Virchows Archiv
https://doi.org/10.1007/s00428-023-03547-0

BRIEF REPORT

Integrating cytology into routine digital pathology workflow: a 5-year journey

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Received: 22 January 2023 / Revised: 13 March 2023 / Accepted: 20 April 2023

Abstract

Despite recent advances in digital imaging, the adoption of digital cytology is challenging due to technical limitations. This study describes our 5-year institutional experience with the implementation of digital cytology. The routine cytology workflow included conventional two-step screening by cytotechnologists, followed by sign out by pathologists. We introduced sign out of cytologic cases using a microscopic digital imaging platform operated by cytotechnologists, which allowed for remote review of slides by cytopathologists via video streaming. We also provided cytologic correlation to support the virtual slide-based sign out of histopathological specimens and for a weekly pathology-radiology conference. In addition, positive cytology cases were archived for integration into the laboratory information system and for prospective computational pathology studies. We also summarized lessons learned over the years and outlined our vision for future developments. This unique experience may serve as a role model for other institutions.

Keywords Digital pathology · Cytology · Whole-slide imaging · Telecytology

Introduction

Cytopathology and digital pathology are two distinct fields of pathology that have received increased recognition in recent decades. Cytopathology is widely used for diagnostic purposes, including cancer screening, and is reported as one of the most sought-after subspecialties on the pathology job market [1]. Digital pathology, which is based on whole slide images (WSI) produced by slide scanners, is a rapidly developing field driven largely by technical advances. It allows for remote work by pathologists and integration with downstream artificial intelligence (AI) algorithms. A blend of cytopathology and digital pathology, referred to as digital cytology, may have multiple use cases, including primary diagnosis by telecytology, rapid evaluations, remote consultation, various educational activities, quality assurance, and advanced image analysis [2].

However, the adoption of digital cytology into routine pathology workflows is challenging due to technical limitations. These limitations include the time required for scanning, storage needs, training requirements, lack of interoperability among multiple vendors, need for IT support, costs, and limited validation studies. Additionally, digital cytology has challenges related to morphological interpretation of 3-D structures of cells and tissue fragments, and focus challenges, such as difficulty in automated focusing in thick smears and in low cellularity specimens. Furthermore, there are workflow challenges such as handling slides with multiple stains, navigating slides for screening and interpretation, and remote rapid onsite evaluations [3].

Among the limitations mentioned above, the most important one is the acquisition of three-dimensional cytologic images. There are two advanced scanning modes that can deal with the 3-D issue: the *z*-stack mode and the extended depth of field (EDF) mode. The *z*-stack mode is an image

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Published online: 29 April 2023

acquisition method where images are captured from multiple planes along the *z*-axis above and below the subject plane to digitally reproduce what is viewed through the microscope. EDF is a way of image processing that integrates the best-focused images at each vertical plane into a single plane image file [3]. Both advanced scanning modes, however, have inherent technical limitations, with a slow scanning speed (up to 1 h per direct smear at 40×) being the major one. Another approach to facilitate telecytology is video microscopy, where a microscope digital camera streams video on a screen. It can be further equipped with screen sharing, remote control (robotic microscopy), and *z*-axis video. Ultimately, the output stream can be converted in WSI format.

Due to all the above complexities, there are a few reports available on successful implementation of routine digital cytology, which were mainly limited to rapid evaluations [4]. Herein, we report our institutional experience with implementing diagnostic digital cytology into daily clinical practice.

Materials and methods

Kameda Medical Center (Kamogawa, Japan) installed WSI scanners in 2017 and achieved 100% digital workflow for biopsies and surgical specimens in 2019 [5]. In 2018, we began utilizing telecytology to support the handling of over 20,000 cytologic specimens annually. To facilitate digital transition, the cytology workflow was switched to liquid-based cytology (SurePath™, Becton Dickinson, Franklin Lakes, NJ) with the primary aim of avoiding any areas that would not be scanned in direct smears. We also optimized the protocol of Papanicolaou stain by slightly diluting the staining solutions to match the colors on digital images with those seen under a microscope.

