Frozen section telepathology by whole-slide imaging

Andrew J Evans

Abstract

Frozen sections represent an ideal niche application for telepathology. This review covers the key aspects of using telepathology for this purpose. While several options exist for remote reviewing of frozen section slides such as sending selected static images by e-mail, real-time video microscopy and statistic/dynamic robotic microscopy, the use of whole-slide imaging technology will be emphasized in this review. The performance characteristics of whole-slide imaging systems in various frozen section practice settings, based on validation studies or actual patient care, will be discussed as well as issues to consider when implementing whole-slide imaging telepathology to cover frozen sections.

Keywords telepathology; frozen section; whole-slide imaging

Introduction

Telepathology (TP), the transmission of pathology images and patient information for various clinical applications,[1] has been used in various forms to facilitate intraoperative pathology consultations by frozen section for over 30 years. Remote intraoperative assessment of frozen sections by TP can be performed by several different modalities including static images sent by e-mail, real-time video microscopy, whole-slide imaging (WSI) as well as recently released hybrid devices capable of both real time video microscopy and WSI (Table 1). The practice settings in which TP can be used for frozen section assessment include entirely remote reporting with no on-site pathologist and providing quality assurance support to a lone on-site pathologist. Another application is the provision of subspeciality frozen section coverage to several on-site pathologists who are not comfortable reporting specific types of frozen sections, such as those arising during neurosurgery[2] (Table 2).

The first documented series of cases where TP was used for frozen section coverage by Nordrum et al.[3] took place between two centres in Norway in the early 1990's. Images from frozen section slides were transmitted across a two-way video and telephone network with a capacity of 2 Mb per second. A video camera mounted on a microscope with computer-driven motorized stage and focus functions allowed pathologists 400 km away to remotely review slides as a series of video and still images. The first 17 cases included incisional breast biopsies as well as frozen sections from cervix, ovary, thyroid, scrotum, larynx, stomach, tonsil, anus and subcutis specimens. While Nordrum et al. reported 100% concordance between the intraoperative and final diagnoses, they noted that it took pathologists an average of 15 minutes to examine each frozen section slide. Subsequent improvements in technology saw the appearance of encouraging studies like that of Kaplan et al. in 2002,[4] where robotic microscopes were used to retrospectively review 120 consecutive frozen sections from 21 different organs using internet-based TP. Frozen sections originating from institutions in the United States and Germany within the United States Army Medical Department were reviewed with 100% concordance between the TP and glass slide diagnoses. Of note, it took pathologists an average of only 2 minutes and 50 seconds to render a frozen section diagnosis with the robotic system.

Compared to the technology available for Nordrum et al. in 1990,[3] and even Kaplan et al. in 2002,[4] recent years have seen significant improvements in digital pathology technology resulting in vastly improved image quality. Remote viewing speeds have also improved due to marked increases in available bandwidth and computing power. In particular, the emergence of commercially available WSI scanners in 2003 was a major leap forward in this regard.[5,6] WSI is a process whereby a digital rendering of a glass slide created by a scanner can be manipulated by viewing software and examined at levels of resolution under 0.5 μm per pixel.[6] The WSI scanning process results in the production of a virtual slide that closely replicates the viewing experience of a light microscope. The virtual slide file can be archived indefinitely, annotated and re-reviewed at any time without appreciable deterioration in image quality.[5] In the setting of a typical single block frozen section, the scanning process for a 15 × 15 mm tissue section takes no more than 2 minutes which allows turnaround time benchmarks to be comfortably met.[7] The

Modalities by which frozen sections can be reviewed by telepathology

- Static images sent by e-mail
- Real-time video microscopy
- Static/dynamic robotic microscopy
- Whole-slide imaging (virtual microscopy)
- Hybrid devices capable of real-time video microscopy and whole-slide imaging

Table 1

General practice settings where telepathology can be used for frozen section coverage

1) Remote diagnoses with no pathologist at the site where the frozen section originates
   - specimen review and any sampling must be delegated to a non-pathologist
2) Remote diagnosis with pathologists at the site where the frozen section originates
   - specimen review and sampling is carried out by an on-site pathologist
   - review and reporting of diagnoses is carried out by the telepathologist
3) Quality assurance/second opinion remote with pathologists at the site where the frozen section originates
   - telepathology is used to support an on-site pathologist who reviews the frozen section and reports the diagnosis

Table 2

Andrew J Evans *MD PhD FRCPC Department of Pathology, University Health Network, University of Toronto, Toronto, Ontario, Canada.* *Conflicts of interest: none declared.*

cost of WSI scanners ($30,000-$250,000 U.S), the time required to scan slides and the current inability to examine frozen section slides or intraoperative cytology preparations in the Z-axis in a timely manner have been seen by some as drawbacks to the use of WSI.[8] As such, some pathologists may opt to use real time video robotic microscopy devices. Newer generation hybrid devices now offer the flexibility of robotic video microscopy with full Z-axis capability as well as WSI scanning. As demonstrated in a recently published validation study, hybrid devices would be particularly suited to intraoperative settings such as neuropathology where touch preparations may be routinely examined.[9]

