Review Article

Should Uncertainty Concerning the Risk of Malignancy Be Included in Diagnostic (Nongynecologic) Cytopathology Reports?

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In diagnostic cytology, the known site-specific false positive rates at various anatomical sites for the risk malignancy (ROM) when a confirmed malignant diagnosis is made are comparatively well documented. ROM figures for diagnostic cytology specimens may vary according to the anatomical site of the specimen, the exact nature of the specimen received, the staining method(s) used, and the use of additional laboratory techniques including molecular profiling; furthermore, they often differ to some extent from institution to institution, between differing cytologists within the same institution, and over time. A brief literature review for a selected group of routine diagnostic cytology specimens shows a published ROM for a confirmed malignant diagnosis as follows: bile duct brushings, ~99% (range, 97%-100%); breast fine needle aspiration, 98.5% (range, 92%-100%); serous effusion fluid, 98.9% (range, 90%-100% although lower for squamous cell carcinoma, mesothelioma, and lymphoma), pulmonary endobronchial ultrasound cytology, ~99% (range, 86.6%-100%); thyroid FNA, 98% (range, 97%-99% if NIFTP tumors are excluded), salivary gland FNA, ~90%; (range 57%-100%) and lateral neck cyst FNA, ~99% (range, 95.5%-100%). Because most diagnostic cytology specimens have a small but accepted false-positive rate, this information is vitally important for the clinical management of patients and for shared patient decision making. In our view, the known false-positive rate for a given diagnostic cytology specimen could be included within the cytology report to assist in explaining the limitations of the diagnostic cytology interpretation and help facilitate the clinical decision-making process. ***Cancer Cytopathol* 2021;129:16-21**.

KEY WORDS: cytology; diagnosis; fine-needle aspiration; malignancy; uncertainty.

INTRODUCTION

All diagnoses in pathology and cytology are made based on the assessment of pathological features of given specimen(s) using standard procedures based on known and described diagnostic criteria. An individual pathologist or cytologist may also seek a second opinion from colleagues in a departmental review or multidisciplinary meeting. Furthermore, relevant clinical, imaging, and other information, including ancillary techniques and molecular test results, may factor into the final diagnosis. Although the field of cytology has adapted to new developments, particularly molecular techniques and methods of sample acquisition (eg, endobronchial ultrasound, endoluminal ultrasound, and stereotactic image–guided fine needle aspiration [FNA]), the process of diagnosis remains essentially unaltered.

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The development of unified international terminologies for reporting diagnostic cytopathology—including The Bethesda System for Reporting Thyroid Cytopathology,[1] The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology,[2] The Paris System for Reporting Urinary Cytology,[3] The Milan System for Reporting Salivary Gland Cytopathology,[4] The Papanicolaou Society of Cytopathology System for Reporting Respiratory Cytology,[5] and The International Academy of Cytology/Yokohama System for Reporting Breast Fine Needle Aspiration Cytopathology,[6] among others—has enabled international alignment of many reporting terminology systems. Many of the new terminology systems include discussions of the risk of malignancy (ROM) in the various reporting categories, although not all the international terminologies include ROM data, and quoted ROMs may be altered over time or after terminology revisions. The ROMs are, for example, included in The Bethesda System for Reporting Thyroid Cytopathology,[1] The Milan System for Reporting Salivary Gland Cytopathology,[4] The Papanicolaou Society of Cytopathology System for Reporting Respiratory Cytopathology,[5] and The International Academy of Cytology/Yokohama System for Reporting Breast Fine Needle Aspiration Cytopathology[6] (Table 1). Although ROMs within the subcategories are quoted in these documents and this information is available to cytologists, clinicians, and multidisciplinary teams, it is not currently included within the issued cytology reports in most circumstances. Is there a case for doing this?

The concept of including ROMs in cytology reports is not new,[7,8] and a comment about ROM may be included in a report if the ROM is known in the literature.[9] However, this practice might well be considered by some to be unnecessary, potentially undermining the validity of a report, while others will quite reasonably argue that published statistics for ROM may not accurately reflect their own individual practice or the practices of multidisciplinary teams at their institutions. There is also significant heterogeneity in published reports of ROM at various anatomical sites for nongynecologic cytology. Physicians routinely encounter diagnostic uncertainty in practice. Despite its impact on health care utilization, costs, and error, the definition and extent of diagnostic uncertainty is poorly understood. One definition could be the "subjective perception of an inability to provide an

TABLE 1. International Terminology Systems for Nongynecologic Cytology and Risk of Malignancy

