International Journal of Laboratory Hematology
The Official journal of the International Society for Laboratory Hematology

ORIGINAL ARTICLE INTERNATIONAL JOURNAL OF LABORATORY HEMATOLOGY

Performance evaluation of a dynamic telepathology system (Panoptiq™) in the morphologic assessment of peripheral blood film abnormalities

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doi:10.1111/ijlh.12294

Received 12 May 2014; accepted for publication 18 August 2014

Keywords
Telepathology, blood film morphology, performance evaluation, haematology laboratory practice

SUMMARY

Introduction: The study evaluated the performance of a dynamic imaging telepathology system (Panoptiq™) as a diagnostic aid to the identification of peripheral blood film (PBF) abnormalities.
Methods: The study assumed a laboratory personnel working in a clinical laboratory were operating the telepathology system to seek diagnostic opinion from an external consulting hematopathologist. The study examined 100 blood films, encompassing 23 different hematological diseases, reactive or normal cases.
Results: The study revealed that with real-time image transmission in live scanning mode of operation, the telepathology system was able to aid reviewers in achieving excellent accuracy, that is correct interpretation of morphologic abnormalities obtained in 83/84 of the hematologic diseases and 12/12 of the reactive/normal conditions (Sensitivity: 0.99; Specificity: 1.00). In contrast, when only saved static images in digital capture mode of operation were reviewed remotely, interpretative omissions occurred in 8/84 of the hematologic diseases and 0/12 of the reactive/normal conditions (Sensitivity: 0.91; Specificity: 1.00). It is hypothesized that real-time operator-reviewer communication during live scanning played an important role in the identification of key morphologic abnormalities for review.
Conclusion: Our study showed the Panoptiq system can be adopted reliably as a dynamic telepathology tool in aiding community laboratories in the triage of PBF cases for external diagnostic consultation.

INTRODUCTION

As its inception through the use of video microscopy in 1968 [1], telepathology or 'the practice of pathology at a long distance' [2, 3] has become a growing field and increasingly relevant in the modern era of integrated pathology services. Telepathology is being increasingly accepted as part of the routine consultative services in

anatomical pathology [4], However, in haematopathology, there are few reports on the general application of telepathology in the morphological assessment of the peripheral blood film (PBF). The difficulty in the adoption of telepathology in daily practice is likely due to a combination of human, process and technology barriers. Most importantly, PBF review is a complex interpretative process requiring effective communication between skilled technologists and pathologists as well as systematic examination of the PBF, starting with macroscopic examination of the stained film, with progression from low-power to high-power microscopic examination [5]. Furthermore, many digital imaging systems currently available have limited magnification options available for viewing haematopathological specimens, and whole slide imaging for such specimens on high magnification would require prolonged digital scanning time and high storage requirements [4, 6, 7].

In this study, we report the evaluation of the performance of a new dynamic imaging system (Panoptiq™, ViewsIQ, Richmond, BC, USA) [8], when applied to the practice of telehaematopathology, as a diagnostic aid to the review of PBF morphologic abnormalities and compared to the gold standard of light microscopy. This digital imaging system integrates with the existing microscope and permits the users in the referring laboratory to switch between low and high magnification modalities with ease, as well as to digitally stitch together multiple fields of view, into a single panoramic view in real time. The panoramic view can be transmitted as a saved image or a dynamic live image through internet to an outside institution. The ultimate goal of the study is to understand whether the new telepathology system can reliably assist laboratory personnel in a community hospital seeking a diagnostic opinion from an expert haematopathologist in a remote location.

MATERIALS AND METHODS

Digital imaging system

The Panoptiq system is a new image stitching-based system that coverts regular light microscopes into a real-time digital slide scanner. The Panoptiq system consists of a digital video camera, a desktop computer and the Panoptiq software [8]. A video demonstrating the set-up and operation of Panoptiq system can be viewed on YouTube (http://youtube/hpTwDiqBX1I). The camera is mounted to the camera port of a regular light microscope and captures the magnified slide view at 15 frames/s (Figure 1). The camera outputs the digital video images to the PC that runs the software. As the user views the slide, the software captures the current microscope field of view and stitches it to the previous fields of view, creating a single panoramic scan. These real-time stitching images of the microscope view can be reviewed remotely and instantaneously, referred to as live scanning (LS) mode. Alternatively, the images can be scanned and saved as still image file (SVS format), referred to as digital capture (DC) mode. In DC mode, the saved scan can be e-mailed to the remote viewer or placed in a network drive accessible by the remote viewer for consultation. Compared to the LS mode, the remote viewer is limited to viewing the area scanned by the

