Cytopathology in Focus: Adequacy in cytopathology: an overview with a focus on FNA of lymph nodes and mass lesions

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January 2023—The definition of "adequate" per the Merriam-Webster dictionary is "sufficient for a specific need." In cytopathology, it is defined by the quantity and quality of the cellular material sampled. The final interpretation of a cytopathology report is almost universally preceded by an adequacy statement. While the essence of "adequacy" stays the same, its application varies depending on the specimen type and the site sampled. Furthermore, in the current era of personalized medicine, the definition of adequacy has expanded from "enough cells to make a morphologic diagnosis" to "enough cells to make a diagnosis and perform ancillary studies."

To achieve consistency in the usage of the criteria for adequacy, standardized terminology systems supported by national and international professional organizations have been implemented successfully in cervical, thyroid, salivary gland, urine, and serous fluid cavity cytopathology. Others have been conceived recently, and more are in the pipeline. The adequacy criteria described in the published classification systems stem from the review of the published literature, surveys of practicing pathologists, the practical experience of the contributing authors, and targeted research studies performed during the development of classification systems to fill in gaps in the literature.[1] Ultimately, the goal of a published classification system is to establish a common language for pathologists and clinicians. With this aim in mind, these systems often provide an associated risk of malignancy for each diagnostic category, including "non-diagnostic/inadequate," which in turn provides the basis for patient management.

Table 1 summarizes some of the published criteria for defining specimens as adequate. The common theme in each system is quantitative (number of cells) and qualitative (distinct and clear visualization of cells); acellular/sparsely cellular or degenerated samples are typically interpreted as non-diagnostic/inadequate for evaluation. There are, however, some specimen types/sites, such as bronchial brushing, bronchoalveolar lavage, cerebrospinal fluid, lymph nodes, bone lesions, and synovial fluids, for which the adequacy criterion is not clearly defined and others (i.e. serous effusions, salivary gland, and voided urine) for which the adequacy criterion is not fully accepted.

One such site with poorly defined adequacy criteria is lymph node cytopathology. For example, a common specimen in many pathology laboratories is an endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA) of an enlarged or PET-avid lymph node. For EBUS-FNA, adequacy depends on the result. If metastatic carcinoma is present, sufficient material to prepare a cell block is likely necessary for immunohistochemistry or molecular testing. When atypical lymphoid cells (regardless of quantity) are seen at the time of rapid onsite evaluation (ROSE), aspirate material is needed for flow cytometry, slides for cytomorphologic evaluation, and material for a cell block to potentially perform immunohistochemistry and molecular testing. At a minimum, approximately 50,000 cells per tube is considered amenable for flow cytometry analysis, and sampling errors (poor viability, peripheral blood contamination, and hypocellular specimens, for example) are the major reasons for sensitivity failures in flow cytometry.[2] Thus, adequacy criteria for lymph nodes historically have been largely subjective. Most studies focused on EBUS-FNA of mediastinal lymph nodes have defined an inadequate specimen as a sample lacking the following: tumor cells, granulomatous inflammation, or a significant amount of lymphoid tissue with or without anthracotic pigment-laden macrophages.[3] It is not unusual for these specimens to be highly cellular but

composed almost exclusively of reactive bronchial cells. In the absence of lymphoid cells or tumor cells, it is critical that such a specimen be interpreted as non-diagnostic and not “negative for malignancy” to avoid a false-negative diagnosis.[4] The question, however, remains as to how many lymphoid cells are sufficient to call the sample an adequate representation of a lymph node and to ensure a true negative interpretation. Suggested criteria vary, including “many small lymphocytes,” “lymphocytes comprising 30 percent or more of the cells,” “more than 40 lymphocytes per high-power field,” and “more than 100 lymphocytes per low-power field.”[4]

In May 2019 in Sydney, Australia, a steering committee of international cytologists proposed a system for reporting lymph node FNA, which included efforts to reduce the variability of the adequacy criteria used. According to the proposed Sydney System, inadequate or insufficient FNA of a lymph node includes cases that cannot be diagnosed due to scant cellularity, extensive necrosis, or technical limitations that cannot be overcome.5 The group emphasized that lymph node FNA should be interpreted by cytopathologists in a proper clinical context and in correlation with the clinical indication, ultrasound examination, performance of FNA by palpation or ultrasound guidance, and availability of ROSE/adequate triaging at the time of the procedure.

