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Validation of Remote Digital Pathology based diagnostic reporting of Frozen Sections from home

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ABSTRACT

Background: Despite the promising applications of whole-slide imaging (WSI) for frozen section (FS) diagnosis, its adoption for remote reporting is limited.
Objective: To assess the feasibility and performance of home-based remote digital consultation for FS diagnosis.
Material & Method: Cases accessioned beyond regular working hours (5 pm–10 pm) were reported simultaneously using optical microscopy (OM) and WSI. Validation of WSI for FS diagnosis from a remote site, i.e. home, was performed by 5 pathologists. Cases were scanned using a portable scanner (Grundium Ocus®40) and previewed on consumer-grade computer devices through a web-based browser (http://grundium.net). Clinical data and diagnostic reports were shared through a google spreadsheet. The diagnostic concordance, inter- and intra-observer agreement for FS diagnosis by WSI versus OM, and turnaround time (TAT), were recorded.
Results: The overall diagnostic accuracy for OM and WSI (from home) was 98.2% (range 97%–100%) and 97.6% (range 95%–99%), respectively, when compared with the reference standard. Almost perfect inter-observer (k = 0.993) and intra-observer (k = 0.987) agreement for WSI was observed by 4 pathologists. Pathologists used consumer-grade laptops/desktops with an average screen size of 14.58 inches (range = 12.3–17.7 inches) and a network speed of 64 megabits per second (range: 10–90 Mbps). The mean diagnostic assessment time per case for OM and WSI was 1:48 min and 5:54 min, respectively. Mean TAT of 27.27 min per case was observed using WSI from home. Seamless connectivity was observed in approximately 75% of cases.
Conclusion: This study validates the role of WSI for remote FS diagnosis for its safe and efficient adoption in clinical use.

Introduction

The benefits of digital pathology (DP) are myriad and profound, with various applications viz. primary diagnosis, second opinion, education, quality assurance, multidisciplinary meetings and artificial intelligence-based algorithms.[1–3] A static telepathology link set up for a second opinion between our centre and a sister institution in a prototype rural area in the year 2000 is regarded as a seminal work in the field of digital pathology in India.[4,5] Our previous validation studies performed as per the College of American Pathologists (CAP) recommendations have endorsed the non-inferiority of whole slide imaging (WSI) over conventional optical microscopy (OM) for primary surgical pathology diagnosis.[6–10] Emergence of the Covid-19 pandemic provided a golden opportunity for the expansion of DP by enabling the continuity of diagnostic surgical pathology services remotely.[11,12] Our team being the very early adopter of remote DP reporting from home, which was started on 21 March 2020.[13]

Intra-operative consultation/frozen section (FS) diagnosis, also called *"Hot Seat diagnosis"*, is a demanding and challenging job for pathologists. In the recent past, increasing utilisation of WSI for intra-operative consultations has been observed to overcome the shortage of pathologists, with emphasis on sub-specialisation and centralisation of pathology services.[14] In addition to financial constraints to adopting this technology, there are concerns, especially for FS, pertaining to the scanner's capabilities in handling FS slides, the timely transmission of digital slides to the remote location and the need to render the diagnosis within stipulated timelines.

Advancements in the WSI technology, information technology(IT) infrastructure and better connectivity, along with validation studies for FS consultation across the globe, have endorsed its safe adoption for clinical use for telepathology/remote reporting (Table 1).[14–28] Till date, the role of DP in FS diagnosis was primarily based on experience over the digital network established either within the same hospital or between a group of hospitals within the same health system (hub and spoke model) in a con-

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Table 1
Comparison of the current study with the major published WSI studies on remote FS reporting.

Author, year	Number of cases (slides)	Scanner (scanning magnification)	Diagnostic accuracy	Location of the reporting station	Mean scanning time (range)	Mean reporting time/case	TAT
Ramey J et al. 2011	67 cases (210 FS slides	20× with an Aperio Scanscope	89% (8% Minor & 3% major discordances)	Mobile, high-resolution viewing devices – iPads	2:46 min	4:59 min/case or 1:20 min/slide	NM
Ribback et al., 2014	1204	Mirax Desk	98.35%	Within hospital network	2–7 min	NM	10:58 ± 8:19 min
Pradhan D *et al.* 2016	20 cases (60 slides)	Panoptiq dynamic imaging system (Prosilica GT camera attached to an Olympus B × 45 microscope Panoptiq 3 version 3.1.2 software) and WSI using ×20 using an Aperio XT Scanscope (Leica)	98.3% for Panoptiq images and 100% for Aperio WSI	Compare Glass slide vs Panoptiq Panoramic image vs WSI within the hospital network	5–10 min	NM	NM
Cima *et al.*,2018	125 cases (436 slides)	Navigo (20 X)	97%	Within the hospital network from another building	12 min	3 min	26 min
Perron E et al. 2014	104 cases	Hammamatsu Nanozoomer	98.1%	Remote off-site in the hospital set up	4:46 (1–25 min)	2:07 (1–10) min	20:01 min (range, 8–43)
Huang, Y et al. 2018	5233 cases	Motic EasyScan, China	99.77%	Within the hospital network of 71 centres using an online website-based TP consultation platform, http://www.hypathology.com	10 min	NM	30 min (In 5101 cases of the TP platform, 3058 cases took less than 30 min, 1809 cases took between 30 and 60 min, and 234 cases took more than 60 min)
French JMR *et al.* 2019	65	Lieca Aperio CS2 (20 X)	96.7%	Remote off-site in the hospital set up	NM	NM	27.5 min (21.75–38.5 min)
Laurent-Bellue A *et al.* 2020	386 cases (441 slides)	Leica Biosystems Aperio (20 X)	92.7%	Remote off-site in hospital setup (two hospitals)	3–6 min (Digitalization plus transfer)	1–10 min	36 min
	238 cases (307 slides)	Leica Biosystems Aperio (20 X)	93.9%	Remote off-site in hospital set up (2 hospitals)	3–6 min (Digitalization plus transfer)	1–10 min	38 min
Menter T *et al.* 2020	42 (30 + 12)	DP 200 (40X)	100%	Remote off-site in the hospital set up	4 min (1–9 min)	2 min (1–7 min)	11 min (6–22)
Griffin J *et al.,* 2020	211	Hammamatsu Nanozoomer (20 x)	92.6%	Remote off-site in the hospital set up	NM	NM	NM
Kaushal *et al.*, 2021	60 (120 slides)	Grundium Ocus® (20 x)	95%	Within the hospital, another building	1:47 min	1:08 min	15 min
Marletta S et al 2022	60 cases (80 slides)	NTP NED. Micro. DP® microscope-based scanner at 40× magnification	95.1%(organ suitability) 100%(cancer risk)	Reporting using Tablets	NM	NM	NM
Girolami I et al 2022	100 cases (pilot phase)	D-Sight (Menarini) at 20× & 40×	85%	Remote off-site in hospital set up in hub & spoke model	NM	NM	NM
	2058 cases (3078 Slides [routine diagnosis]	D-Sight (Menarini) at 20× & 40×	92%	Remote off-site in hospital set up in hub & spoke model	4:52 (3:57–7:45 min)	10–30 min	NM
Kantasiripitak C *et al* 2022	63 cases (295 FS slides)	Motic Easy Scan, (40 X)	99%	Remote Reporting using Laptops	2 min	1 min	NM
Current study 2022	60 cases (252 Slides	Grundium Ocus® (40 X)	97.6%	Remote Home Reporting using consumer-grade Laptops/desktop	4:55 min	5:54 min	27.27 min