The equipment used for digital cytology included the Panoptiq digital image platform (ViewsIQ, Vancouver, Canada) and Motic EasyScan (Motic, Xiamen, China). The Panoptiq platform is a video microscopy tool that consists of an image capturing module with a high-performance digital camera mounted on a microscope and Panoptiq software, which digitally stitches multiple fields of view into a single panoramic view in real-time, further able to be saved in WSI format. It was used to manually scan each cytologic slide, pen-dotted after the screening step. The 4× objective was used to create digital maps in which regions of interest were later targeted and *z*-stack volumes were embedded with the 20× or 40× objective. The slides were scanned by cytotechnologists who received iterative training on the image scanning. Digital image on the monitor was shared through an online video meeting software, Webex (Cisco System, Inc., San Jose, CA). Consumer grade monitors with 4K resolution were used for viewing of digital slides. The Motic scanner was used for EDF scans obtained at 40× and saved in SVS format.

Ethical approval was obtained from the Institutional Review Board of Kameda Medical Center (IRB 20–132).

Results

We have implemented digital cytology in various aspects of our routine pathology workflow, including remote sign out, cytologic correlation for histopathological sign out, supporting clinical conferences, and archiving (Fig. 1).

The primary use case for digital cytology is the sign out of cytology cases using a live digital microscope operated by cytotechnologists (Fig. 1a). Similar to most institutions, our routine cytology workflow involves the initial screening of cytologic specimens by two cytotechnologists. Cases with positive findings or discordance are further reviewed by a senior cytotechnologist. Then, cases with malignancy, suspicious for malignancy, or other notable findings are signed out by a cytopathologist, where the digital sign out step has been introduced.

The digital sign out session is conducted remotely, as the attending personnel are often located at different sites. Schematically (Fig. 1a), the cytotechnician, typically accompanied by a junior resident, operates Panoptiq and streams a digital slide, specifically areas with atypical or suspicious cells, to the cytopathologist located in the central office to confirm or modify the initial diagnosis. This process began in 2018 and covers 25–30 cases per week. As a result, 1800 cases were remotely reviewed and signed out digitally by pathologists in the initial 16 months, which accounted for approximately 70% of all positive cases in the laboratory. Later on, this level fluctuated between 50 and 90%, being influenced by factors such as staff turnover, individual preference by cytopathologists, and COVID-related restrictions for part-time working doctors. The approximate distribution of digitally signed out cases is the following: 30% gynecologic cytology, 20% effusions, 15% urine, 15% fine-needle aspirates (thyroid, breast, lymph nodes, etc.), 10% bronchoalveolar lavage, and 10% other.

Secondly, we widely use the digital cytology system to provide cytologic correlation to support the digital sign out of histopathological specimens (Fig. 1b). Over 1900 biopsy and surgical cases had cytologic correlation in the first 2 years (about 20 per week), and this load level has been maintained continuously. In our institution, cytologic correlations are most effective when core needle biopsy (e.g., transbronchial lung biopsy) yields specimens that are suboptimal for histopathological evaluation due to their small size or ambiguous tissue findings. For example, in the illustrative case (Fig. 2), the tissue of the bronchial wall was limited with very

