Digital pathology for intraoperative frozen section diagnosis of thoracic specimens: an evaluation of a system using remote sampling and whole slide imaging diagnosis

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ABSTRACT

Background Digital pathology is now used for primary diagnostic work as well as teaching, research and consultation. In our multisite institution service reorganisation led to histopathology being located in a separate hospital from some surgical specialities. We implemented remotely supervised specimen sampling and frozen section diagnosis using digital pathology. In this study we assessed the concordance of glass and digital slide diagnosis using this system.

Methods We reviewed cases from the first 2 years of digital frozen section reporting at our institution. Cases with potential digital to glass slide discordance were reviewed by three experienced thoracic histopathologists. The reasons for discordance were determined and common themes identified. We also reviewed critical incidents relating to digital pathology during the study period.

Results The study population comprised 211 cases. Frozen section to final diagnosis concordance between digital and glass slide diagnosis was found in 196 (92.6%) cases. The 15 potentially discordant cases were reviewed. Intraobserver concordance between glass and digital slide review ranged from 9/15 to 12/15 cases across the three pathologists. Glass slide review diagnosis showed better concordance with ground truth in two cases; digital slide review was more accurate in two cases. One relevant critical incident was identified during the study period.

Discussion This is the largest study to examine digital pathology for thoracic frozen section diagnosis and shows that this is a safe and feasible alternative to glass slide diagnosis. Discordance between digital and glass slide diagnoses were unrelated to the processes of whole slide imaging and digital microscopy.

BACKGROUND

Digital pathology has grown from niche research interest to a viable alternative to glass slide based diagnosis. In this capacity, digital pathology has potential benefits for patient safety, service quality and efficiency.[1] The validity of digital pathology diagnosis has been established by concordance studies[2 3] and centres are now making primary diagnoses by whole slide imaging.[4] Frozen section diagnosis is an important part of histopathology practice and has its own unique challenges: Tissue sections and staining can be suboptimal, only a small proportion of the whole case is available for assessment and the required decision-making is often time critical and binary (eg, positive vs negative margin, deciding on the type and extent of tumour to determine the extent of surgery). In our multisite tertiary referral institution, histopathology centralisation resulted in thoracic pathology moving to a hospital site three miles from the thoracic surgery unit. We designed a system based around digital pathology to continue an intraoperative frozen section service for thoracic specimens.

The system comprises two elements. Specimen inspection and sampling is undertaken by an advanced practitioner biomedical scientist (ABMS) at the remote site under teleconference supervision from the consultant histopathologist reporting the frozen section. The ABMS has hands-free communication with the histopathologist via a telephone earpiece and microphone. The specimen can be seen by the histopathologist via a video link from the sampling hood and direction given for sampling the specimen. Biomedical scientists underwent specific training and supervision in sample dissection prior to the implementation of the system.

After dissection, frozen sections are cut on a standard cryotome and rapidly stained with H&E following standard procedures. Slides are scanned on a Hammamatsu Nanozoomer and viewed digitally at the remote site by the reporting histopathologist. A report is then given verbally to the surgeon or further sampling, levels or rescanning can be requested. When the system was first implemented slides were scanned at 40× resolution (0.23 µm/pixel). As we gained experience with the system the reporting consultants agreed that scanning at 20× resolution (0.46 µm/pixel) provided a digital slide that was appropriate for diagnosis while reducing acquisition time and delay from sampling to diagnosis. This study describes our experiences from the first 2 years and lessons learnt from the implementation of this system.

METHODS

All thoracic frozen sections reported digitally between February 2014 and January 2016 were identified from our laboratory information system and the corresponding histopathology reports were retrieved. The type of specimen, reason for frozen section, frozen section diagnosis and final diagnosis were recorded using Microsoft Excel (Microsoft Cooperation, Redmond, Washington,

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Box 1 Criteria for non-concordance

- A metastatic tumour was identified as a primary tumour or vice versa.
- A malignant tumour identified as a benign process or vice versa.
- An incorrect malignant diagnosis was made that would lead to inappropriate management.
- A resection margin was incorrectly diagnosed as involved by or free from malignancy.
- A non-concordant result arose from a sampling error (eg, the tumour was present in the tissue submitted by the surgeon but not present on the slide examined by frozen section).
- The reporting pathologist deferred to paraffin section in the original frozen section report.