TAT – turnaround time, NM – not mentioned, WSI – whole slide imaging, TP – telepathology, min – minute.

trolled working environment. However, few investigators have attempted its clinical validity for the remote FS sign-out beyond conventional hospital networks.[14] Further, there is a paucity of literature, especially from developing countries, regarding the use of WSI for FS diagnosis.[8,21,28]

A prospective validation study was undertaken to evaluate the feasibility and performance of home-based remote digital consultation for FS diagnosis. To the best of our knowledge, this is the first-ever study conducted on the diagnostic utility of WSI for remote home FS diagnosis using a portable digital scanner system and consumer-grade computer workstation systems from a developing country like India.

Materials and methods

A blinded prospective observational study comparing WSI versus conventional OM for intra-operative/FS diagnosis from home was performed following approval from the institutional ethics committee.

Case enrolment, scanning and remote reporting

Extended FS services were requested for 2 weeks by the hospital administration beyond regular working hours from 5 pm to 10 pm in August 2021 in Tata Memorial Hospital, Mumbai, India. FS accessioned during this period were reported simultaneously using 2 modalities viz. OM from FS room and WSI from home. Routine FS service during these extended working hours was continued conventionally by assigning an additional evening duty shift to a consultant pathologist and histo-technologist on a daily rotation basis. The intra-operative treatment decisions were taken based on the onsite diagnosis offered using conventional OM in the FS room.

The FS slides were digitised by the trained histo-technologist in the FS room using Grundium Ocus@40 (Tampere, Finland), a portable microscope-based scanner at 40X magnification (0.25 μm/pixel) using an either automated or manual selection of area of interest (AOI). Scanning commands were executed through the existing office computer in the FS room. This scanner has its own in-built computer system with 500 GB internal storage and preinstalled scanning software, image viewing software, image server, and a web server. Functional capabilities of the scanner in handling the FS slides were assessed onsite with respect to the scanning of different types of slide preparations, i.e., haematoxylin and eosin (H&E) and toluidine blue (TOLB) stained slide(to assess versatility), successful scanning rate (number of the first-time scan and rescans), scanning speed (scan time per slide) and image size for each case. The possible reasons for failed scans, if any, were also recorded.

All FS slides for a particular case, including those, with multiple FS parts, were scanned. FS from different/multiple sites for a given case were considered individual parts. For each unique FS, a minimum of 2 slides were selected, including each H&E and TOLB-stained slide, as per the existing department practice for slide preparation in FS.

The scanning technologist performed pre-scanning quality checks so that the glass slide preparation variables did not compromise digital image quality. All slides were preserved for glass slide evaluation at a later date. The selected FS cases were categorised into 3 broad categories, viz. primary diagnosis, margin and lymph node status, based on the original clinical request.

Two resident pathologists were posted in the FS room on a rotation basis to coordinate the scanning and relaying of the clinical information and digital cases to the reporting pathologists. The cases were previewed and evaluated independently by 5 pathologists (including 3 specialist pathologists and 2 general pathologists at various stages of their career in the field of diagnostic pathology) from home using personal consumer-grade laptops/desktops computer devices on a web-based image viewing software (https://grundium.net). The image database was accessed through the internet using the HTTPS protocol coupled with timed Lightweight Directory Access Protocol (LDAP) authentication in collaboration with the IT department of the hospital. Four pathologists had prior experience with DP for primary surgical pathology diagnosis. A short training, enabling familiarisation with the digital platform and reporting, was imparted to the fifth pathologist. The resident pathologist shared the relevant clinico-radiological information and case details through a Google spreadsheet. FS diagnosis was also conveyed through the same Google spreadsheet by each reporting pathologist from home. Each reporting pathologist ensured data privacy and data integrity.

A Google form was created to collate data from each pathologist regarding hardware specifications of the computing device, including monitor (type of device, model, processor, operating system, RAM, monitor size, screen resolution, colour bit depth, colour format and navigation tools used) along with network specifications (web browser and internet connectivity speed) at remote reporting stations.

Diagnostic assessment; WSI versus OM

Each FS case was evaluated twice by all 5 pathologists independently, blinded to the original onsite FS diagnosis and other pathologist's diagnoses. Each diagnosis rendered by the reading pathologist on FS case (whether by WSI or OM) was termed a "read". Hence, there were 10 "reads" per FS case/part besides the reference (i.e., onsite) diagnosis (Fig. 1). The initial