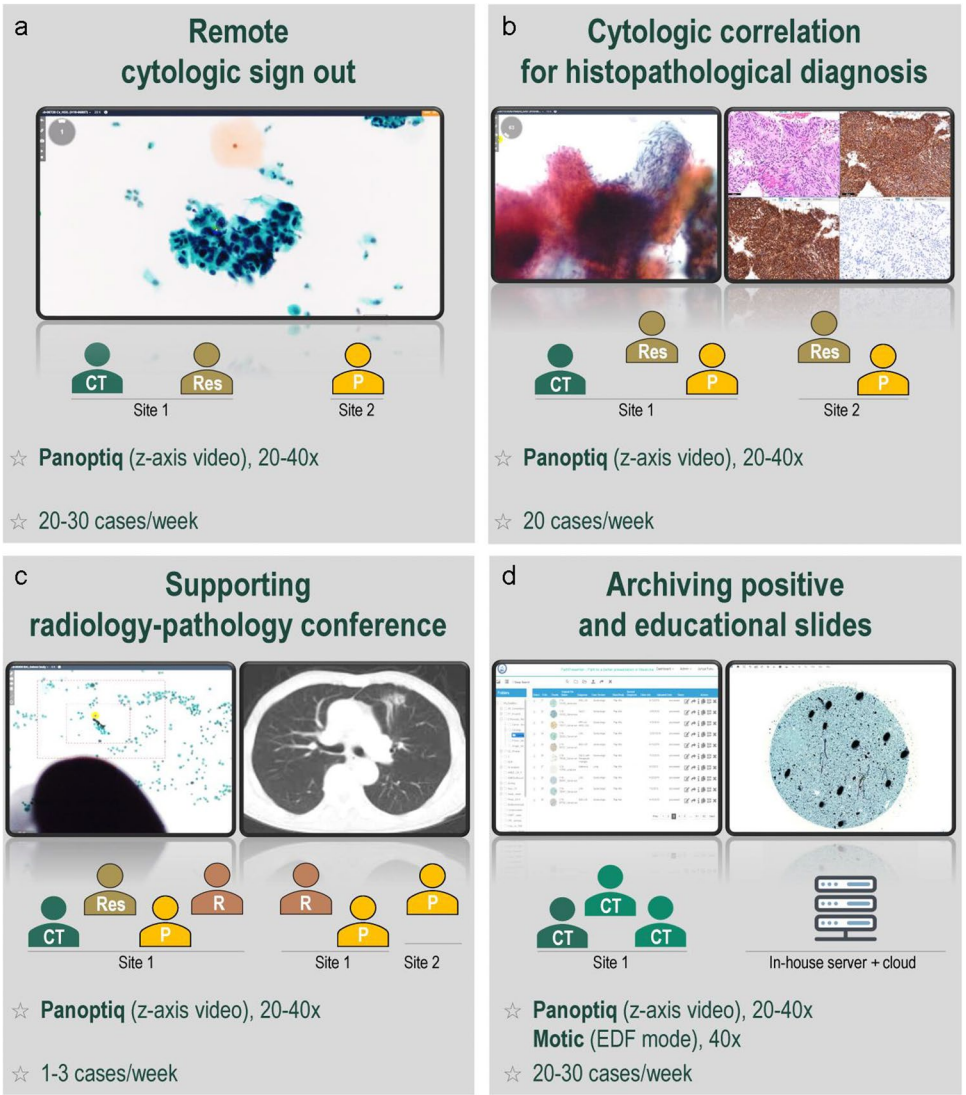

Fig. 1 Institutional use cases of digital cytology. Schematic layout of primary diagnosis via remote sign out (**a**), cytologic correlation for histopathological sign out (**b**), support of radiology-pathology and multidisciplinary conferences (**c**), and archival of educational cases and digital slides positive for malignancy (**d**). CT, cytotechnologist; Res, resident; P, pathologist; R, radiologist

few atypical glands, which were suspicious for malignancy. However, the needle washout cytology specimen obtained during the same procedure revealed classic adenocarcinoma cells. The final diagnosis was lung adenocarcinoma, despite the limited number of neoplastic glands in the tissue.

The digital cytology system also provides additional support for radiology-pathology conferences (1–3 cases per week), where we discuss cytology, histopathology, and radiology findings of challenging cases for diagnostic and educational purposes (Fig. 1c). This approach is also well-accepted by clinicians during multidisciplinary team discussions, such as tumor boards.

