“Digital Pathology: Will machines replace the pathologist

and a microscope?”

# Introduction

Healthcare is at the forefront of digitalisation, with the use of tablets and hospitals and the introduction of telehealth spreading across the world. A cause of this is the increasingly financially untenable position of healthcare systems everywhere, no more so than the NHS. The question of whether the job of a pathologist and a microscope will eventually be replaced by a machine is a microcosm of a conundrum occurring in many areas of health. What does robotic surgery mean for the role of surgeons, and how do automated readings of health biomarkers alter the job of a nurse? These are similar riddles to be answered regarding the effect of technology. Critical analysis of the issue is required by pathologists themselves to ensure that this process occurs for the better of the profession and the patients it serves.

Digital pathology began with telepathology; the transmission of slide images over large distances via satellite, and now contains many different aspects including Whole Slide Imaging, quantitative analysis and even molecular techniques such as Fluorescent In-Situ Hybridisation. Before looking at whether these technologies will mean the end of the pathologist and the microscope, or either one of the two, we must first understand how they work and what benefits they bring.

# The beginnings: Advent of Telepathology

Telepathology, as defined by one of its founders Dr Ronald Weinstein, is "the practice of pathology at a long distance"(1). His vision for remote pathology began in 1986 when he successfully tested a satellite link between Fort William Beaumont Army Medical Centre in El Paso, Texas, and Washington DC. The robotic microscope and video camera was located in Texas, with the technology being controlled and images being viewed in Washington on a computer.(2) The paper, when published, was ground-breaking and the machinery was shown on display all over the country. Several research labs around the world began trying to set up their own telepathology lab, some opting for a replica of the video uplink whilst others attempting to use a static images approach with various sections at increased magnification. 10 years later though and Weinstein was finding that uptake of this technology was proving to be exceedingly slow.(3) He cites a number of reasons such as high set up cost of the machinery, as well as problems with resolution and, of course, intermittent satellite connection. With the static images there was the added issue of incorrect field selection to add to the problems. The spark was lit, however, and articles on telepathology were being published year on year at an ever increasing rate. General advances in image capture resolution, computer processing power and the internet assisted in this research. By 2001, Weinstein was describing its progress as following an S-curve, with the initial period of "incubation" representing a stagnant level of development, followed by a rapid rise in activity.(4) Fast forward to today and we see, almost 3 decades on, that telepathology is being implemented in numerous hospitals around the world for routine use, with a mixture of static images, remote robotic microscopy and whole slide imaging (WSI) being used to analyse slides in Pittsburg from as far as China.(5) While its uses cannot be extended to all aspects of pathology at the moment (for example full diagnosis using WSI has not received FDA approval, though it has for certain machines by EU and Canada), elements such as frozen samples from surgical pathology are perfectly capable of being analysed by remote technology.

# Whole Slide Imaging and Data Management

Over the years, many different methods of digital slide representation have been tested. Basic photography is far too simplistic to fully analyse a slide, as there are not only multiple focal lengths (particularly in cytology) to incorporate but also specific areas which require further enlargement to identify smaller objects. Using Whole Slide Imaging (WSI) the range of magnification accessible can be from x10 to x40, the standard range of values found on a light microscope(6). WSI imaging software is capable of taking photos at various focal lengths and magnifications and compiling them into a single file, to be accessed using the appropriate software. The images are stored in a tree branch system, with regions of increased magnification only being loaded when selected by the viewer, preventing all the images from having to be loaded at the same time. This gives a greater degree of information being easily accessible, with the option of zooming in and changing the focal length to look at slides through the z-plane. This can all be done on a single monitor and therefore at any remote location with a calibrated computer. Having the slide stored digitally means that the image will remain intact and will not degrade, unlike physical slides when stored for a long period of time. This makes a digital system a far better alternative for long term storage, as it is also space saving.

However, despite the flexibility that WSI provides, it comes at a cost. The data a single image can take up is large enough at such high resolution, but to scan and compile the multiple images required from a slide, all into one file can take up to 3.9GB of storage space, and between 1-3 minutes to scan(7) (Frozen section samples have been shown to take between 3-14 minutes in some studies(8)). This means a huge amount of data storage is required for a digital lab to be able to function adequately. A Dutch academic pathology lab, scanning approximately 500 slides a day, required 175GB of data daily, amounting to 5TB per month.(9) This level of data storage is best handled with cloud-based solutions, which have been specifically designed to handle such a workload. The cost of setting up such a storage system, along with the scanner itself ($100'00 - $150'00(7)), and training for staff could mean that the high initial start up cost is a major stumbling block for labs, and hence the reason for a lack of integration with this technology world-wide. As always though, competition will drive prices down. Over the past 5 years, more than 10 different companies have started to provide WSI on the market, and with this level of participation there are more than enough players to compete for improved technology and decreasing price tags.