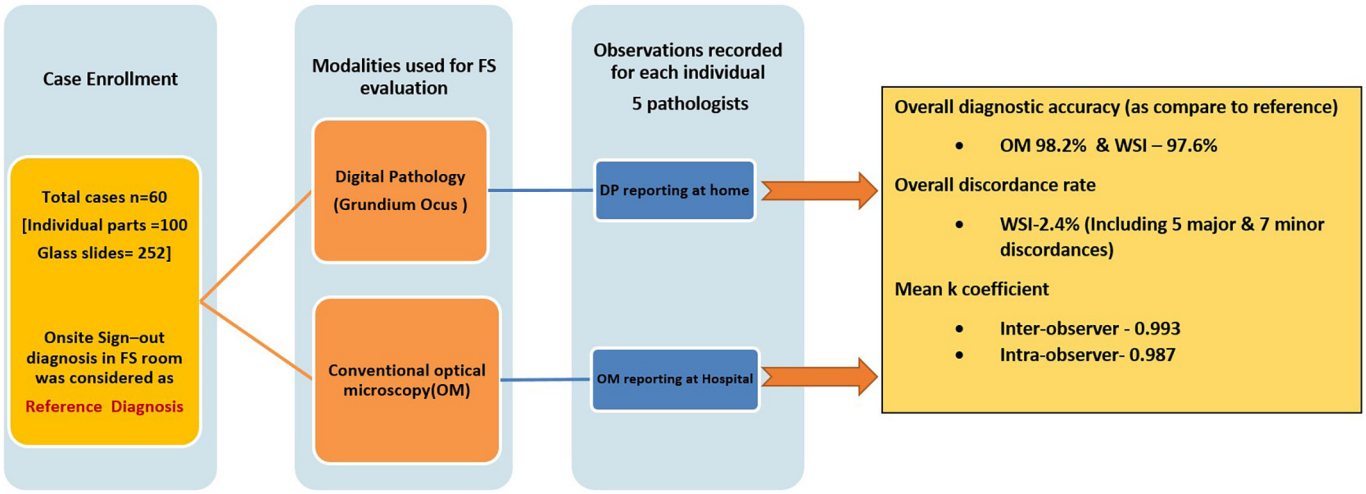

Fig 1. Workflow design & key findings for the remote FS validation study.

digital assessment was performed at home, followed by a glass slide review using the consultant's office microscopes, after a minimum washout period of 1 month.

The same clinical details available at the onsite FS consultation were provided to all reporting pathologists during remote digital sign-out and glass slide evaluation. The original sign-out diagnosis, offered by the reporting pathologist stationed in the main FS room using the existing OM in the FS room, was considered a reference standard. The top-line diagnoses rendered either on WSI or OM by participating pathologists were compared against this reference diagnosis to evaluate the diagnostic accuracy and inter-observer concordance. The intra-observer concordance rate was also recorded for each participating pathologist (using paired WSI versus OM reads). Concordant diagnoses were documented as absolutely correct (perfect match-coded as A1) and essentially correct (near perfect match coded as A2) as compared to reference diagnosis. Diagnostic discrepancies were classified as minor (coded as B) and major (coded as C) discordances, depending on the level of clinical impact they can cause. All discrepant diagnoses were discussed with participating pathologists, and a consensus reference diagnosis was established after evaluating the permanent paraffin section of the corresponding FS, if required. In addition, inter-observer, as well as intra-observer kappa agreement for WSI versus OM, were calculated based on unweighted kappa statistics. To establish the non-inferiority of WSI over OM for remote reporting, the cut-off criteria of difference of <5% compared to the reference standard was adopted.[10]

The level of confidence for reporting for each FS case was compared for both modalities (WSI versus OM) by all pathologists individually on a scale of 1–3; wherein 1 denoted low, 2 denoted average and 3 denoted high level of confidence for the diagnosis rendered. Deferral, if any, with reason/s for deferral was recorded. Network-related issues such as WSI latency (lag in image loading after opening the digital image) while evaluating digital images remotely were assessed on a scale of 1–3 for each case; wherein 1 denoted highly unstable connection or transmission of poor quality images precluding any pathologic evaluation via telepathology, 2 denoted slow, unstable connection or incomplete image processing and transmission of all the fields of image, precluding a confident diagnosis via telepathology and 3 denoted stable connection with the nearly flawless transmission and image processing to render a comfortable diagnosis via telepathology.

Diagnostic assessment time; turnaround time (TAT)

Turnaround time (TAT) for FS was the interval between receiving tissue in the FS room and communicating the diagnosis to the operating surgeon. This time consisted of slide preparation time (SPT) and slide interpretation time (SIT). SPT refers to the interval between receiving tissue and the availability of glass slides/digital images for review by the pathologist. Hence, scanning time and image relay time for remote TP consultation were added to SPT. The trainee resident doctor recorded the time in the FS room, at which the tissue was received and when a diagnostic image was first available to the pathologist. SIT referred to the interval between the receipt of the first diagnostic image of the case by the pathologist and the communication of the diagnosis, recorded by the reporting pathologist at home. Hence, TAT = SPT (inclusive of scanning time & relay time) + SIT. The individual pathologist recorded and compared the time to arrive at a diagnosis for both modalities, i.e. FS room and remote location.

After all cases were reviewed by both modalities; data was compiled and analysed on an Excel spreadsheet by the study coordinator.

Results

Sample cohort

A total of 60 FS cases (after excluding 6 FS cases that were deferred for glass slide sign-out) comprising 100 individual parts and 252 slides (including 127 H&E and 125 TOLB) were included for digital sign-out from home between the 2 and 20 August 2021. Amongst deferral cases, 3 had significant digital artefacts, 1 had freezing artefacts, 1 lung biopsy had excessive anthracotic pigment obscuring histomorphology evaluation, especially on WSI and 1 for a second opinion (Fig. 2).

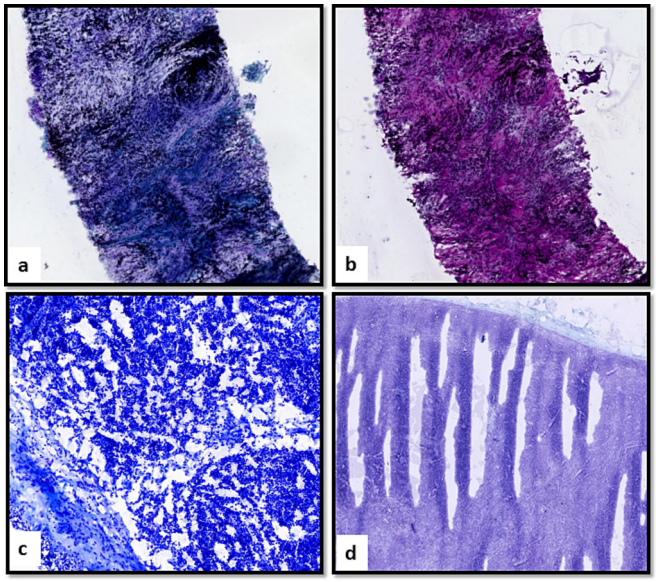

Fig 2. Photomicrograph of deferred FS cases; Alung biopsy with excessive anthracotic pigment obscuring histomorphological details, (a: Toluidine blue; 10× & b: H&E; 10×). A lymph node with significant freezing artefacts in the form of holes (c: Toluidine blue; 10×) and large chatters (d: H&E; 10×) on the FS slides.

The average number of slides per case was 4 (range = 2–14 slides). The distribution of these 100 FS parts, according to the clinical indications, was: lymph node status (n = 35/100), margin assessment (n = 32/100) and primary diagnosis (n = 33/100). Cases across all sub-specialities were incorporated in the study, including maximum cases from the head and neck region (n = 16), gastrointestinal tract (n = 13), thoracic (n = 12) and breast (n = 10).

