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Making Cytological Diagnoses on Digital Images Using the iPath Network

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Key Words

Telemedicine · Cytology · Still images · Pitfalls · Diagnostic accuracy · Telelearning

Abstract

Background: The iPath telemedicine platform Basel is mainly used for histological and cytological consultations, but also serves as a valuable learning tool. **Aim:** To study the level of accuracy in making diagnoses based on still images achieved by experienced cytopathologists, to identify limiting factors, and to provide a cytological image series as a learning set. **Method:** Images from 167 consecutive cytological specimens of different origin were uploaded on the iPath platform and evaluated by four cytopathologists. Only wet-fixed and well-stained specimens were used. The consultants made specific diagnoses and categorized each as benign, suspicious or malignant. **Results:** For all consultants, specificity and sensitivity regarding categorized diagnoses were 83–92 and 85–93%, respectively; the overall accuracy was 88–90%. The interobserver agreement was substantial ($\kappa = 0.791$). The lowest rate of concordance was achieved in urine and bladder washings and in the identification of benign lesions. **Conclusion:** Using a digital image set for diagnostic purposes implies that even under optimal conditions

the accuracy rate will not exceed to 80–90%, mainly because of lacking supportive immunocytochemical or molecular tests. This limitation does not disqualify digital images for teleconsulting or as a learning aid. The series of images used for the study are open to the public at <http://pathorama.wordpress.com/extragenital-cytology-2013/>.

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Introduction

There are a number of studies on the concordance of second-opinion diagnoses on histological [1–6] and cytological images. The latter studies have focused on cervical smears [7–11] or on both gynecological and nongynecological [2] as well as mixed nongynecological cytology [12, 13], whereas few have focused on fine-needle aspirations (FNAs) from a single organ like the pancreas [14], thyroid gland [15, 16], liver [17] or urinary tract [18]. Most of these studies on telehistology as well as on telecytology report a concordance rate of 80–90% between the diagnoses made on digital images and the reference diagnoses made on the regular glass slides. Therefore, telecytology is now increasingly being used for obtaining a second opinion, rapid diagnosis during surgical interven-

Table 1. Reference diagnoses

Neoplastic	n	Nonneoplastic	n
Adenocarcinoma not otherwise specified	21	Fibrocystic change of the breast	8
Non-small cell carcinoma	13	Goiter	8
Breast carcinoma	12	Urothelial atypia, benign	12
Lymphoma	7	Urothelial atypia G2	4
Urothelial atypia G3	6	Epidermoid cyst	2
Small cell carcinoma	5	Ductal cyst salivary gland	1
Squamous cell carcinoma	5	Squamous metaplasia	2
Papillary thyroid carcinoma	2	Endometriosis	1
Acinus cell carcinoma	1	Lymphadenitis	7
Prostatic adenocarcinoma	1	Granulomatous inflammation	3
Embryonal carcinoma	1	Giant cell granuloma	1
Mesothelioma	1	sinus maxilaris	1
Melanoma	1	Inflammation	3
Follicular neoplasia thyroid	2	Mastitis	1
Vocal cord dysplasia	1	Lipoid pneumonia	1
Borderline tumor ovary	1	Pleura eosinophilia	1
Mucinous cystic neoplasia	1	Eosinophilic pneumonia	1
Mesenchymal tumor	3	Fungi	2
Fibroadenoma of the breast	1	Herpes vaginalis	1
Pituitary adenoma	1	Gout, knee joint	1
Pleomorphic adenoma	1	Reactive mesothelial change	8
Warthin tumor	4	'No tumor'	8
Total	91	Total	76

Table 2. Reference diagnoses related to topography

Topography	n	M	SM	B	SB
Effusions	40	20	3	17	–
Urine/bladder washings	24	7	3	14	–
Bronchial secretions	16	12	1	3	–
FNA lymph node	22	12	1	9	–
FNA mediastinum	7	4	2	1	–
FNA breast	15	6	–	9	–
FNA thyroid gland	10	0	2	8	–
FNA salivary gland	7	1	–	6	–
Other sites ¹	26	10	5	10	1
Total	167	72	17	77	1

¹ FNA from lung (3), pancreas (3), duodenal wall (2), ovary (2), liver (1), testicle (1), skin (1); BAL (3), other washings (2); brushings and fresh tissue scrapings (7), synovial effusion (1).

tions or replacing on-site microscopy [19, 20]. The opportunities provided by digital systems, which can be used by cytopathologists, have also repeatedly been described in this journal [21, 22].

The aim of this study on image-based telecytology is to identify factors that may influence observer concordance and the reliability of telecytological diagnoses beyond preparatory and photographic faults. Additionally, we aimed to provide a cytological image series as a learning set.