The concept that adequacy is intrinsically tied to correlation with the clinical context has become core to reporting FNA cytopathology. Returning to the definition of adequate, the “clinical need” for the procedure must be known to determine whether the material is sufficient. If an FNA is targeting a mass lesion, the aspirate should contain material that corresponds to or helps explain the presence of a mass. For example, a sample from an EBUS-FNA of a lung nodule should contain abnormal material that helps answer the question “what is this nodule?”—whether it be necrotizing granulomatous inflammation, a benign hamartoma, or adenocarcinoma. If the FNA is cellular but composed of pulmonary alveolar macrophages and/or benign respiratory epithelium, the sample does not provide an answer to the clinical need for the procedure and is non-diagnostic/inadequate. In contrast, an FNA can be hypocellular or acellular but still be adequate in certain clinical contexts. For example, a cystic mass in the parotid gland or pancreas that reveals abundant clean mucin is providing a diagnostic clue that there is a mucin-producing abnormality, which although not diagnostic of a specific entity is an abnormal finding that helps narrow the differential diagnosis. When interpreting an FNA performed for a mass lesion, solid or cystic, this concept can be applied across many primary sites and doesn’t require a standardized reporting system with complex or confusing criteria.

In each case that is not adequate, communication is key to ensure the patient workup continues and they aren’t lost to follow-up. Consequently, it is recommended that an explanatory comment be included stating the reason for the non-diagnostic/inadequate specimen, such as: “The findings in this case do not appear to explain or be representative of the reported mass lesion. As a result, the case is best categorized as non-diagnostic and repeat sampling should be considered.”

In summary, the criteria for adequacy in many cytopathology specimen types is still evolving. However, the underlying theme continues to be focused on the question: Is the material sufficient to help answer the clinical question? In cytopathology, this question will continue to be related to specimen quantity and quality, as well as correlation with the clinical scenario.

Table 1. Adequacy criteria

Standardized system	Specimen type	Adequacy criteria
The Bethesda System for Reporting Cervical Cytology	Cervical cytology	Must be well-visualized/preserved squamous/metaplastic cells Conventional smear: minimum of 8,000–12,000 Liquid-based: ≥ 5,000 Lab discretion if >2,000 cells in setting of chemotherapy, radiation, postmenopausal, hysterectomy >25% of cells must not be obscured by inflammation, bacteria, or interfering substances Any atypical or diagnostic cells
	Anal cytology	Must be well-visualized/preserved squamous/metaplastic cells without significant degenerative changes or obscuring bacteria or fecal matter Conventional smears: ≈2,000–3,000 nucleated squamous cells (NSC) ThinPrep: ≈1–2 NSC/ hpf SurePath: ≈3–6 NSC/hpf Any atypical or diagnostic cells
The Bethesda System for Reporting Thyroid Cytopathology	FNA of thyroid nodules	≥6 groups of well-visualized follicular cells with ≥10 per cluster Abundant colloid Features of lymphocytic thyroiditis Any atypical or diagnostic cells
The Paris System for Reporting Urinary Cytology	Voided urine	>30 mL without non-urothelial features obscuring urothelial morphology Any atypical or diagnostic cells
	Instrumented urine	Non-obscured, "cellular specimen"; however, there is insufficient data for specific criteria Any atypical or diagnostic cells
The Milan System for Reporting Salivary Gland Cytopathology	FNA of a mass lesion in a major salivary gland	Well-prepared slides not limited by artifacts or obscuring of diagnostic material Must contain more than just normal salivary gland elements in the setting of a clinically or radiologically defined mass Any atypical or diagnostic features (including mucin in a cystic lesion)
The Papanicolaou System for Reporting Pancreaticobiliary Cytology	FNA of pancreatic mass lesions	Unobscured by artifacts, hemorrhage, or necrosis and well preserved Provides diagnostic or useful information about the solid or cystic lesion sampled (not just GI contamination or benign pancreas), such as clean mucin in a cyst or any atypical or diagnostic features
The International System for Reporting Serous Fluid Cytopathology	Peritoneal cavity fluid, pleural effusion	Unobscured and not limited by artifact >50–75 mL of fluid Any atypical or diagnostic cells
The International Academy of Cytology Yokohama Standardized Reporting System for Breast Cytology	FNA of breast mass	Unobscured and not limited by artifact Seven tissue fragments each with 20 or more epithelial cells Any atypical or diagnostic features or necrosis

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