Onsite technical assessment of the scanner

The first-time successful scanning rate was 93.6% (236/252). Sixteen slides (6.4%) were successfully scanned on the second attempt. The mean scanning time per H&E and TOLB stained slide was 4 min and 24 s (range; 0:40–28:00 min) and 4 min and 55 s (range; 0:50–30:00 min), respectively. Three slides of H&E and 5 slides of TOLB consumed more than 10 min to scan. The reason for prolonged scanning in these cases was the disruption in the connectivity between the scanner and the computer workstation used to execute the scanning command. It was required to reboot the scanner device on 3 occasions to re-establish the connection, which, on average, took an additional 4 min to restart the scanning process.

A total digital data of 220.97 GB were generated by scanning these 252 slides. The mean storage space occupied per slide for H&E-stained slides was 0.978 GB (range: 0.09–6.39 GB), and for TOLB-stained slides was 0.804 GB (range: 0.1–6.39 GB). Hence, there was no significant difference between scanning time and storage space occupied for H&E versus TOLB for FS slides.

Diagnostic assessment; WSI versus OM

A total of 1000 diagnostic reads (OM-500 and WSI-500) by 5 pathologists were recorded to evaluate the diagnostic accuracy and reproducibility of DP for FS diagnosis from home as compared to OM. In the current study, overall diagnostic accuracy compared with the reference standard for OM and WSI was 98.2% (range 97%–100%) and 97.6% (range 95%–99%), respectively (Fig. 1). A total of 21 discordant reads out of 1000 diagnostic reads were recorded, including 9/500 for OM and 12/500 for WSI by all

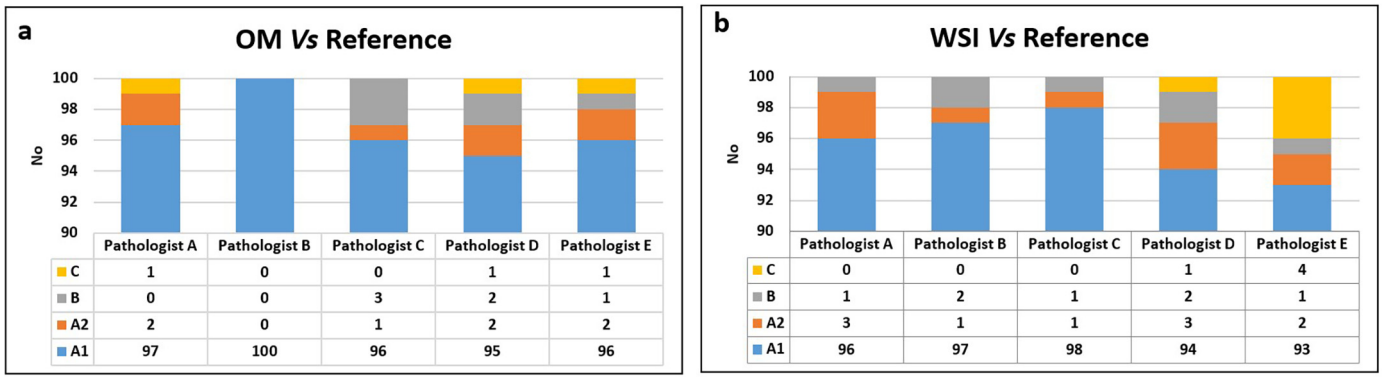

Fig 3. Bar diagram shows the diagnostic accuracy of OM versus reference standard (a) and WSI versus reference standard (b). Concordance (Absolute [A1] and essentially correct [A2]) and Discordance (minor [B] and major [C]), OM: Optical microscopy, WSI: whole slide imaging.

5 pathologists, as compared to the reference standard. The overall discordance rate for OM was 1.8% (9/500) [including 0.6% (3/500) major and 1.2% (6/500) minor discordances]. The overall discordance rate for WSI was 2.4% (12/500) [including 1% (5/500) major and 1.4% (7/500) minor discordances]. Hence, the overall difference between the clinically significant discrepancies by WSI for remote reporting and OM diagnosis was only 0.6%, and the difference was not statistically significant. The mean difference in the diagnostic accuracy for WSI as compared to the reference standard was <5% for all observers. Pathologist E observed a maximum of 5 discordances (4 major and 1 minor) on WSI evaluation (Fig. 3A & B).

There was almost perfect inter-observer agreement (k > 0.9) for OM (mean k coefficient of 0.979) for all 5 pathologists when compared to the reference standard. Almost perfect inter-observer (as compared to reference standard), as well as intra-observer (as compared to individual OM) agreement for WSI, was detected for 4 pathologists with mean k coefficient of 0.993 and 0.987, respectively. Near-perfect (k > 0.8) inter-observer (0.875) and intra-observer (0.848) kappa concordance for WSI was observed by the fifth Pathologist (E) (Fig. 4A & B).

All discordances (major and minor) observed in this study were summarised in Table 2, and a few examples were illustrated in Fig. 5. The major discordances were noted in 5 cases, including 3 for margin assessment and 1 each for lymph node status and primary diagnosis. All 6 cases of minor discordance were for primary diagnosis.

The overall confidence level was low for remote reporting by WSI compared to the OM for all the participating pathologists. Pathologist A recorded the highest level of confidence in reporting FS cases using WSI remotely, whereas pathologists B and E rated a relatively higher number of cases with level 2 of confidence as compared to others (Fig. 6).

The mean glass slide and digital artefact rate for FS cases in this cohort, as observed by all pathologists, were approximately 3% (38/1260 glass reads) and 9.6% (122/1260 digital reads), respectively. Common glass slide artefacts were freezing artefacts (n = 12), uneven and thick sections with folds (n = 11), faint staining, especially TOLB (n = 10), overstaining (n = 3) and mounting-related issues (n = 2). Common digital artefacts were focal out-of-focus images (n = 30 reads), blurring (n = 24), pixelated images (n = 19), stitching errors (n = 19), very dark/dull images (n = 6) and missing tissue parts (n = 3) (Fig. 7). Interestingly, a higher number of digital artefacts were observed in TOLB slides (n = 36) compared to H&E slides. None of the digital slides, except the one with significant digital artefacts (n = 3), were deferred during evaluation (Fig. 2).