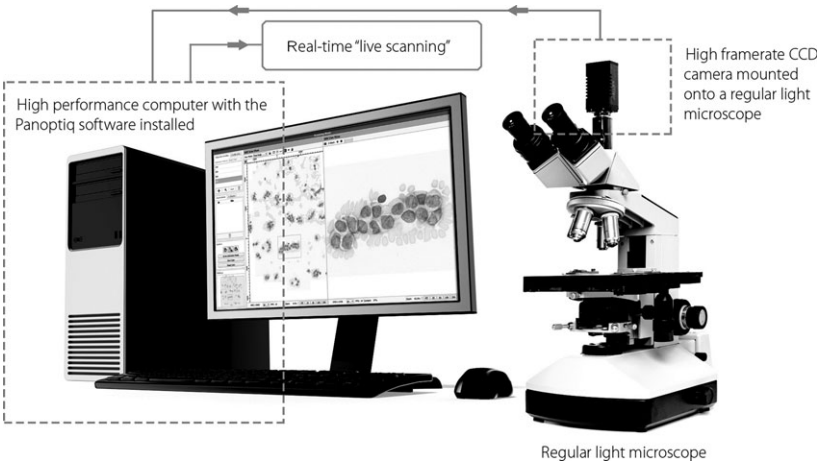

Figure 1. Illustration of the Panoptiq systems Setup - Image is captured through the high framerate camera as the user views the peripheral blood film on the microscope. Subsequently, the image output is processed through the high performance computer using the Panoptiq software which facilitates the real-time "live scanning" of the captured image into a paranomic image.

microscope user and any unscanned portion of the slide is not accessible. The Panoptiq® system works with the range of objectives on the microscope in clinical laboratory and has been verified to stitch images ranging from 2 to 100× objectives.

Study design

A total of 100 PBF (study slides) were randomly chosen from 213 cases of archival patient materials or supplementary external proficiency PBF samples within the study period from 1 February 2012 to 31 January 2013, using a block randomization method and prepared for the digital imaging study. The study slides encompassed 23 different haematological conditions in 5 disease categories and a control category comprised of reactive or normal cases (Table 1).

Table 1. List of disease conditions included in the digital image study

Disease categories	Case selection
I. Acute leukemias	12
Acute promyelocytic leukaemia	4
Acute myeloid leukaemia	4
Acute lymphocytic leukaemia	4
II. Myelodysplastic/myeloproliferative neoplasms	20
Chronic myelogenous leukaemia	4
Polycythemia vera	4
Essential thrombocythemia	4
Myelodysplastic syndrome	4
Chronic myelomonocytic leukaemia	4
III. Mature B-cell neoplasms	16
Chronic lymphocytic leukaemia	4
Hairy cell leukaemia	5
Lymphoma	6
Myeloma	1
IV. Red cell/platelet abnormalities	28
Microangiopathic haemolytic anaemia	4
Immune thrombocytopenia	4
Polychromasia (blood loss)	4
Autoimmune haemolytic anaemia	4
Megaloblastic anaemia	4
Oxidative haemolysis	4
Sickle cell anaemia	4
V. Red cell inclusion/parasites	12
Hyposplenism/asplenism	4
Malaria (*Plasmodium falciparum*)	3
Malaria (*Plasmodium vivax*)	4
Babesiosis	1
VI. Normal/reactive conditions	12
Reactive neutrophilia	4
Reactive lymphocytosis	4
Normal	4
Total	100

The study design was created to evoke the use of the Panoptiq system in the context of a real laboratory working environment, in which a laboratory personnel working in a community laboratory. In the study, Pathologist A, a board-certified (FRCPC) anatomical pathologist, receiving fellowship training in haematopathology, operated the Pantoptiq system to obtain a diagnostic opinion from a consultant haematopathologist from a remote location. The study slides were divided into two sets of 50 slides each (Set A and Set B), containing equivalent numbers of slides for each disease condition. Haematopathologists I and II, both are board-certified (FRCPC) academic haematopathologists, examined the selected slides under both the LS and DC modes of operation by the Panoptiq system (Figure 2).