Materials and Methods

Materials

Specimens from 167 patients (93 female, 74 male) were included in the study. One of the authors (L.B.) had selected all consecutive cases of clinical cytology over a time period of 3 months if they met the following criteria: informative in terms of cell content and staining quality allowing a diagnosis, and at least a minimal degree of educational value for students gaining their first experience in cytology. Cases allowing only a trivial or uninformative diagnosis were not included in the study, i.e. paucicellular specimens such as negative voided urines or cerebrospinal fluids, specimens containing necrotic material without vital cells or pure blood, and FNAs which were nondiagnostic because of poor fixation or mechanical artifacts. The mean age of the patients was 60 years (range 1–91). The majority were FNAs from various sites (43.1%), followed by effusions (23.1%), urine and bladder washings (4.4%), bronchial and a few other secretions (6.6%), smears and brushings mainly from the respiratory tract (5.4%), bronchoalveolar lavages (1.8%), fresh tissue scrapings (3.6%) and one spinal fluid (0.6%). Two of the fresh tissue scrapings taken during the frozen section procedure were stained with hematoxylin and eosin. All other specimens were wet-fixed and Papanicolaou-stained. The reference diagnoses made on the original slides comprised 91 benign and malignant neoplasms and 76 nonneoplastic lesions (tables 1, 2).

Study Design

The slides of each case had been prescreened by experienced cytotechnicians and reviewed and signed out by L.B. of the Institute for Pathology, University Hospital Basel. These original diagnoses were used as reference diagnoses for the study. The results of ancillary tests (i.e. immunocytochemistry, ICC, or fluorescence in situ hybridization, FISH) were considered in 14 cases. The diagnoses were documented in the local electronic database.

Microphotography was also performed by L.B. The images were captured using the AXIO Imager A1 microscope equipped with an AxioCam and AxioVision 4.6 software (ZeissTM, Jena, Germany). Four to five images were captured from each of the 167 cases at a resolution of 150 dpi and a size of 1,024 × 768 pixels, and uploaded together with the case description (see below) on the iPath forum 'Basel Telecytology'. The iPath telemedicine platform has been developed at the Institute for Pathology, University Hospital Basel, as an open-source tool and worldwide forum for consultation, real-time discussions and continuing training [23–25].

Only after the images of all cases had been uploaded were they made accessible to the consultants. The usual iPath procedure was

Table 3. Substantiation of M and B reference diagnoses

Method	Reference diagnoses neoplastic	Reference diagnoses nonneoplastic
Histology	60	11
FISH	4	5
ICC	3	4
Repeat cytology	1	4 ^a
Case history	5	8 ^b
Clinical background	1	12
Follow-up	1	4 ^c
No further information	18	25
Total	93	74

^a In 1 patient with negative sputum cytology, urine cytology later showed cells of poorly differentiated squamous cell carcinoma.

^b All patients had a history of tumor.

^c One year later, 1 patient with tumor-negative bladder washing had urothelial tumor pTaG3 with a ki67 proliferation rate of 20%.

simulated: the Basel division of cytology worked as 'submitter' and four independent pathologists not involved in the primary diagnoses played the role of 'consultants'. Three of the consultants (A, B and D) are board-certified cytopathologists and one (C) is a surgical pathologist with a special interest in cytology. Consultants C and D are members of several iPath discussion groups and are experienced in making diagnoses on digital images. The four consultants reviewed the cases within a time frame of 2 months.

After registration (at <http://telepath.patho.unibas.ch/ipath/>) all images and case descriptions were accessible to the four 'consultants'. They could only read the clinical information, including gender, age, tumor history if present, topography of the lesion and type of cytological material. They could neither see the reference diagnoses nor the comments of the other consultants before they had written their own comments. Their comments consisted of a free text diagnosis and of a categorization of the diagnosis into: malignant (M), benign (B), suspect, probably malignant (SM), suspect, probably benign (SB) or material not diagnostic (ND).

Final Evaluation

The final evaluation of the data was performed after a period of more than 5 years. The reference diagnoses were categorized in the same way as the consultants' diagnoses as M in 72 (43.1%), as B in 77 (46.9%), as SM in 17 (10.3%), and as SB in 1 (0.6%) of the 167 cases (table 2).

The plausibility of the reference diagnoses was substantiated by histology, ICC and/or FISH in 87 cases (52.1%), and by repeat cytology, case history, follow-up and/or clinical background in 37 cases (22.2%; table 3). The ICC tests were mostly used in effusions to identify epithelial cells, FISH (UroVision®) was used on urocytological specimens [26] and PCR was performed once on an effusion specimen with atypical lymphoid cells to test for clonality. In the 2 cases in which the diagnosis of all consultants differed from the reference diagnosis the original smears were reviewed. In the reference diagnoses no misdiagnoses were identified.