Finally, all positive cytology slides are archived for integration into the laboratory information system and for prospective computational pathology studies (Fig. 1d). For this purpose, we primarily use WSIs produced by slide scanner operating in EDF mode or, rarely in *z*-stack mode.

Discussion

Over the past decade, the adoption of digital pathology has been increasingly seen in clinical practice worldwide, as multiple validation studies have demonstrated high agreement between glass slides and whole slide images in histopathology [6]. Various use cases, ranging from primary diagnosis to remote consultation [7], have established a framework for workflow recommendations and guidelines [8, 9]. Conversely, the implementation of telecytology in clinical practice has lagged behind digital pathology, with a limited number of publications primarily focusing on technical aspects and validation studies [2].

According to the leading professional societies, implementation of digital pathology in daily practice should be preceded by in-house validation [8, 9]. In compliance with this requirement, our facility has validated the Panoptiq

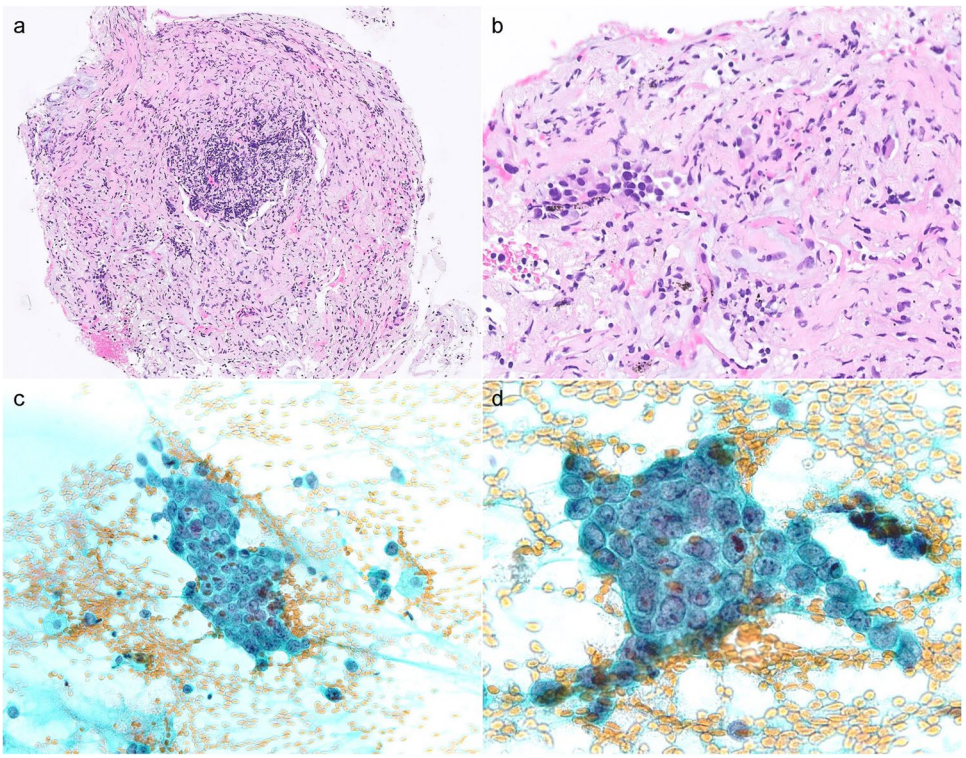

Fig. 2 Cytologic correlation for histopathology diagnosis. Bronchoscopic biopsy specimen of limited size showing a few atypical acini, suspicious but not conclusive for malignancy (**a**, **b**). Needle washing cytology with definite adenocarcinoma cell clusters (**c**, **d**). Hematoxylin and eosin, 100× (**a**), 400× (**b**). Papanicolaou stain, 200× (**c**), 600× (**d**)

digital imaging system prior to implementation, for both primary diagnosis [10] and consultation [11].