Reviewer bias was eliminated by ensuring that cases were randomized to both sets and the LS and DC images viewed by one haematopathologist were from different sets. For the LS mode of operation, WBC, haemoglobin and platelet values accompanied each slide along with a standard statement as to whether the abnormality being interrogated was 'a white blood cell abnormality', 'a red blood cell abnormality' or 'a platelet abnormality'. A statement signifying 'previous history of acute myeloid/lymphoblastic leukaemia' was provided for four cases containing extremely rare blasts. For the two cases of plasma cell leukaemia, a statement stating 'monoclonal protein present' was provided. Slides with no morphological abnormality were also provided for examination; however, in this instance, false statements suggesting a white blood cell, red blood cell or platelet abnormality were provided. Both haematopathologists were warned that the statements regarding the presence of a certain blood cell component abnormality may be false to increase vigilance surrounding the diagnoses. The intent was to simulate possible erroneous diagnostic impressions offered by the laboratory personnel in a community laboratory or rural hospital setting. For Set A and B slides, live scanning performed by Pathologist A was first read by Haematopathologist I and II, respectively, at 10× magnifications, within the central area of the blood smear in which the red

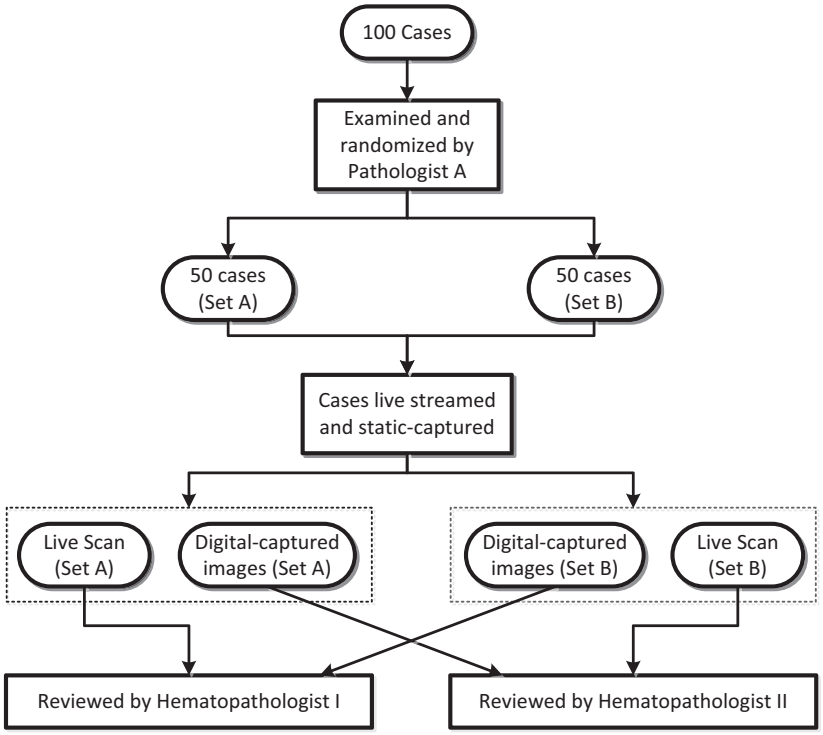

Figure 2. Overview of study design. Both Hematopathologists I and II performed LS and DC analysis on cases using the Panoptiq system. Reviewer bias was eliminated by ensuring that cases were randomized to both sets and the live scan and digital capture images viewed by one hematopathologist were from different sets.

blood cells appear evenly dispersed with no flattening or distortion artefacts [9]. The view was then switched to scanning at 50× magnification by Pathologist A in an area representative of the overall slide and/or demonstrating the abnormal cells. Communication between the scanning operator (Pathologist A) and the reviewers were carried out via telephone. The scanning procedures were discontinued when the Haematopathologists signified to the scanning operator that they were able to come to a diagnosis. The Haematopathologists could ask for further information about the CBC or differential (if available) as needed. While conducting the imaging in LS mode, the remote operator (Pathologist A) would save the scanned LS images as digital capture images (DC) for the DC mode of operation. These images were used by the second haematopathologist to examine the cases reciprocally. In the DC Mode of operation, the consulting haematopathologist was provided with the same standard statement and print out with attached CBC and differential values as in the LS model of operation. In the study, there was a minimal 3-week washout period between the review of the same PBF cases in the LS and DC modes for both haematopathologists.