Data Analysis

After the four consultants had made their diagnoses the data were transferred from the iPath to an Excel table. The data were analyzed in three ways:

(1) The number of categorized diagnoses of the consultants was decreased by grouping the SM into the M and the SB into the B category in order to simplify statistical analysis. The diagnosis of 'atypical urothelial cells grade G2 or G3' in urine and bladder washings and the diagnosis of 'suspicious for follicular neoplasia' in thyroid FNAs were categorized as M. The agreement between categorized diagnoses of each consultant with the categorized reference diagnoses was calculated for accuracy by assigning each consulting diagnosis as true positive (TP), false positive (FP), true negative (TN) or false negative (FN) with regard to tumor, irrespective of whether the tumor was malignant or benign. From these data sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for the diagnosis of malignancy were calculated for each consultant separately.

(2) The specified diagnoses of the consultants were also compared with the specified reference diagnoses. The number of the consultant's diagnoses agreeing with the specified reference diagnosis was registered in each case.

(3) The accuracy rate of the categorized diagnoses was related to the topographic origin of the cytology specimens, and it was tested whether the diagnostic performance depended on the type of cytological material and/or on the kind of lesion.

Statistics

Specificity, sensitivity and the other accuracy parameters were calculated according to the corresponding contingency table for each expert observer. Interobserver concordance was calculated by means of the free marginal multirater Fleiss kappa using the 'irr' package installed in R i386 version 2.15.2. The concordance of two raters was tested by Cohn's kappa (<http://www.R-project.org>).

Results

Concordance of Categorized Diagnoses

It is remarkable that in only 61 (41.0%) of the 151 cases the diagnoses made by consultants with respect to M versus B were concordant among themselves and with the reference diagnoses. The consultants often assigned a suspicious diagnosis: consultant A in 34 of all cases (20.4%), B in 50 (29.9%), C in 53 (31.7%) and D in 36 (21.6%). Consultants B and C used the categories SB and SM significantly more frequently than consultants A and D ($p = 0.005$). However, neither the difference of accuracy between consultants B and C ($p = 0.64$), nor that between consultants A and D ($p = 0.79$) was significant.

After grouping the SM and SB categories into the M and B categories, respectively, the diagnoses of the four consultants widely concurred with the reference diagnoses. Sensitivity, specificity, predictive values of positives and negatives, and the overall accuracy based on the data

Table 4. The rates of the four accuracy parameters for each of the four consultants

Accuracy parameter	Cons. A	Cons. B	Cons. C	Cons. D
TP	80	80	75	81
TN	72	67	64	73
FP	6	13	13	7
FN	8	7	14	6
Total	166 ^a	167	166 ^a	167

^a Consultant refused to make a diagnosis in 1 case.

Table 5. The rates of the quality parameters for each of the four consultants

Accuracy parameters with regard to malignancy	Cons. A	Cons. B	Cons. C	Cons. D
Sensitivity	90.9	91.9	84.3	93.1
Specificity	92.3	83.7	83.1	93.1
PPV	93.0	86.0	85.2	92.0
NPV	90.0	90.5	82.0	92.4
Overall accuracy	91.6	88.0	83.7	92.2
Accuracy of specified diagnosis	86.7	80.2	78.3	86.8

Values are percentages.

Table 6. Cohen's κ -values for the diagnostic concordance between the individual consultants

Consultants	κ -value and 95% CI for diagnosis of malignancy (n = 167)	κ -value and 95% CI for specified diagnoses (n = 167)
A/D	0.750 (0.664–0.834)	0.214 (0.017–0.409)
A/C	0.723 (0.638–0.808)	0.294 (0.116–0.472)
A/B	0.734 (0.648–0.820)	0.109 (–0.061–0.279)
B/D	0.702 (0.614–0.791)	0.219 (0.038–0.400)
C/D	0.672 (0.584–0.761)	0.192 (0.018–0.366)
B/C	0.706 (0.618–0.794)	0.381 (0.209–0.553)

Interpretation of κ -values: <0.2, poor; 0.21–0.4, fair; 0.61–0.8, substantial/good agreement.

¹ Cohen's κ -values show strong agreement with regard to the diagnosis of malignancy and fair agreement with regard to the specified diagnoses.

shown in table 4 ranged from 82.0 to 93.1%. The highest values were achieved by the most experienced consultants A and D (table 5).