USA). In addition, we scrutinised our department's critical incident reporting system for any adverse events relating to digital pathology.

We employed a two-stage process to identify discordant cases. Reports were reviewed by one of the authors (JG) and cases judged to be discordant if the frozen section diagnosis and the final diagnosis differed according to the criteria in box 1. We chose deliberately broad discordance criteria to capture all possible incidents where the use of digital pathology may have contributed to discordance. In the second stage, the frozen section slides for all discordant cases were retrieved from filing and a concordance study of light versus digital microscopy performed. All discordant cases were anonymised and reviewed individually by three consultant histopathologists with tertiary referral experience of thoracic pathology (JPB, PK and SKS) to determine the reason for discordance. The relevant clinical details that were available at the time of the original frozen section were provided at the time of review. The review consultants were asked to come to one of three options: a definitive diagnosis, a differential diagnosis with the option of favouring one diagnosis, or to defer to paraffin sections. Conventional glass slides were reviewed first followed by digital slides with a 'washout period' of at least 6 months. Ground truth was defined as the final case diagnosis. This study was classified as a service evaluation project by our institution's Clinical Effectiveness Unit.

RESULTS

Digital frozen section diagnosis was carried out in 213 consecutive cases. Insufficient data were available for two cases leaving a study population of 211 cases. Lung resections accounted for 197 (93.4%) of the cases; the remainder comprised mediastinal (seven cases, 3.3%), pleural (three cases, 1.4%) and thoracic lymph node biopsies (four cases, 1.9%). Based on the clinical information provided by the operating surgeon, confirmation of malignancy was the most common reason for frozen section (203 cases, 96.2%), followed by assessment of resection margins (six cases, 2.8%) and assessment of the feasibility of resection (two cases, 1%). Initial report review identified 196 cases (92.9%) with concordance between the original digital frozen section diagnosis and the final diagnosis rendered after full specimen sampling according to the relevant cancer reporting dataset from the Royal College of Pathologists. Immunohistochemistry was used as required for determining the final diagnosis from the full surgical specimen.

For 15 cases (table 1), the initial intraoperative diagnosis made on the digital image of the frozen section was judged discordant with the ultimate diagnosis given in the final histopathology report by our prospectively agreed criteria (after full sampling and immunohistochemistry where required). For each of these cases the glass slide of the intraoperative frozen section and the digital image of that slide were reviewed separately by each of three pathologists. Intraobserver concordance between the glass and digital slide was observed in 12/15, 11/15 and 9/15 cases for the three pathologists, respectively. In four cases, either no pathologist or only one pathologist gave the same diagnosis on the reviewed digital image as they did on the reviewed glass slide (cases 8, 9, 14, 15; row one 'LM review vs DP review' in figure 2). There were nine cases where the digital slide review diagnosis given by at least two pathologists was different from the original intraoperative digital slide diagnosis.

Table 1 List of non-concordant cases, original digital diagnosis and final diagnosis with area of difficulty grouped thematically

Case	Original digital frozen diagnosis	Final diagnosis	Area of difficulty
1	Necrotic amorphous matrix with focal high-grade atypia	Amyloid	Special stains required
2	NMCS, may represent lymph node sampling	Extranodal marginal zone lymphoma	IHC required
3	Atypia but no definite malignancy seen. Defer to PS	Renal cell carcinoma metastasis	PS required for diagnosis
4	Necrosis, could represent neoplasia or inflammation. Defer to PS	Non-small cell lung cancer	Malignancy obscured by necrosis
5	No neoplasia, inflammation and possible vasculitis	Adenocarcinoma in situ and actinomyces	In situ malignancy obscured by inflammation
6	No carcinoma. Could be inflammatory or carcinoid	Pneumocytoma	Uncommon diagnosis, required PS
7	No malignancy seen	Squamous cell carcinoma	Sampling error
8	Epithelial neoplasia. Cannot answer clinical question of primary versus metastatic	Primary lung squamous cell carcinoma	Required IHC
9	Atypical cells present. Defer to PS	Renal cell carcinoma metastasis	PS required for diagnosis
10	Carcinoid	Prostate cancer metastasis	Required IHC
11	Lung infarct with obliterated vessels	Poorly differentiated adenocarcinoma with necrosis	Malignancy obscured by necrosis
12	Neoplasia, unable to type	Adenosquamous carcinoma	Mixed tumour required IHC and PS
13	Poorly differentiated neoplasm	Epithelioid angiosarcoma	Uncommon diagnosis, required IHC
14	Inflammation, no malignancy	Minimally invasive adenocarcinoma	Malignancy obscured by inflammation
15	No obvious carcinoma, PS required to rule out lymphoma	Small cell carcinoma	Lymphoma as a potential mimic of small cell carcinoma