To prevent reviewer bias in the case selection process, all of the study slides were randomized and re-examined by the haematopathologists using light microscopy after a washout period of >3 weeks, upon completion of both the LS and DC portions of the study. [10, 11] This was a validation step to ensure that in the opinions of both of the haematopathologists, the PBF slides contained sufficient diagnostic clues for the pre-assigned disease conditions first labelled by Pathologist A. Only cases with consensus diagnoses agreed upon by both haematopathologists *via* light microscopy were included in the comparative diagnostic performance analysis. In total, four cases were excluded as follows: myelodysplastic syndrome (one case), immune thrombocytopenia (one case) and polychromasia/blood loss (two cases).

Statistics

All statistical analyses were performed using SPSS program (SPSS v21, Chicago, IL, USA). The Cohen's d statistic was used to establish the minimum effective sample size for each of the main disease categories, aiming to maintain a statistical power of ≥80% and a significance level of 5%. Diagnostic performance

Table 2. Performance evaluation of the Panoptiq system using the LS and DC modes of operation

		Live scanning (LS)				Digital capture (DC)				LS *versus* DC
		Correctly classified/ total cases (*n*)				Correctly classified/ total cases (*n*)				
	Disease categories	Disease	Non-disease	Sensitivity	Specificity	Disease	Non-disease	Sensitivity	Specificity	Kappa
I.	Acute leukemia	12/12	84/84	1.00	1.00	12/12	83/84	1.00	0.99	0.95
II.	Myelodysplastic/myeloproliferative neoplasms	18/19	77/77	0.95	1.00	17/19	77/77	0.89	1.00	0.97
III.	Mature B-cell neoplasm	16/16	80/80	1.00	1.00	15/16	80/80	0.94	1.00	0.93
IV.	Red cell/platelet abnormalities	25/25	71/71	1.00	1.00	22/25	71/71	0.88	1.00	0.91
V.	Red cell inclusions/parasites	12/12	84/84	1.00	1.00	10/12	84/84	0.83	1.00	0.90
	All	83/84	12/12	0.99	1.00	76/84	12/12	0.91	1.00	0.82

analysis, including sensitivity and specificity, was calculated for evaluation of the telepathology performance. The two-tailed proportion *z*-test was used to assess statistical significance, and the Cohen's kappa statistic was used to measure the inter-rater agreement between LS and DC modes of operation.

RESULTS

Performance evaluation of the Panoptiq system

When compared to the gold standard of light microscopy, the Panoptiq system achieved excellent accuracy with the LS model of operation (Table 2). The pathologists were able to establish the correct interpretation of the morphologic abnormalities in nearly all of the haematologic disease cases (Overall: 83/84 cases). The only mismatch was a case of chronic myelomonocytic leukaemia, being interpreted as a reactive infection/inflammatory condition by digital scanning method (Haematopathologist II). No reactive or normal conditions were misclassified as having a haematologic disease (12/12 cases). With the DC mode of operation, the pathologists were able to make a correct interpretation in the majority of disease cases (Overall: 76/84 cases), while no reactive or normal conditions were misclassified as having a haematologic disease (12/12 cases). One case of lymphoma was misinterpreted as acute myeloid leukaemia by DC.

There is an overall good concordance between the LS and DC mode of operations, suggesting that both modalities are useful in providing assessments on the variety of haematologic disorders/conditions seen on peripheral blood films. However, the DC mode yielded a lower sensitivity than the LS model of operation (Overall sensitivity – DC: 0.91, LS: 0.99; $P = 0.02$). Haematopathologist I and II contributed to 2/8 and 6/8 of the diagnostic omissions in DC mode, respectively (Table 3). The crucial diagnostic omissions in the DC method were confined to the Group IV (Red cell abnormalities) and Group V (Red cell inclusion/parasites) categories (Combined sensitivity of Group IV and V – DC: 0.87, LS 1.00; $P = 0.02$). These were likely related to pathology conditions that contained scant or spotty diagnostic clues, for example low density of red cell inclusions or parasites. Other factors contributing to the lower sensitivity in DC mode of operation could include morphological overlap

