pitfalls in Salivary Gland Cytology // Acta Cytologica. – 2024. – Vol. 68. – No. 3. – P. 194–205. – DOI: 10.1159/000538069.
4. Niu S., Hou Y. Salivary gland Cytology, the new and the Old, a Pattern-Based approach // Human Pathology Reports. – 2024. – Vol. 36. – Art. 300742. – DOI: 10.1016/j.hpr.2024.300742.
5. Sakamoto S., Kikuchi K. Expanding the cytological and architectural spectrum of mucoepidermoid carcinoma: The key to solving diagnostic problems in morphological variants // Seminars in Diagnostic Pathology. – 2024. – Vol. 41. – No. 4. – P. 182–189. – DOI: 10.1053/j.semdp.2024.04.001.
6. Sharma Kala P., Gupta M., Thapliyal N. Efficacy of Fine-Needle Aspiration Cytology in Diagnosing Secretory Carcinoma of Salivary Gland: A Systematic Review and Meta-Analysis // Acta Cytologica. – 2024. – Vol. 68. – No. 2. – P. 83–106. – DOI: 10.1159/000536249.
7. Carillo A.M., De Luca C., Pisapia P. et al. Molecular testing in salivary gland cytopathology: A practical overview in conjunction with the Milan system // Cytopathology. – 2024. – Vol. 35. – No. 3. – P. 330–343. – DOI: 10.1111/cyt.13363.