The overall interobserver concordance was substantial ($\kappa = 0.791$). The best interobserver agreement was observed within the diagnosis of malignant cases ($\kappa = 0.829$), while less agreement was observed in the identification of benign cases ($\kappa = 0.763$). The κ values between A and D, A and C, B and D, and B and C indicated fair agreement, but it was poor between consultants A and B and only slight between B and D (table 6).

Concordance of Specified Diagnoses

The overall interrater concordance with respect to the specified diagnoses was also substantial ($\kappa = 0.784$). However, despite this good overall concordance some remarkable disagreement occurred among the participants regarding the special type of both neoplastic and nonneoplastic lesions.

The most challenging fields included classification of lung cancer and lesions of salivary glands, lymph nodes and the urinary tract. In 6 cases (3.6%) all diagnoses diverged in different ways from the reference diagnosis. The most spectacular case was an immunocytochemically proven prostatic adenocarcinoma in a peritoneal effusion, which remained unrecognized by all consultants (fig. 1). Other examples were non-small cell carcinomas (NSCC), one of which had been interpreted as breast carcinoma (1×), another as lymphoma (2×) and two as small cell carcinoma (SCC; 1× each). Three of five SCCs were diagnosed as NSCC. Misinterpretation as reactive cell change occurred in two pulmonary adenocarcinomas found in bronchial secretion (1× each). The acinus cell carcinoma of salivary glands was misdiagnosed as oncocytoma (1×), as Warthin tumor (1×) and as adenocarcinoma not otherwise specified (1×). The consultants agreed with the reference diagnosis in only 1 of the 4 Warthin tumors. In each of the other 3 cases the lesion was misinterpreted as adenoma, glandular cyst and pharyngeal carcinoma (1× each).

There were difficulties in differentiating between lymphadenitis and lymphoma. One FNA from reactive lymphadenitis was misinterpreted as low-grade non-Hodgkin leukemia (NHL; 2×) and one as high-grade NHL (1×), twice as high-grade NHL, and a third simply as not further specified lymphoma. The FNA from a diffuse large B cell lymphoma was once misdiagnosed as lymphadenitis and the FNA of Burkitt lymphoma was considered as unspecified 'lymphoma' (1×) or even misdiagnosed as lymphadenitis (2×), while only one consultant made the correct diagnosis. A case of low-grade NHL

Fig. 1. Peritoneal effusion with cells of prostatic adenocarcinoma misinterpreted as benign by all consultants. **a** Although there is no foreign population apparent at first glance, the poorly cohesive carcinoma cells show eccentric nuclei with variable size and shape, prominent nucleoli, and cytoplasmic vacuoles. Papanicolaou stain. Original magnification $\times 400$. **b** The prostatic origin of the adenocarcinoma is confirmed by immunocytochemical expression of prostate-specific acid phosphatase.

Fig. 2. Peritoneal effusion in a patient with chronic pancreatitis misinterpreted as lymphoma by all consultants. There is a monotonous small lymphocytic population with nuclear grooves. Multiplex-PCR showed no evidence of clonality. Papanicolaou stain. Original magnification $\times 630$.

in an effusion was misinterpreted as inflammation ($1\times$) and high-grade NHL ($1\times$), respectively. In 1 controversial case of peritoneal effusion the reference diagnosis was reactive lymphocytosis (ICC and multiplex NHL PCR without evidence of lymphoma and clonality), while all four consultants favored high-grade NHL (fig. 2).

There was considerable disagreement in the classification of urothelial atypia. In the 5 cases with the reference

diagnosis of benign urothelial cells, eight of the twenty consultants' diagnoses indicated a neoplastic lesion, including suspicious (G2, $5\times$) and high-grade urothelial neoplasia (G3, $1\times$), and a not further specified 'papillary tumor' ($2\times$). A case with the reference diagnosis of high-grade urothelial neoplasia (G3) was misinterpreted as mild atypia (G1) by two consultants.

Discussion

The study included consecutive routine cases from mixed sites and simulated the diagnostic procedures on the iPath telepathology platform under optimal conditions. Unlike 'real-life' situations, the number of images was confined to 3–5 images. However, they were captured by an experienced cytopathologist from optimally prepared specimens and consciously selected fields on the slides. Thus, major limitations, such as unsatisfactory fixation and deficient photographic technique [11, 14, 28], which frequently hamper the diagnosis on digital images sent via iPath by colleagues from countries with limited resources, were excluded. Importantly, the wet-fixed and mostly Papanicolaou-stained cells remained transparent and allowed the evaluation of the nuclear chromatin pattern as the most important cytological criterion of malignancy. The study shows that experienced cytopathologists are able to differentiate on still images between benign and malignant lesions with an accuracy of about 90%, and also with high interobserver concordance.