Classification	The Bethesda System for Reporting Thyroid Cytopathology/UK Royal College of Pathologists Thy Terminology	The Milan System for Reporting Salivary Gland Cytopathology	Papanicolaou Society of Cytopathology System for Reporting Respiratory Cytology	The International Academy of Cytology Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy Cytopathology
Cytology specimen	Thyroid FNA	Salivary gland FNA	Lung cytology	Breast FNA
ROM in malignant category	97-99%[a]	90%	86.6%-100%[b]	99%-100%
ROM in suspicious category	50-75%[a]	60%	50%-100%[b]	84.6%-97.1%
False-positive rate	1%-3%	10%	~1%	<1%
References	1,15,16	19	47,48,49	50,51

Abbreviations: FNA, fine needle aspiration; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; ROM, risk of malignancy.
[a]NIFTP excluded.
[b]Endobronchial ultrasound of lymph nodes & lung lesions.

accurate explanation of the patient's health problem,"[10] which for pathology and cytology would include information conveyed in pathology reports.[11] Ideally, decisions about cancer treatment should be based on patients' full understanding of the benefits, harms, and uncertainties associated with alternative courses of action, which are central to informed decision making.[12] However, in practice this is difficult to achieve in cancer care, despite its ethical desirability.[13] The International Organization for Standardization (ISO) standard 17025, section 7.8.3.1, states:

> …test reports shall, where necessary for the interpretation of the test results, include where applicable, the measurement uncertainty presented in the same unit as that of the measure and or in a term relative to the measure and (e.g. percent) when it is relevant to the validity or application of the test results. The management of uncertainty would also include the risk of malignancy in cytology reports if there was any significant albeit minimal risk of diagnostic uncertainty on a particular result.[14]

As such, the ISO accreditation standards suggest that this may well be advisable. Some specific examples are provided in the sections that follow.

THYROID FNA

For thyroid FNA cytology, the ROM for a Bethesda category VI result (equivalent to a Thy5 result in the United Kingdom) if NIFTP tumors are excluded is in the range of 97% to 99%,[1,15,16] which implies a false-positive rate of 1% to 3%. There is a case for including this information in reports of Bethesda category VI/Thy5 thyroid FNA cytology.[17] This may have little impact clinically if the operative policy for patients is to undertake a thyroid lobectomy to confirm the diagnosis; however, if a positive FNA cytology from a lateral neck lymph node shows cytological features of papillary thyroid carcinoma, this could lead to radical neck dissection, administration of radioiodine, or, in the case of anaplastic thyroid carcinoma, radiotherapy or neoadjuvant drug therapy. Use of *BRAF V600E* mutation analysis on FNA cytology may be useful as a double proof of malignancy in this situation if papillary carcinoma is suspected, although *BRAF V600E* mutation has low sensitivity.[18] Hence, for thyroid FNA, there definitely is a case for including the implied 97% to 99% ROM information in reports of malignancy.

SALIVARY GLAND FNA

The Milan System for Reporting Salivary Gland Cytopathology states that the implied ROM for a category VI '*malignant*' result is 90%, with a comment that intraoperative consultation may be helpful to determine the need for surgery and that the extent of surgery depends on the type and grade of malignant tumor.[19] Salivary gland cytology is a particularly problematic area, because the diagnosis has relatively poor interobserver reproducibility. A systematic review and meta-analysis of 92 studies with a total of 16,546 FNAs with surgical follow-up confirmed a 91% ROM on FNA cytology. The nonmalignant cases were either nonneoplastic lesions (2%) or benign neoplasms (7%) on histopathologic follow-up.[20] The use of statements in reports confirming the relatively high (~10%) risk of a false-positive result may therefore be useful to clinicians and patients for salivary gland FNAs.

LATERAL NECK CYSTS

The diagnosis of lateral neck cysts is known to be a problematic area in pathology and cytology. Firat et al[21] identified 1 benign branchial cyst that was reported as highly suspicious of carcinoma. Kaye et al[22] reported that of 22 lesions confirmed to be a benign branchial cyst, 1 was suspicious of squamous cell carcinoma. Kadhim et al[23] reported that of 34 patients with a cytology aspirate from a benign branchial cleft cyst, 1 was reported as cytologically suspicious of squamous cell carcinoma. Begbie et al[24] reported that of 30 cases of benign branchial cleft diagnosed on FNA, 1 led to an unnecessary neck dissection due to a cytological diagnosis of metastatic squamous cell carcinoma. Slater et al[25] reported that 2 of 24 patients with benign branchial cleft cysts with atypical squamous cells subsequently were found not to have squamous cell carcinoma. Conversely, other series have not reported false-positive cytology results in lateral neck cysts.[26-31] The overall ROM for FNA cytology of lateral neck cysts is below 100%, implying the need to use ancillary techniques in cell block (eg, human papillomavirus [HPV] testing), needle core biopsy, or intraoperative frozen section to confirm a cytological diagnosis of malignancy if radical surgery such as neck lymph node dissection is proposed.[32] It should be noted that the specificity of p16 immunohistochemistry outside of the oropharynx is limited because of the potential mimicking of p16/HPV-positive metastatic oropharyngeal squamous cell carcinoma.[33]

p16 immunohistochemistry is positive in up to 20% to 30% of cutaneous head and neck squamous cell carcinomas unrelated to HPV, and approximately 40% of benign lymphoepithelial cysts are also p16-immunopositive within the epithelial lining, although the staining is typically patchy and involves less than 50% of the epithelium.[34]