Diagnostic assessment time and turnaround time; WSI versus OM

The overall mean diagnostic assessment time (SIT) by all pathologists for OM (1:48 min) was significantly less as opposed to remote reporting using WSI (5:54 min) across all specimen types for FS diagnosis. Pathologist B took less time to report on WSI than other pathologists (Fig. 8). The mean glass slide preparation time (SPT) per frozen slide for H&E and TOLB was 12 min 59 s (range; 3:50–28:12 min) and 11 min 20 s (range; 3:40–25:03 min), respectively, with an average of 12:09 min/case. Further, an additional mean time of 9:23 min (including 4:28 min for H&E and 4:55 min for TOLB slide) per frozen section case was required for scanning. Hence, an average TAT of 27.27 min (SPT + SIT,

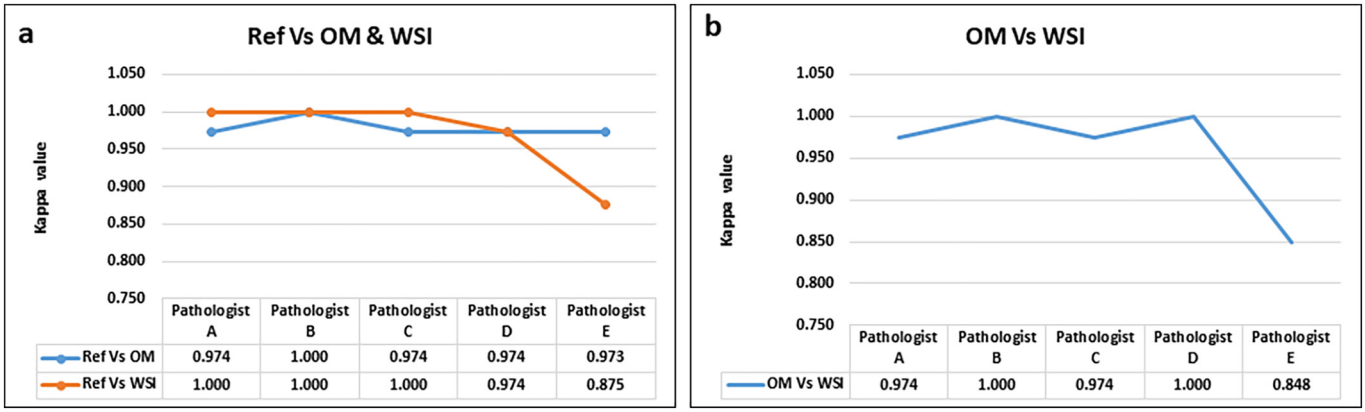

Fig 4. Line diagram shows inter-observer agreement (a) of 5 pathologists using OM and WSI as compared to a reference standard and intra-observer agreement (b) of pathologists between their own OM and WSI observations for remote reporting of frozen sections.

Table 2
Summary of discordant FS diagnostic reads (OM & WSI).

Sr No	Specimen type	Reference diagnosis	Glass slide diagnosis	Digital diagnosis	Modality (OM/WSI) and discrepant pathologist	Discordance category
1	Lung Resection Bronchial cut margin	Free of tumour	Margin involved by tumour	Free of tumour	Pathologist A- OM	Major
2	Lung Resection FS1 – Vascular cut margin	Free of tumour	The vessel wall shows a tumour	Involved by tumour	Pathologist D- Both OM & WSI	Major
			Free of tumour	Involved by tumour	Pathologist E – WSI	
	Lung Resection FS2- Revised Bronchial Margin	Free of tumour	Free of tumour	Involved by tumour	Pathologist E – WSI	
3	Common bile duct margin	Inflamed mucosa with reactive atypia. No invasive Tumour	Free of tumour	Low-grade dysplasia at the margin. No invasive tumour	Pathologist E – WSI	Major
4	Axillary lymph node sampling	1 out of 6 lymph nodes shows metastasis (1/6)	Reactive Lymph nodes (0/6)	1 out of 6 nodes show micrometastasis	Pathologist E – OM	Major
5	Breast nodular lesion biopsy	Intraductal papilloma	Multiple tiny papillomas with apocrine change	DCIS	Pathologist E – WSI	Major
6	Mediastinal mass excision	Myxoid liposarcoma	Myxoid neoplasm	Malignant nerve sheath tumour	Pathologist A – WSI	Minor
7	Uterus – Hysterectomy with B/L salpingo-oophorectomy	Endometrioid adenocarcinoma FIGO Grade II Invading less than half of the thickness of the uterine wall	Endometrioid adenocarcinoma, FIGO II. Invading less than half of the thickness of the uterine wall	Endometrioid adenocarcinoma, FIGO II. Invading more than half of the thickness of the uterine wall	Pathologist B – WSI	Minor
			High-grade endometrioid adenocarcinoma (grade III), infiltrating less than half of myometrium	High-grade endometrioid adenocarcinoma (grade III) invades more than half of myometrium	Pathologist C – both OM & WSI	
8	Lung biopsy	Granulomatous inflammation	Granulomatous inflammation	Chronic inflammation, No granulomas or malignancy	Pathologist B, E – WSI	Minor
9	Porta hepatis (deposit) in a case of Carcinoma stomach	Fibro-collagenous tissue with sparse chronic inflammation	Granulomatous inflammation. Await paraffin processing for a definitive diagnosis	Negative for malignancy	Pathologist C – OM	Minor
			Negative for malignancy	Suspicious but deferred for the Second Opinion	Pathologist E – WSI	
10	Adnexal mass	Mucinous cystadenoma	Borderline mucinous neoplasm, no stromal invasion	Mucinous neoplasm, no definite invasion. Await paraffin processing	Pathologist C – OM	Minor
11	Tissue from Left orbital apex & superomedial orbit	Inverted papilloma	Inverted papilloma with moderate dysplasia	Inverted papilloma with moderate dysplasia	Pathologist D – Both OM & WSI	Minor

OM- Optical microscopy, WSI- Whole slide imaging, FS- Frozen section, DCIS- Ductal carcinoma in situ.

i.e., (12.09 + 9:23) + 5:54 min) per FS case was recorded in our study using WSI from a remote location for FS diagnosis.