There is a growing trend for healthcare institutions to consolidate services creating integrated networks. This can create situations where some hospitals in a given network have no on-site pathologist to cover frozen sections.[10] The distances between the centralized and affiliate sites can be appreciable, such that travel of pathologists to those sites just to cover frozen sections becomes difficult if not impossible. Travelling shorter distances may also be difficult to justify in terms of lost productivity for the pathologists doing the travelling. Having a single on-site pathologist to cover frozen sections also creates challenges from a quality perspective, in that no colleague is available to help with a difficult frozen section. TP is a viable solution to the challenges that arise in such settings and is an excellent niche application for WSI. WSI can allow pathologists to remotely review frozen section slides using technology proven to perform at a level equivalent to light microscopy.[11–14] The pathologist can also obtain assistance from colleagues with challenging cases and avoid the lost productivity associated with travelling to the remote site.[10,11]

There are several undeniable challenges that come with using TP to review frozen sections in the absence of an on-site pathologist. Frozen section reporting is a time-sensitive activity. The College of American Pathologists laboratory accreditation program requires ≥90% of single block frozen sections to be reported within 20 minutes from the time tissue arrives in the frozen section suite.[7] The standard frozen section work flow for the histotechnologist and pathologist involves specimen accessioning, gross examination, selection of tissue to be examined at frozen section, freezing, cutting, staining, cover slipping, histologic examination by the pathologist and communication of the diagnosis to surgical colleagues. The use of TP adds the extra steps of slide scanning if WSI is used and a pathologist logging in to a server in order to view the images. As such, the work flow needs to be well-rehearsed if TAT requirements are to be met. Activities that are generally performed by pathologists, such as the sampling of tissue to be frozen, must now be delegated to the surgeon, a pathologist assistant or the histotechnologist even though the technology exists for pathologists to digitally review the gross specimen. Frozen sections are frequently distorted by crush and/or freezing artefacts and frozen section slides are typically thicker than the standard 5 μm used for properly fixed paraffin-embedded sections. All of the above issues can combine to make frozen section reporting one of the most stressful activities performed in surgical pathology, with or without the additional overlay of TP.

Validation studies

Over the past 10 years, several publications on the use of WSI for frozen section coverage in patient care situations have appeared,[2,10,11] most of which have focussed on validating the use of this technology. The first published study involved a pilot project of 15 cases in Kyoto, Japan[15] which provided proof-of-concept that reliable and timely frozen section diagnoses could be made by WSI. Fallon et al.[12] reviewed scanned slides from 52 archival frozen sections from the complete spectrum of benign, malignant and borderline ovarian tumours. Upon comparing WSI diagnoses made by study pathologists to those made by the original pathologists made at the time of surgery by light microscopy, they observed 96% concordance. Discrepancies were not attributed specifically to use of WSI and, in some cases, the WSI diagnoses were more accurate than those given at the time of surgery. Of note, discrepant cases typically arose for lesions known to be associated with interobserver variability when reviewed by light microscopy.

In addition to reviewing WSI frozen sections on monitors associated with standard office computers, there is also interest in using mobile devices such as laptops, tablets and cell phones to review digital pathology images, including those associated with frozen sections. In the first of two companion studies, Ramey et al.[16] compared WSI diagnoses made using desktop and laptop computers to the original glass slide diagnoses made at the time of surgery. They observed complete diagnostic concordance in 91% of the 72 consecutive frozen sections (overall κ value = 0.84) that were scanned at 20× magnification and subsequently reviewed by eight pathologists. Any discrepancies were minor in nature and would not have altered surgical management. The results were independent of the type of frozen section. They reported essentially identical results when these virtual slides were reviewed on a tablet (iPad) during the second study.[17]

The body of validation literature can be expected to grow as more institutions looking to implement WSI for frozen section coverage perform their own validation studies. Recently released guidelines from the CAP provide an excellent resource for carrying out these necessary studies.[18] Since intraoperative pathology consultations can involve diverse specimen types, it will be extremely helpful for new users to publish their validation experiences for WSI (and other TP modalities) with respect to unique intraoperative consultation scenarios. One example is performing neutrophil counts in peri-prosthetic soft tissue during revision arthroplasty surgery. Surgeons send frozen sections for neutrophil counts as a surrogate for the presence of infection.[19] Neutrophil counts in excess of 10 per high power field have been shown to be sensitive and specific for the presence of infection, causing the surgeon to defer the revision arthroplasty until an infection has cleared.[20] Only limited data exists on the use of WSI for this purpose. Bradshaw et al.[21] reviewed four of these cases as part of a general WSI frozen section validation study. Three of the four pathologists expressed discomfort about providing neutrophil counts using scanned slides. Despite this lack of comfort, the authors noted there were no discrepancies between WSI and glass slide diagnoses for cases involving neutrophil counts. Similar concerns with respect to using WSI to assess inflammatory cells were raised in a validation study by Wilbur et al.[22] This study addressed the use of WSI for secondary consultations on challenging cases including those requiring the assessment of inflammatory and/or infectious lesions in paraffin sections. While more data are needed on this particular application of WSI, it is likely that at least 40× scanning (creating