BILE DUCT BRUSHING CYTOLOGY

For bile duct brushing cytology, the known published ROM approaches 100% in the published literature; however, the various studies show a range of false-positive results of 0% to 3%.[35-40] The possible reasons for these false-positive results include primary sclerosing cholangitis,[41] chronic pancreatitis, inflammatory conditions that mimic malignancy, or the presence of a bile duct stent that was unknown to the reporting cytologist or that the reporting cytologist did not consider when formulating the diagnosis.[42] Multidisciplinary teams managing hepatobiliary lesions are aware of some of the problems of interpretation of bile duct brushing cytology, including its relatively low absolute sensitivity for malignancy and the very small but known false-positive rate; regardless, there is a case for including a statement about the 0% to 3% false-positive ROM in bile duct brushing/washing cytology reports.

PLEURAL FLUID CYTOLOGY

Serous effusion cytology has a very high specificity for malignancy with very low false-positive rates described in the literature. In a comprehensive meta-analysis of serous effusion cytology, Farahani and Baloch[43] reported a mean ROM of 98.9% for all serous effusion fluids, and in 31 studies of pleural fluid cytology, the mean ROM was 99.2%. However, pleural effusion cytology for some pulmonary malignancy subtypes (eg, squamous cell carcinoma, mesothelioma, and lymphoma cytology) is less helpful,[44,45] as the cytological features of malignant mesothelioma overlap with those of benign reactive pleural changes. The problem of diagnosis of malignant mesothelioma on cytology is highlighted by the fact that a significant minority (37%) of respondents to a survey stated that clinicians at their own institution would not treat a patient definitively based on a cytological diagnosis of malignant mesothelioma in an effusion fluid or FNA specimen because of this diagnostic uncertainty.[46] Therefore, a statement about the risk of false-positive diagnosis may be unnecessary for reports of adenocarcinoma on pleural fluid cytology, but there would certainly be a case for including it in cases of suspected malignant mesothelioma or suspected lymphoma.

PULMONARY CYTOLOGY

In the recently published Papanicolaou Society of Cytopathology System for Reporting Respiratory Cytology, the ROM for category VI malignancy is 86.6% to 100%.[47] False-positive endobronchial ultrasound cytology (EBUS) has been reported in the literature. Layfield et al[48] reported an ROM of 87% in EBUS cytology, implying a false-positive rate of 13%. Sun et al,[49] in a series of 49 samples obtained from lymph node lesions, identified 1 false-positive case comprising strips of dysplastic squamous epithelium with rare lymphocytes in the background that histologically revealed a reactive lymph node. As such, the published literature appears to make a clear case for stating the false-positive ROM in EBUS cytology reports.

BREAST CYTOLOGY

The positive predictive value (PPV) of a malignant breast FNA biopsy diagnosis should approach 100%, based on adherence to specific key cytological criteria for diagnosis of carcinoma that distinguish malignant FNAs from proliferative lesions, metastases, and other primary breast malignancies. In the recent literature, the PPV for malignancy averages 98.5%, with a range of 92% to 100%.[6] Two recent studies that used the category definitions of the IAC Yokohama System reported a ROM of 99.0% and 100%.[50,51] False-positive breast cytology is very rare and is usually caused by errors in the interpretation of proliferative breast lesions, particularly intraductal papillomas and fibroadenomas. Although in many countries the diagnosis of breast malignancy by FNA is followed by a confirmatory core needle biopsy, in many low- to middle-income countries, patients are treated based on the cytological diagnosis, justifying the inclusion of a statement about the risk of false-positive FNAs.

CONCLUSION

This review summarizes some of the known limitations of effusion fluid, washing, lavage, and FNA cytology and makes the case for inclusion of the known site-specific risks of false-positive malignant calls in cytology reports. With the development of international terminology site-specific systems for reporting of serous fluids, FNA, and

EBUS cytology, there is a case for including this information in cytology reports to ensure clear communication of the uncertainty of results to clinicians and patients to better enable shared patient care.

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