Table 3. Interpretative omissions by Panoptiq in digital capture mode

Diagnosis by microscopy	Case (*n*)	Attributable remarks
Hyposplenism/asplenism	1	Howell Jolly Bodies were interpreted as stain debris
Autoimmune haemolytic anaemia	1	Polychromasia and nucleated red cells were noted, but spherocytes were mistaken as slide artefacts
Megaloblastic anaemia	1	Insufficient diagnostic clues present. Oval macrocytes but not hypersegmented neutrophils were noted
Malaria (*P. falciparum*)	1	Malarial parasites were not detected due to low parasitemia with few ring forms
Sickle cell anaemia	1	Anemia with hypochromic red cells and asplenic features, but the hallmark sickle cells were not detected
Lymphoma	1	Mantle cell lymphoma. Malignant cells were interpreted as leukemic blasts
Chronic myelomonocytic leukemia	1	Insufficient diagnostic clues. Minimal dysplastic changes in the neutrophilic series
Essential thrombocythaemia	1	Insufficient diagnostic clues. Marked thrombocytosis were present

between disease entities, quality of the slide preparations or scanning approach between the two haematopathologists resulting in variability of digital material available for the review by the second haematopathologist. Another contributing factor is the absence of exchange of information when operating in the DC mode. Overall, these results suggest that the new dynamic telepathology system is useful in conveying morphological abnormalities of PBF and the LS function, in particular, is a reliable screening tool for clinical laboratories requesting diagnostic consultations from more specialized centres.

DISCUSSION

In recent years, there has been an accelerated technological development in the use of digital telepathology in anatomical and clinical pathology disciplines. Key benefits of telepathology are the ability to provide timely accessibility to remote expert pathology review, and good education and knowledge transferal to the front line technical workers in a laboratory. The Panoptiq system represents a newer generation of dynamic microscopy system, which permits the user to transmit either static or dynamic images to remote locations through an internet connection. Advances in image processing and high performance computing technologies have enabled the real-time stitching of high-quality images, at both low and high magnifications. Upon viewing the stitched images, the user can zoom in-and-out to facilitate the diagnosis and evaluation of the PBF slides. In our study, the Panoptiq system yielded comparable performance to conventional microscopy for PBF interpretative review with the LS mode of operation. With the capability to conduct live scanning and viewing, the operator of the specimen slides and the consulting pathologist can engage in a bi-directional dialogue to convey essential clinical information and to co-select the desirable morphological anomalies of interest for review. An advantage of the LS mode of operation is that it simulates the actual diagnostic process where the consulting haematopathologist takes ownership of guiding the screening process, by first obtaining a low objective scanning of the blood smear, followed by an inquisitive zoom-in approach towards recognizing fields of interest and targeting abnormalities, while engaging in constant communication and feedback with the operator from the referring laboratory. This mode of operation is suited towards distant pathology consultation, when there is already a morphologic query in mind so that the exploration can be targeted towards specific fields of interest. In contrast, the DC method lacked the effective communication between the operator and reviewer of the blood smear in choosing the right fields for scanning and reviewing and may lead to crucial diagnostic errors.

This study has several limitations. First, it was performed in a single institution; and hence, there were relatively few cases of individual diseases included in the study. In addition, the study did not consider the issue of operator's bias, as the same pathologist was

involved in the selection and presentation of the PBF samples for review. Also, the study did not address the issue of interprofessional practice variance. Nonetheless, in our opinion, Panoptiq system serves as a good diagnostic tool and is well suited to a smaller hospital setting, in aiding the triage of PBF cases for diagnostic consultation. Our study also highlighted the fact that despite good performance with the use of static images for case consultation, the lack of effective communication between the operator and reviewer remains a major barrier and could induce systems vulnerability and critical diagnostic omissions.

Telepathology is still in its early stages of technological evolvement and implementation. Despite the demonstration of good diagnostic performance comparable to conventional microscopy in our study and others [12–15], challenges still remain before it can be safely introduced to supplement routine practice for manual blood film review [16]. incorporate digital imaging system successfully into routine laboratory haematology workflow, a standardized imaging capturing strategy must be developed and adopted by regional laboratory services. The strategic plan must include the understanding of the unique service requirements of the laboratory, the need for dependable telecommunication infrastructure of the laboratory networks, proper standard operating procedures, diligent technologist training and continuous competency assessment to ensure standardized and high quality PBF scanning and review process. Professional organizations such as the Canadian Association of Pathologists and the Digital Pathology Association have published guidelines for telepathology service in anatomical pathology using whole slide scanning [10, 11]. Development of similar professional guidelines related to the general application of telepathology in haematopathology would be of great benefit to ensure high-quality professional practice standards.

ACKNOWLEDGEMENTS

The authors would like to thank Jim Yakimec, Kanwal Deol, Todd Markin, Sandie Delvecchio, Sharlene Zwick and Kathy Blok for their technical assistance with this project.

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