# Quantitative Analysis and Molecular Techniques

As far back as 1986, coincidentally the same year as Weinstein's experiments with telepathology, the use of computer-aided image analysis of slides was being explored(10). It took a long time for the technology and the algorithms designed for the process to be sophisticated enough to produce comparable results with human analysis. These were due to a number of factors including a lack of standardisation in preparation of slides, natural variation in cells leading to large generalised parameters being used for the measurement of features, and compression issues when the file is saved in certain formats, leading to a potential change in the pixel colour distribution each time it is opened and analysed. It is only now that these algorithms have been designed to actively account for many of these variable factors. Some types of algorithms currently available include texture analysis, object segmentation and identification, structure analysis and automated classification(11). With algorithms to analyse morphological features and spatial arrangement, their potential benefits in the histological grading of neoplasia have been identified over a decade ago(12), an area where subjective assessment by individual pathologists have proven to be inconsistent(13). The use of such automated image analysis is part of a bigger trend towards quantitative measurements of characteristics. It removes the subjectivity of individual analysis that can sometimes prove inconsistent(13,14), whereas set parameter being used by a computer to assess data will always produce hard figures that can be categorised effectively.

Immunohistochemistry, such as chromogenic stains, have been subject to this change to quantification. Whereas before, the use of staining was to identify presence or absence of marker being searched for, higher diagnostic standards have lead to fluorescent staining taking its place. Biomarkers such as HER-2 found in some breast cancers are easier to identify using techniques like Fluorescent In-Situ Hybridisation (FISH) over the traditional immunohistochemical methods(15). The fluorescent molecules show a constant rate of photon emission that can be easily detected and quantified(16), meaning that for digital analysis, all you need is the correct algorithm. Again, studies using the HER-2 biomarker have shown that this incorporation of computer detection and quantification leads to more objective analysis of the fluorescence(17), hence delivering more accurate results for the use of diagnosis. The combination of Tissue Microarray (TMA), where up to a thousand tissue samples are arranged on a paraffin block to be analysed simultaneously with biomarker identification, can now be used more effectively because of digitalisation too.(18) This is due to the sensitive natures of scanners and the quantification of computer-assisted image analysis. Previously, analysis of the paraffin block had to be done using a light microscope and comparative, subjective analysis by eye. Again, HER-2 is a good example of how the combination of FISH, TMA and digital analysis enables high-throughput and accurate quantification, enabling for more objective results to be procured from samples(19). While this change does mean less work done by the pathologist and more by the machine, the final interpretation of the data cannot be done by the computer. That job still, and always will require a pathologist.

Many molecular techniques involving computer assistance are being increasingly relied upon for diagnosis as we move towards a more personalised medical approach to treatment. Biomarkers have become essential to understand the nature of the cancer an individual suffers from, and allows us to tailor the treatment plan accordingly. This is only possible now because of the molecular techniques that have been developed, however it does inevitably lead to time historically spent looking at slides being taken away to perform these tasks. Arguably the machines used in these molecular techniques are somewhat fulfilling the prediction of replacing the microscope, but the importance of the pathologist in understanding the data and producing a diagnosis from it still remains.

# Comparisons to Teleradiology

 Interestingly, Weinstein compares the field of teleradiology as going through a similar phase as telepathology at roughly the same time in 1997(3). However, currently we see that the digitalisation of radiology is almost universal, where as pathology has not followed at the same pace. A major factor in the difference between the two fields is the need for accurate colour representation(7). This is far more difficult to standardise (compared to the mostly monotone images used in radiology) as screen monitor set up and scanning equipment all vary, though the use of Macbeth colour checkers, currently used in other forms of telemedicine, have been suggested(20). A change in colour can lead to misdiagnosis by a pathologist, and if the use of automated scanning and computer image-analysis is involved, the colour change could lead to an incorrect reading and interpretation.

Another issue specific to pathology is error in focussing due to artefacts. When using a light microscope, the pathologist is in charge and can bring whichever areas of the slide he wants into focus, ignoring any artefacts that are irrelevant. With WSI, the artefacts can cause incorrect focusing, similar to what occurs with a digital camera when it struggles to focus, and it can result in blurry, useless images. This is a waste of time and processing power, resulting in the compilation of huge image files that will eventually be discard and require the pathologist to start over. This problem can potentially be resolved by pre-scans with alterations to colour saturations to identify artefacts in the slide(21,22).These solutions remain in its infancy however, and have not been proven to work on a large scale as yet.