IHC, immunohistochemistry; NMCS, no malignant cells seen; PS, paraffin section.

Figure 1 Concordance review summary. For each row, green represents concordance between the comparison described in the corresponding row and red represents discordance. The case number corresponds to the cases in table 1. DP, digital pathology; LM, light microscope; DFS, digital frozen section.

In eight cases the review diagnosis given by all three pathologists was different on both glass and digital slides from the 'ground truth' diagnosis (figure 1) indicating that discordance in these cases was unlikely to be due to the process of slide scanning and viewing on a screen. The diagnoses in these cases included amyloid, adenosquamous carcinoma, in situ malignancy obscured by inflammation, pneumocytoma, a squamous carcinoma not originally sampled, an epithelioid angiosarcoma, and a prostate cancer metastasis (examples shown in figure 2). For a further two cases (case 14 and 11), there was better concordance of the glass slide review diagnosis with ground truth compared with digital slide review versus ground truth. Conversely, there were two cases (cases 8 and 9) where no pathologist's review diagnosis using the glass slide was concordant with ground truth, but the digital image was concordant for one and two pathologists, respectively.

One critical incident relating to digital pathology was identified during the study period. In this incident, the whole slide image was suboptimal and had blurring artefact together with a stripy alteration in contrast (figure 3). An attempted rescan resulted in complete scanner failure and the rapid travel across the city of the reporting pathologist to view the frozen section via light microscopy. The root cause of the scanner failure was coverslip mounting solution adherent to the lens which had presumably occurred during slide loading. This was resolved by cleaning the lens with Xylene and the scanner was operational within 48 hours. The incident was classified as a near miss as no patient harm had occurred.

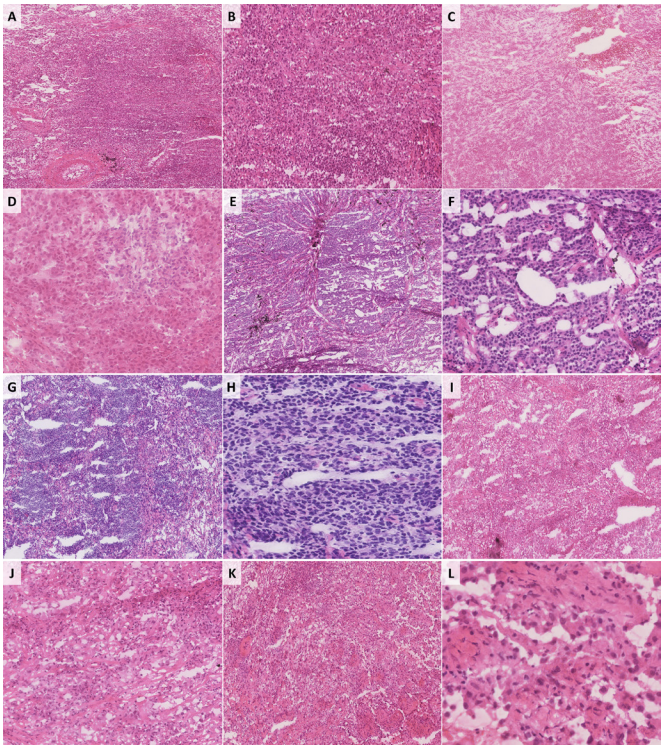

Figure 2 A selection of non-concordant cases. A and B: adenocarcinoma in situ and actinomyces, C and D: epithelioid angiosarcoma, E and F: metastatic prostate adenocarcinoma, G and H: minimally invasive adenocarcinoma with inflammation, I and J: metastatic renal cell carcinoma, K and L: sclerosing pneumocytoma. Images on left side of panel at 10×, images on right side at 40×.