Our 5-year journey taught us valuable lessons that may be helpful for those considering a digital cytology transition. The most important was that since the existing equipment and technical solutions available on the market are not able to efficiently substitute a screening step in a mid-scale laboratory, we recognized that digital solutions would be more helpful at later stages of the cytologic workflow, such as double-checking positive and indeterminate cases and sign out by cytopathologists. We also found that digital cytology was effective in supporting radiology-pathology conferences, tumor boards, and other multidisciplinary team discussions. In addition to the ability to work remotely, another major advantage of the digital mode was a high educational attainment, with a high rate of engagement among residents and fellows.

Considering laboratory workflow, digital cytology still requires an ample manual input, particularly for screening, which is entirely done with conventional microscope, and scanning. In our case, we needed to hire a secretary to handle cytology slide scanning and quality control. This helped us maintain the turnaround time, which did not change after switching to digital cytology. From a technical standpoint, video microscopy coupled with either an advanced imaging platform or simple screen sharing sufficed for diagnostic purposes, while *z*-stack and EDF scans were useful for archiving. EDF is a reasonable alternative to *z*-stack for gynecologic samples. According to the cytopathologists' perceptions, it offers diagnostically sufficient quality for screening even when scanning with 20×. This magnification can also be used for archiving purposes, such as monitoring temporal changes in cervical smears over a long follow-up period. However, most of our cytopathologists suggest that non-gynecologic cytology requires scanning and evaluation at 40×, with a preference for *z*-stack over EDF mode. Of note, we did not use digital approaches for rapid cytology evaluations as they are not widely utilized in our institution. Furthermore, our experience with the robotic scanner was suboptimal due to the high latency of the device and the inability to synchronize remote control with actual slide movement.

In the short and medium terms, we will continue to apply digital cytology routinely for all the use cases described above. We also realized that the technical approach to remote digital sign out (choice of scanning mode and related workflow) may vary based on individual preferences of cytopathologists. Therefore, we are currently exploring modifications of the workflow to use conventional *z*-stack scanning, especially for non-gynecologic cytology. If successfully tested, this will support the need for a mid- or high-throughput scanner with *z*-stacking capability. Another obvious direction that we are currently investigating is the development of a highly sensitive in-house AI for screening purposes, with the aim of minimizing the false-negative rate, a key quality control measure in gynecologic cytology [12].

Based on our experience, AI tools allow efficient automation of tedious screening tasks [13].

In conclusion, we have shared our institutional experience of implementing diagnostic digital cytology, highlighting its possible applications, technical issues, tips for efficient workflow, and future directions. This unique experience may serve as a model for adoption by other institutions.

Author contribution AB: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, writing—original, review, and editing. AY: data curation, formal analysis, investigation, methodology, writing—original. JM: formal analysis, investigation, writing—review. TH: formal analysis, investigation, writing—review. JF: conceptualization, methodology, writing—review, and editing. All authors read and approved the final manuscript.

Data Availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval Institutional Review Board of Kameda Medical Center (IRB 20–132).

Competing interests J. F. is an advisor for N Lab Corp., outside the submitted work. Other authors declare no conflict of interest.