Digital reporting workstations and connectivity at remote FS sign-out

Computer systems used by pathologists for remote FS reporting from home were consumer-grade laptops (n = 4) and desktops (n = 1) with an average screen size of 14.58 inches (range = 12.3–17.7inches) and a screen resolution ranging from 1366x768 to 2736x1824. The computer units used had Intel Core i5 (n = 3), i7 (n = 1) and Celeron (n = 1) processors, operating on a 64-bit Windows 10 Home (n = 4) and Mac OS (n = 1), 8 GB RAM (except 4 GB RAM in 1 system) and run at 1.5–3.4 GHz. Displays devices used by all pathologists had a colour depth of 8-bit colour depth, sRGB colour format and SDR (Standard dynamic range), brightness power of 300 cd/m^2 and a contrast ratio of at least 1000:1. Four pathologists used the mouse to navigate the cases, whereas 1 pathologist used the laptop touchpad. Network connectivity speed ranged from 10 to 140 megabits per second (Mbps), averaging 64 Mbps. On the network connectivity scale of 1–3, for remote digital reporting from home, 3/4th of cases were reported at a seamless connectivity rate of 3 (average 75.66% cases and 83.3% slides) followed by an intermediate connectivity rate of 2 (average 22.02% cases and 15.07% slides) and extremely poor connectivity rate of 1 (average 2.32% cases and 1.74% slides). One pathologist had an almost seamless digital connection, while 3 pathologists faced more connectivity glitches, as summarised in Table 3. Based on the pathologist's experience during remote reporting from home, the unstable internet connectivity had resulted in a lag in opening/pixelation of images; hence, screening all the fields of digital images was time-consuming. Another concern about the remote reporting from home was the fear of missing the small focus of metastatic tumours in lymph nodes on the small screens and about timely communication of the FS results to the operating surgeon.

Discussion

A high diagnostic concordance (97.6%) for remote FS reporting was accomplished in this study using a low-cost portable digital slide scanner and consumer-grade laptops/desktops by 5 pathologists. Several studies have demonstrated accuracy rates of over 90% for WSI systems for FS compared to conventional microscopy[8,16–28] (Table 1). In addition to successful validation for remote FS sign-out as per CAP recommendation (discordance rate <5%), there was almost perfect intra- and inter-observer agreement amongst pathologists, highlighting the reproducibility of this WSI system in routine clinical use. Pathologist E, the one with lower concordance amongst all observers, had the least sign-out experience for both OM and WSI, compared to the rest.

The present study used a low-cost portable digital slide scanner (Grundium Ocus@40), which could effectively handle our FS slide load with a first-time successful scanning rate of 93.6%. On average, the scanning time per slide @40x magnification was <5 min, which was in concordance with high-end scanners used in other studies (Table 1).[8,16–28] Scanning at 20x can significantly reduce the scanning time (Average –

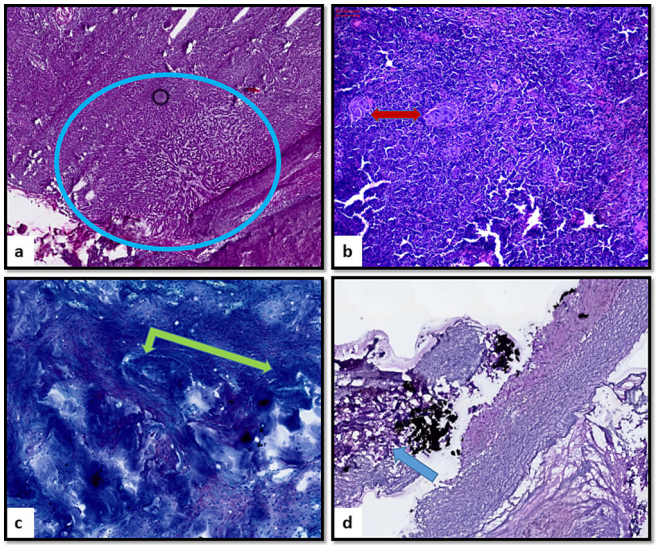

Fig 5. Photomicrograph of a few discordant FS cases. A scanty area of metastasis toward the edge of an axillary lymph node in the case of carcinoma breast (a: H&E; 4×) and foci of micro-metastasis in another case (b: H&E; 10×) was challenging to identify using WSI on small consumer-grade monitors at home. A mucinous adenocarcinoma of the appendix wherein scanty tumour foci (arrowhead) were masked by mucin and difficult to identify on Tol B stain. (c: 10×). Vascular margin with a focus of crushed tissue with anthracotic pigment (arrow), misinterpreted as involvement by a tumour in case of neuroendocrine tumour of lung (d: H&E; 10×).

1:47 min/slide) using the same scanner as demonstrated in our previous study on FS.[8] Further, the image quality of these digitalised slides was reasonably good, despite few artefacts observed in these digital FS slides as expected due to inherent nature of FS glass slide preparation (more section thickness, folds and freezing artefacts – Figs. 2 and 7). Only 3 cases were deferred due to significant digital artefacts. The majority of digital artefacts (focal out-of-focus areas, blurring and pixelation artefacts) in this study could be attributed to the network connectivity and small screen size of the computer devices used at remote locations and were not related to the performance of the scanner. Interestingly, a higher number of digital artefacts were observed with TOLB compared to H&E-stained FS slides in this study, which was not documented earlier.

The results of this study provided a unique opportunity to compare onsite FS diagnosis with DP-based remote reporting from home in a real-world scenario which would allow allaying the scepticism/apprehensions with remote FS sign-outs for clinical use in future. The present study was performed in accordance with the recent CAP recommendations for validating WSI, including a broad spectrum of commonly encountered FS cases in an oncology setting and addressed all pertinent issues one may encounter in a real-world clinical environment.[9,10] Based on this evaluation of a WSI system for remote FS reporting, attention should be paid to these 3 key considerations: (1) Efficient WSI scanning system to handle FS slides, (2) trained pathologist to report FS in digital format remotely and (3) effective and secured bi-directional digital network for timely and seamless relay of digital images and communication of FS diagnosis.

To date, only a few studies have documented the use of affordable devices such as tablets/smartphones and consumer-grade laptops instead of expensive medical-grade monitors in pathology outside the hospital network for FS remote reporting. Ramey et al[16] were the first to demonstrate FS assessments using WSI on a mobile device (iPad) with a diagnostic accuracy rate of 89%. Marletta et al.[26] also used tablets for WSI intraoperative consultation with 95.1% and 100% accuracy for organ suitability and cancer risk assessment, respectively, for transplant cases. However, these authors have expressed their reservations about using these mobile devices and reported frustrations, delays or errors among the users.[14,16] Recently, Kantasiripitak et al[28] reported 99% concordance for intra-operative lymph node assessment using consumer-grade laptops and a low-cost scanner.[28] The results of our validation study using consumer-grade computer devices would serve as a confidence-building measure to the pathologists, for reporting the FS cases remotely, even in the resource-constrained setting.