DISCUSSION

We have shown that there is a comparable level of concordance between light microscope and digital pathology diagnoses in thoracic frozen section practice. Our initial concordance of 92.9% is in keeping with other digital pathology concordance studies[2] and also similar to studies assessing concordance between frozen section and final diagnoses in the predigital era.[5 6] Review of 15 potentially non-concordant cases showed that non-concordance could often be attributed to factors known to create uncertainty in frozen section practice (eg, rare lesions, those requiring immunohistochemistry or special stains and sampling errors) and that the process of creating and then viewing digitals slides contributed little to any diagnostic discrepancy. Indeed, in eight of the review cases, neither glass nor digital slide review diagnosis was concordant with the ground truth diagnosis indicating that these cases were intrinsically 'difficult' in frozen section practice. Both cases where glass slide diagnosis showed better concordance were examples of tumour obscured by inflammation or necrosis. This may represent a situation where digital slides don't perform as well as glass slides. However, a further case (case 4) also featured obscured malignancy and this was successfully diagnosed on both glass and digital slides.

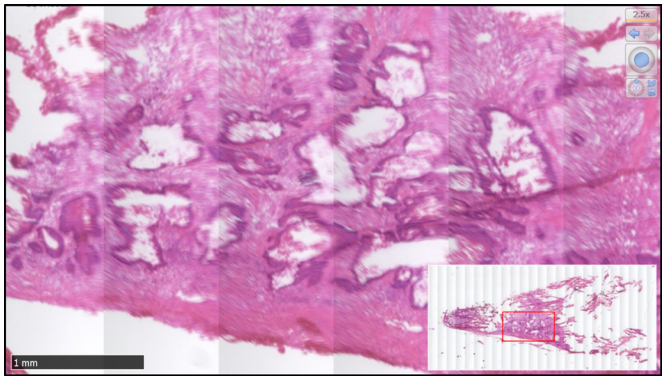

Figure 3 Appearances at 2.5× of stripy contrast pattern associated with coverslip mounting solution on the scanner lens.

We noted an improvement in concordance of digital versus glass slide digital frozen section diagnosis in the review phase compared with the concordance at the time of initial diagnosis. This is most likely secondary to experiential learning from using the digital pathology system. In particular, metastatic renal cell carcinoma and primary malignancy obscured by necrosis or inflammation were recurrent areas of difficulty. These scenarios could be included as cases in a digital pathology validation set as recommended by the Royal College of Pathologists.[7]

This study has some limitations. As a single institution retrospective study each of the review cases will have been seen previously by at least one of the review pathologists. At least a year had elapsed between initial diagnosis and review. Furthermore, we used a long wash our period between glass and digital slide review. These measures will have removed some recall bias, but we could not completely control for this. In the review phase, pathologists were provided with the original clinical details in order to simulate real world reporting of the frozen section. However, the original conversation with the operating surgeon and any additional information this produced could not be reproduced. Any degree of uncertainty or equipoise conveyed by either party in that conversation may not have been recorded in the original written digital frozen section diagnosis.

Ours is the largest study to specifically address digital pathology frozen section practice for thoracic specimens. A recent similar study[8] found that remote site frozen section reporting did not increase turn-around times. While we did not report this metric, our study focused on glass-digital concordance and examined the reasons for discordance through a thorough review process. In addition, we have successfully implemented remotely supervised macroscopic inspection and dissection in contrast to the previous study which utilised sampling by the operating surgeon. We found only one sampling error in our cohort which supports the safety and effectiveness of our approach. Finally, we have included the first reported critical incident in digital pathology practice, a detail that is absent in previous validation and concordance studies and one which adds important safety information to a rapidly developing field undergoing clinical implementation.

We have shown that digital pathology is a feasible and safe way to deliver a remote intraoperative frozen section diagnostic service in the setting of multisite or hub and spoke service organisation and is non-inferior to traditional glass slide diagnosis. Frozen section diagnosis can be challenging and the same principles of safe practice with judicious deference to paraffin sections and immunohistochemistry apply when performing this task using digital slides. Overall, remotely supervised sampling and the use of digital slides does not exacerbate the challenge of frozen section diagnosis.

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