References

1. Zynger DL, Pernick N (2019) Understanding the pathology job market: an analysis of 2330 pathology job advertisements from 2013 through 2017. Arch Pathol Lab Med 143:9–10. https://doi.org/10.5858/arpa.2018-0388-LE
2. Eccher A, Girolami I (2020) Current state of whole slide imaging use in cytopathology: pros and pitfalls. Cytopathol 31:372–378. https://doi.org/10.1111/cyt.12806
3. Hanna MG, Pantanowitz L (2017) Why is digital pathology in cytopathology lagging behind surgical pathology? Cancer Cytopathol 125:519–520. https://doi.org/10.1002/cncy.21855
4. Lin O (2018) Telecytology for rapid on-site evaluation: current status. J Am Soc Cytopathol 7:1–6. https://doi.org/10.1016/j.jasc.2017.10.002
5. Sakamoto T, Furukawa T, Lami K, Pham HHN, Uegami W, Kuroda K, Kawai M, Sakanashi H, Cooper LAD, Bychkov A, Fukuoka J (2020) A narrative review of digital pathology and artificial intelligence: focusing on lung cancer. Transl Lung Cancer Res 9:2255–2276. https://doi.org/10.21037/tlcr-20-591
6. Azam AS, Miligy IM, Kimani PK, Maqbool H, Hewitt K, Rajpoot NM, Snead DRJ (2021) Diagnostic concordance and discordance in digital pathology: a systematic review and meta-analysis. J Clin Pathol 74:448–455. https://doi.org/10.1136/jclinpath-2020-206764
7. Shinohara S, Bychkov A, Munkhdelger J, Kuroda K, Yoon HS, Fujimura S, Tabata K, Furusato B, Niino D, Morimoto S, Yao T, Itoh T, Aoyama H, Tsuyama N, Mikami Y, Nagao T, Ikeda T, Fukushima N, Harada O, Kiyokawa T, Yoshimi N, Aishima S, Maeda I, Mori I, Yamanegi K, Tsuneyama K, Katoh R, Izumi M, Oda Y, Fukuoka J (2022) Substantial improvement of histopathological diagnosis by whole-slide image-based remote consultation. Virchows Arch 481:295–305. https://doi.org/10.1007/s00428-022-03327-2
8. Fraggetta F, L'Imperio V, Ameisen D, Carvalho R, Leh S, Kiehl TR, Serbanescu M, Racoceanu D, Della Mea V, Polonia A, Zerbe N, Eloy C (2021) Best practice recommendations for the implementation of a digital pathology workflow in the anatomic pathology laboratory by the European Society of Digital and Integrative Pathology (ESDIP). Diagnostics 11:2161. https://doi.org/10.3390/diagnostics11112167
9. Pantanowitz L, Sinard JH, Henricks WH, Fatheree LA, Carter AB, Contis L, Beckwith BA, Evans AJ, Lal A, Parwani AV (2013). Validating whole slide imaging for diagnostic purposes in pathology: guideline from the College of American Pathologists Pathology and Laboratory Quality Center. Arch Pathol Lab Med 137:1710–1722. https://doi.org/10.5858/arpa.2013-0093-CP
10. Groen R, Abe K, Yoon HS, Li Z, Shen R, Yoshikawa A, Nitanda T, Shimizu Y, Otsuka I, Fukuoka J (2017) Application of microscope-based scanning software (Panoptiq) for the interpretation of cervicovaginal cytology specimens. Cancer Cytopathol 125:918–925. https://doi.org/10.1002/cncy.21921
11. Yamashiro K, Yoshimi N, Itoh T, Takino H, Nakajima M, Azuma M, Taira K, Makio S, Shiina SI, Hata S, Urabe S, Fukuoka J, Mori I (2019) A small-scale experimental study of breast FNA consultation on the internet using Panoptiq. J Am Soc Cytopathol 8:175–181. https://doi.org/10.1016/j.jasc.2018.12.002
12. Koonmee S, Bychkov A, Shuangshoti S, Bhummichitra K, Himakhun W, Karalak A, Rangdaeng S (2017) False-negative rate of Papanicolaou testing: a national survey from the Thai Society of Cytology. Acta Cytol 61:434–440. https://doi.org/10.1159/000478770
13. Zaizen Y, Kanahori Y, Ishijima S, Kitamura Y, Yoon HS, Ozasa M, Mukae H, Bychkov A, Hoshino T, Fukuoka J (2022) Deep-learning-aided detection of mycobacteria in pathology specimens increases the sensitivity in early diagnosis of pulmonary tuberculosis compared with bacteriology tests. Diagnostics 12:709. https://doi.org/10.3390/diagnostics12030709