Remote FS diagnosis was more time-consuming compared to conventional OM. The median TAT of 27.27 min per case reported in the remote reporting arm in the current study was slightly longer than reported in the literature [range – 11–38 min/case (average 17.75 min) Table 1].[14–28] The longer time TAT in the current study was very significant, as it can challenge the clinical use of this system for FS interpretation as being a failure to meet the expected TAT of less than 20 min for FS reporting as per CAP recommendations.[29]

A frequent technical problem contributing to reluctance to adopt DP for remote FS reporting is slow internet connectivity resulting in longer TATs and misinterpretation in diagnosis.[14,27] Suboptimal connectivity was observed while evaluating approximately 25% of the digital reads in the current study. Although a transmission speed of 1 gigabyte per second (Gbps) range is now being recommended for DP networks, it may not be achievable at times. Further, real-world information about the exact connectivity speed is still lacking in the majority of DP studies for FS. Hence, it is challenging to accomplish the comparative assessment pertaining to this point.

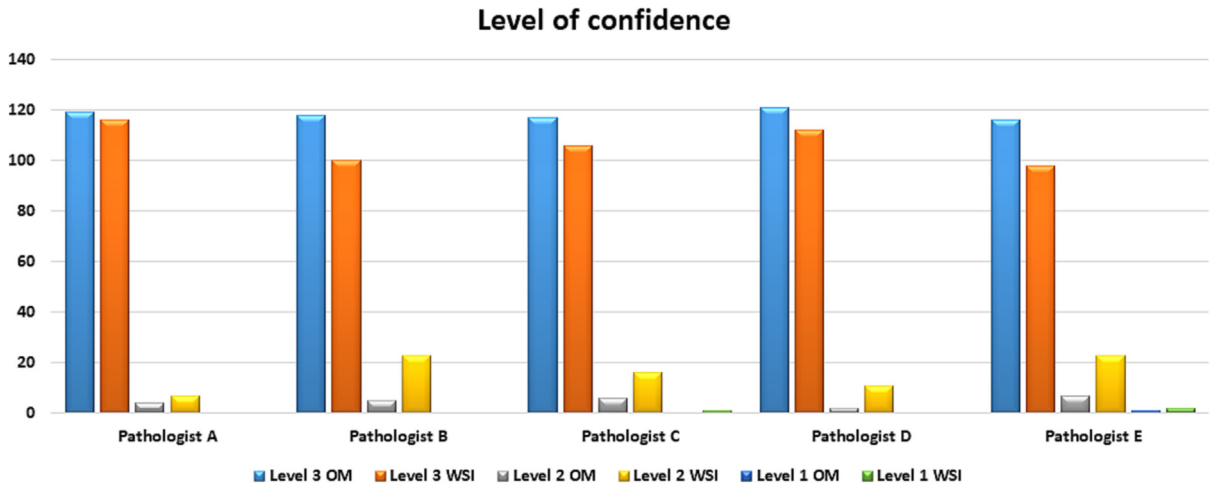

Fig 6. Bar diagram shows the overall level of confidence of individual pathologists for OM and WSI for remote FS sign-out.

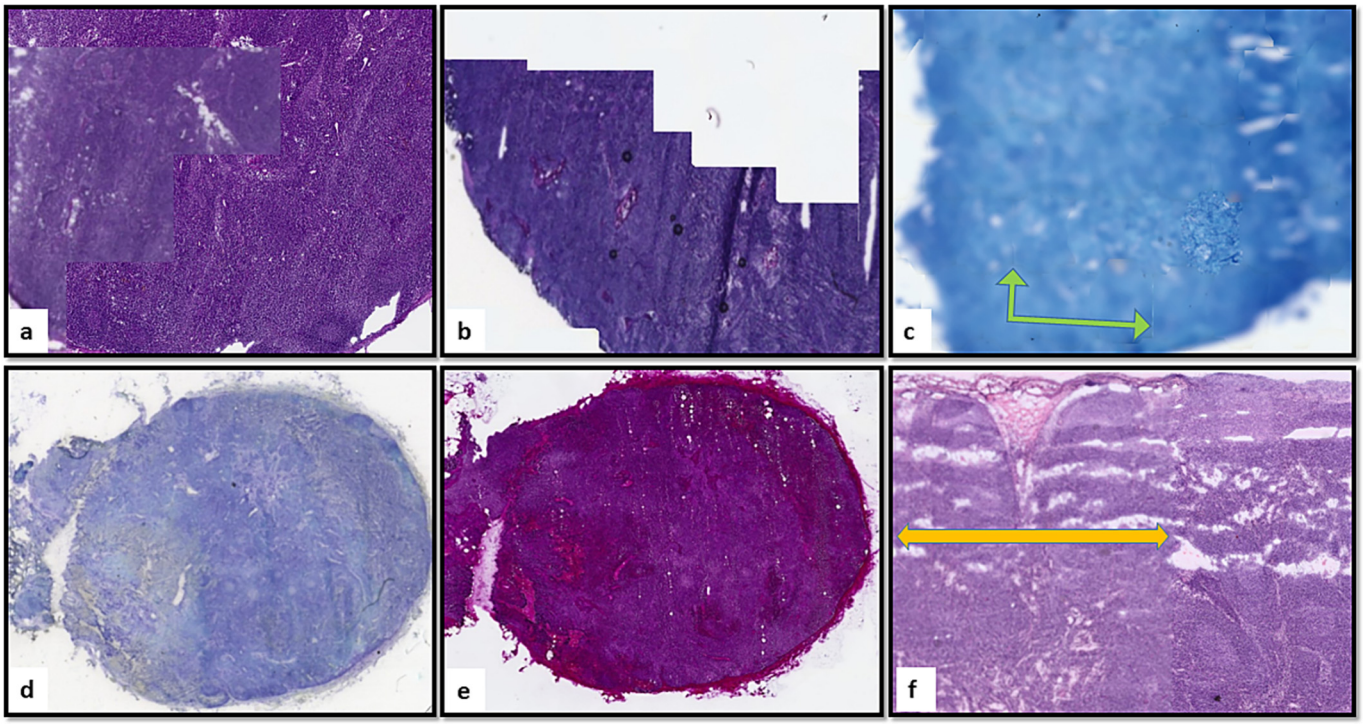

Fig 7. Photomicrograph shows various digital artefacts: Pixelation artefacts (a & b) due to low bandwidth connectivity at home resulting in increased TAT. An example of stitching artefact (c: Arrow) and a completely out-of-focus lymph node on TolB (d) as compared to good quality HE image (e) of the same case. A case with focal out-of-focus areas (arrowhead) due to uneven thickness of frozen section tissue.