Nevertheless, the high overall accuracy found in this and other studies may present a distorted picture, as the high rate of concordance was achieved by putting together definite and 'hedged' [29] diagnoses qualified as 'suspicious'. The relevance of such uncertain diagnoses depends on the clinical setting and therefore could not be tested.

The reluctance to commit to a definite diagnosis has also been found in other studies on telemedical diagnoses [29]. At first glance, the fact that the rate of 'SB' was highest in consultants B and C may be caused by some fear of making an underdiagnosis which could keep the clinician from further examinations to confirm the diagnosis – a common attitude of pathologists. However, we cannot exclude that the limitation to as few as 3–5 images per case had a negative effect on the performance of the consultants, since the screening of the whole cytological slide can be an important part of the diagnostic process in some specimens. Given the selection of representative images, however, we do not view this as a critical factor in our study, but rather believe that our data closely reflect the true level of interobserver variability in extragynecological cytology. In fact, while a comprehensive overview on the accuracy of nongynecological cytology is lacking in the literature due to its wide variety in sites and type of specimens, there have been several important observations from the College of American Pathologists Interlaboratory Comparison Program using regular cytological slides [30–35]. The results of these programs were

similar to those of our image-based study. Together, this draws further attention to typical diagnostic pitfalls and notoriously difficult fields in nongynecological cytology, including the cytology of the urinary tract, respiratory tract, salivary glands, and lymphatic lesions or effusions.

According to one of these studies the misdiagnosis of NSCC as SCC or lymphoma and of SCC as NSCC is not unusual. The main source of error in these cases is the amount of cytoplasm, which may appear small in some NSCC and relatively abundant in well-preserved SCC cells [30]. Another well-known diagnostic problem is lymphoid lesions, which are frequently interpreted as FN or FP because of varying morphological pictures [31]. Such mistakes are avoidable by supplementary ICC, which is necessary in about 10–20% of cases to make an appropriate diagnosis [36]. It has also been shown that adenocarcinomas in FNAs of the breast are often misjudged as fibroadenomas [37] and that failure to diagnose Warthin tumors is common [31, 38].

The diagnostic difficulties and the high interobserver variability in urinary cytology have already been well perceived in previous studies [13, 18, 39]. Our previous online quiz with 246 participants showed that only 34% of the low-grade and 76% of the high-grade urothelial neoplastic lesions (G3) were concordantly assessed by the participants and that the rate of false diagnoses was also relatively high, even among experienced cytologists [18]. Driven by the confusion and worldwide heterogeneity in the classification and reporting of urinary cytology, there is an ongoing initiative to establish an international consensus system, referred as the 'Paris System for Reporting Urinary Cytology', sponsored by the International Academy of Cytology and the American Association of Cytology (<http://paris.soc.wisc.edu/>).

In the case of effusions, the large spectrum of different tumors that can spread into the serous membranes makes a specific diagnosis often challenging, especially when the images contain only a few tumor cells [35], or supplementary immunocytochemical or molecular tests are not available. Thus, differentiation between macrophages or benign mesothelial cells with reactive changes (nuclear atypia, prominent nucleoli, vacuolization of the cytoplasm or formation of pseudoepithelial clusters) from malignant disorders may be difficult on the ground of morphology alone, as shown in our study.

Despite all these different restraints it must be stressed that in general the accuracy of the diagnoses made by telecytology is not essentially different from the accuracy of diagnoses made on the glass slides [8, 9, 12, 13, 16, 40]. It has been shown with specimens of pleural effusions [27],

FNAs of the breast [41] and gynecological smears [9] that interobserver variability was not significantly lower whether the participant pathologists made their diagnoses on digital images or the original glass slides of the same cases. One could assume that using virtual slides instead of still images might improve the diagnostic accuracy and interrater concordance. However, this method is time consuming and does not fit into a patient-oriented service. It also demands good computer network connections and other infrastructural conditions, which are not accessible in countries with restricted resources.

Conclusion

Our study, based on a broad spectrum of cytological specimens, not only demonstrates the accuracy of consulting per telecommunication and highlights difficult di-

agnostic areas and pitfalls, but also confirms that digital images can serve as a useful resource for education and training in cytology. This is supported by another study which showed that the cytodiagnostic performance in thyroid lesions could be improved during different rounds of reviewing digital images [16]. Therefore, digital images are a valuable tool for training in cytology and can help in preparation for board examinations. The image series constituting the basis of our study is now publicly available at the freely accessible Pathorama platform (<http://pathorama.wordpress.com/extragenital-cytology-2013/>).

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