Such issues can mean that the introduction of Whole Slide Imaging and Digital Pathology Workstations can cause major disruption to work flow. A change to new technology in any profession usually results in teething problems, and studies have shown that this disruption to work flow is quantifiable(23). While radiologists would have experienced similar problems for a short while, the full transition to completely computerised work stations meant there was no need for integration, simply conversion, which proved to be a far simpler process. In pathology, the technology available is not currently advanced enough to manage all the tasks of a pathology lab, and so a mixture of old and new is required. Preparation of slides and staining is still a manual process, and integrating this with digital scanning so that they work together harmoniously can potential disrupt work.

Beyond all of these practical issues is an inherent distrust in technology such as WSI. Numerous articles express many pathologists' lack of belief in the competency of new technology, whether it be scanning of slides or automated quantitative analysis (7,16,24). This view point seems rather strange when compared to the number of validation studies carried out, proving the proficiency of numerous technologies such as WSI(25–31), and even showing the capabilities of using a tablets for effectively analysing WSI images on the move(32). Change in perception is something that always takes time, and with light microscopy being the backbone of pathology for over 100 years, change will always be met with some resistance. The question is, will this resistance stall the effective development of this new technology to a detrimental effect on the patients, or is this simply cautious sailing of dangerous waters?

# Changes, good and bad

The increasing use of telepathology has opened up the opportunity for analysis of slides by professionals without the restriction of being at the lab. These slide images can now be sent all over the world over the internet to be viewed and interpreted by any desired professional. This will not only provide new opportunities for international collaboration in research but also reduce delays in hospital by having the option for pathology work to continue overnight in a different time zone, if the demand is great enough. Second opinions are now considerably quicker to acquire with the limitation being data transfer speed.

The advent of wide-spread use of telepathology does however lead to the potential danger of outsourcing internationally to the cheapest offer. Now that slides can be sent and analysed anywhere in the world, the financial burden put on CCGs could mean that pathology is targeted as an area with the potential to reduce costs via outsourcing to the cheapest supplier. The solution  to this problem is complex, but primarily rooted in the continuing internationally high standards of pathologists in the UK. This must be maintained at all costs by keeping the education of pathology at the highest level, using cutting edge resources where ever available. Luckily, these cutting edge resources happen to include much of the technology mentioned already, and it has been proven to be successful in its use for education purposes(33). Cloud-based storage allows trainees to access slides for learning and revision wherever they are, and with the future of pathology inevitably moving towards a more digitally orientated workplace, a familiarity to these types of user interfaces and work patterns will mean easier assimilation with technology and, hopefully, less disruption to workflow for the future pathologist when using new machinery.

The amount of data that hospitals have to manage are becoming exponentially larger and harder to handle, so the solution of cloud-based storage when using digital slides is in line with the changes happening throughout healthcare. New questions arise however over the privacy of data and how they will be kept secure(34). While this is more a problem for the storage providers to consider more than the pathologists using these services, it is still a factor that must be examined and taken very seriously before rushing into large-scale use of this technology for routine hospital work.

# Conclusion

With so many different analytical methods at a pathologists disposal currently, the old fashion image of the pathologist looking down a microscope is increasingly becoming a relic. The uses of light microscopy are being replaced by WSI slowly but surely. However whilst the microscope may morph into a digital camera, the role of the pathologist in the analysis of the image is one that will forever remain vital to the profession. The introduction of automated analysis does mean certain basic tasks of a pathologist are being done for them by the computer. However the knowledge accumulated of years of training and research is what goes into the analysis of each and every case, and that is something that can never be replaced by algorithms, however complex. Some may see the cautious introduction of Automated Image Analysis into pathology as a direct threat to the job of a pathologist, however this is a misinterpretation of the potential the software holds. As Kayser et al(35) puts it succinctly, the use of automated slide analysis does not mean job cuts to pathology departments everywhere, but instead an improvement in teaching and case management, allowing "easy to solve cases" to be dealt with by computers and leaving the complex problems of diagnostically difficult cases to be solved by the professionals.

Pathologists must decide how they want to redefine their role as the requirements of them change, otherwise they risk being overlooked and suffering from cost cutting measures that are inevitable throughout healthcare. It is the pathologist who understands his/her field the greatest. If this technology is to be used for the benefit and not detriment of the patient, then collaboration, not confrontation is required with the people designing and developing all these digital technologies. This way advances can be guided correctly to better integrate into the working environment of a pathology lab. If this opportunity for collaboration is not taken, the role is left to people without specialist and, more importantly, personal knowledge of the field and working environment, and pathologists risk being looked over and dismissed. The importance of a pathologist will never be diminished, even if the tools they use continue to change. It is time now however, to embrace the digital age and see what benefits it can bring.

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