The longer TAT in our cohort could be attributed to longer slide preparation time (mean 12:09 min/FS case) considering continuous back-to-back FS requests, the mandatory practice of preparing and scanning 2 FS slides per case (TOLB and H&E in each FS), scanning at 40x and longer relay time due to low network bandwidth connectivity. As it is not mandatory to report a frozen case using 2 slide preparations per frozen (one HE & other TOLB), if we omit the TOLB slide preparation and scanning of the same FS from our existing FS practice, a significant number of digital artefacts can be avoided. At the same time, it could improve the TAT for remote FS reporting by a minimum of 8–10 min. Hence, refinement in the existing FS workflow and improvement in the network connectivity could help us to bridge the gap between the conventional OM and remote WSI reporting for the FS diagnosis.

The overall confidence level for reporting FS was low using WSI compared to the OM for all the participants. Diagnostic accuracy and level of confidence for remote FS reporting correlated with the pathologist's past experience with DP (as Pathologist E had the least experience with DP). With the increasing and continued use of this technology, the hesitancy amongst the participating pathologist to deal with FS remotely reduced over time as the study progressed. By the end of the study, digital slides

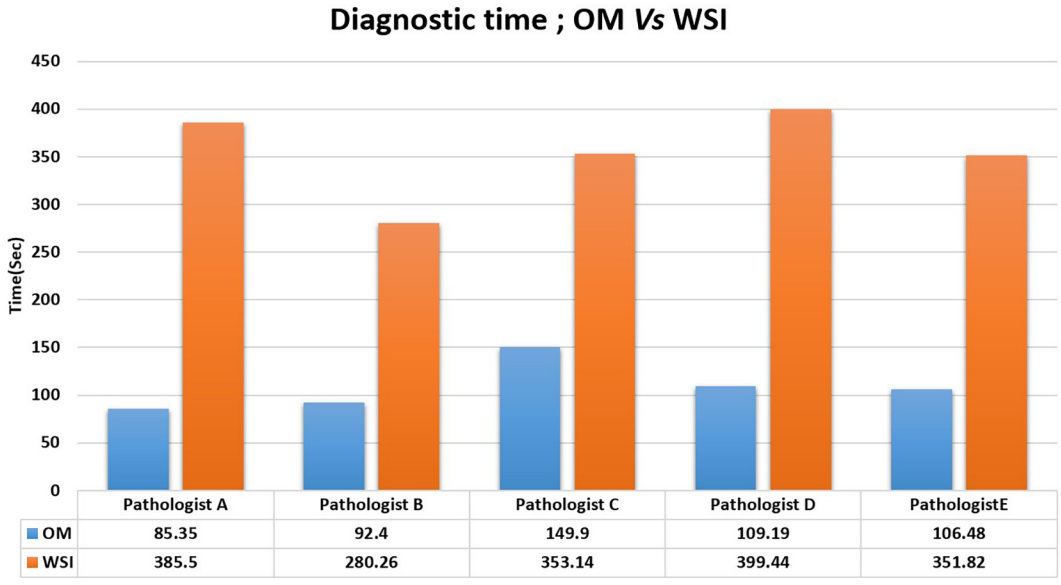

Fig 8. Bar diagram shows mean diagnostic assessment time for OM versus WSI for each pathologist.

Table 3
Network connectivity experience at remote DP reporting.

	Network connectivity					
	Level 3		Level 2		Level 1	
Pathologist	Cases [n (%)]	Slides [n (%)]	Cases [n (%)]	Slides [n (%)]	Cases [n (%)]	Slides [n (%)]
Pathologist A	60 (100%)	252 (100%)	0	0	0	0
Pathologist B	48 (80%)	220 (87.3%)	12 (20%)	32 (12.7%)	0	0
Pathologist C	39 (65%)	184 (73.01%)	16 (26.67%)	52 (20.6%)	5 (8.3%	16 (6.34%
Pathologist D	41 (68.33%)	208 (82.5%)	19 (31.67%)	44 (17.46%)	0	0
Pathologist E	39 (65%)	184 (73.01%)	19 (31.67%)	62 (24.6%)	2 (3.3%	6 (2.38%
Mean (%)	45 (75.66%	210 (83.3%)	13 (22.02%)	38 (15.07%)	3 (1.4%)	22 (1.74%

were perceived as traditional glass slides. All pathologists (except Pathologist E) had experience handling routine surgical pathology cases remotely from home during the COVID pandemic lockdown period cases, which imparted confidence for prospective remote FS evaluation and facilitated its adoption for clinical use.[13] Although setting up remote FS sign-out from home was not an immediate clinical requirement at the inception of this validation study; however, we are now prepared for any such requirement in the future. The success of this remote FS telepathology with WSI was feasible due to low scanner cost, use of simple technologies, bi-directional communication, strong team leadership, IT support, appropriate training, routine FS workflow modification, experienced and dedicated technicians and pathologists.

Further, the confidence gained by the recent applications of telepathology for primary diagnosis from home will open the channels for its utility for other critical applications (e.g., transplant services) wherein rapid and prompt diagnosis is expected. Pathology consultation is required to evaluate organ donors, either to determine the suitability of organs for transplantation or establish the diagnosis of an incidental lesion found during donor assessment (pre-transplant phase) as well as for the assessment of graft rejection (post-transplant phase). Transplantation pathology is a highly specialized field in which the majority of practicing pathologists do not have sufficient expertise to handle critical needs. Many times pathologists encounter requests for handling such specimens beyond routine working hours and expected to render results with in a strict turnaround times. Due to favourable results of the validation studies for telepathology assessment of donor biopsy, there is a growing interest for telepathology service implementation in transplant setting. Hence, many medical centres are embarking on the deployment of remote DP teconconsultation for timely access to expert second-opinion/consultation in both pre- and post-transplant phases.[30,31]

The only limitation of this study was the need for direct integration of the WSI system into the laboratory information system (LIS) workflow. The FS results were communicated to the FS room through online entries made on Google spreadsheets and could not be entered immediately in our existing reporting system. The incorporation of the same in the near future will ensure patient data safety and expedite the timely seamless communication of remote FS reports to the operating surgeon and make it a complete remote DP solution for intra-operative consultation.

Conclusion

In conclusion, this study of validation of FS diagnosis using DP from a remote location in a real-world scenario would help us establish a reliable DP workflow for timely intra-operative consultation, especially during extended working hours and provide subspecialty-based support for FS diagnosis to other satellite centres of our hospital network across India. WSI can be safely adopted for remote FS reporting from home for intra-operative teleconsultation using limited resources (low-cost portable scanners, consumer-grade laptops and low internet bandwidth). Consistent use of DP, training and improvement in IT infrastructure and internet connectivity might help improve the TAT and diagnostic accuracy for remote FS reporting.

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Presentation at a meeting

Pathology Vision, LA, 16–18th Oct 2022 (Digital Pathology Association Conference); Poster presentation.

Conflict of Interest

None.

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