Clinical Applications of Telepathology and Whole Slide Imaging

Anil V Parwani, MD., PhD
Department of Pathology
Anatomic Pathology Laboratory Information Systems
UPMC Shadyside Hospital
University of Pittsburgh Medical Center
Pittsburgh, PA
Goals of Today’s Talk

• Digital Images
  – Current common uses
  – Limitations

• Telepathology

• Whole Slide Images
  – Background and technology
  – Current common uses
  – Clinical Trials
INTRODUCTION

• Pathology is “IMAGE-BASED” and “VISUAL”
• A pathologist is perfectly situated to control the imaging process in order to process useful visual and nonvisual data and communicate it to the patient’s health care Team.
• Pathologists’ time is valuable
• A systematic approach maximizes education and training.
The Microscope

- **Functions:**
  - Produce a magnified image without artifact
  - Resolve (separate) details in the image
  - Develop contrast between the details
The Digital Camera

Functions:

• Samples the image so as to retain contrast and resolution
Proven Uses for Digital Images

- Teaching
- CPC conferences
- QA/QC
- Publications
- Image-enhanced reporting
- Consultation
- Telepathology – Store and Forward
- Retrospective case review assisting diagnosis
- Primary diagnosis
- Advanced image analysis
Requisite Skillsets for Pathologist
STATIC IMAGES HAVE LIMITATIONS!!

- Gross imaging is very viable and delivers value to any practice - especially if imaging is operationalized and integrated with the LIS.
- Microscopic imaging, though valuable, is in the beginning of a transformation from a “camera on a microscope” to a more INTEGRATED platform for pathology.
- Image formation is a matter of magnification, resolution and contrast
- Imaging provides added functionality compared to traditional glass slide examination.
Dear Doctor [Name],

Thank you for sharing this information with me. The images show a detailed histological analysis of the [specify tissue]. The images depict various layers and structures, indicating a complex tissue organization.

[Detailed description of the images and analysis goes here.]

Sincerely,

[Your Name]

[Include any additional comments or questions related to the images here.]
Virtual Pathology
“VIRTUAL PATHOLOGY”

• Non-robotic telepathology for expert/subspecialist consultation

• *Robotic* telepathology for full pathology services

• *Whole-Slide Scanning* for:
  – Distance education
  – Telepathology
  – QA/QC, CME, proficiency testing.
  – Primary Diagnosis
TELEPATHOLOGY

Practice of pathology using telecommunications to transmit data and images between two or more sites remotely located from each other.
Telepathology Components

- Telepathology equipment: microscope, a high resolution camera, an image capture board or card in a computer (Windows or Macintosh), software to manage the images and a telecommunication system to transmit images.
- Telecommunications systems
- Human performance
Capture and digitalization of a group of macroscopic and/or microscopic images selected by a pathologist, which are then transmitted through electronic means to a telepathologist.
Dynamic Robot

2x
4x
10x
20x
40x
60x
X
Y
Z
Brighter
Darker
Condenser
Robotic microscopy systems have been reasonably successful in telepathology with tens of thousands of successful cases documented since the mid-nineties.

However these are largely real time, remote control systems that require hands on pathologists involvement and do not provide (as part of there core operations) persistent image storage.
Telepathology

• Non-Robotic: Microscope and Camera is controlled by the referring pathologists who sends “snapshots” to the consultant through a network (many vendors)

• Robotic: Microscope and Camera is controlled by the consultant. (Apollo, Trestle, Nikon Coolscope)

• Both systems can be used effectively in limits situations
Telepathology Applications

- Intraoperative frozen sections
- Routine surgical pathology
- Second opinions
- Surgical pathology consultations
- Expert-to-Expert consultations
- Quality assurance
- Distance education

Whole Slides Images
Automated, High Speed, High Resolution Whole Slide Imaging

• To provide the digital view of the complete slide in context, several new technologies have emerged using Whole Slide Imaging.

• Whole Slide images are digital images of the entire block face or slide. These digitized images are captured, compressed and viewed on any browser over the internet.

• The digital image allows users to view entire microscopic images at any magnification on their monitor.
Slide scanners
Automated, high speed, whole slide imaging began in 1999 when Art Wetzel and John Gilbertson then of Interscope Technologies developed a full automated, high speed device that could image entire slides at high resolution and at a reasonable cost.

It was based on traditional microscope optics, a strobe light linked to a precision stage, and a digital video camera.
FROM HOURS TO MINUTES !!!!!!!

• The interscope scanner had a spatial sampling period (pixel size/optical magnification - a measure of resolution) of 0.33 microns/pixel and could image a slide in five to ten minutes depending on the size of the tissue section and the amount of image compression desired.
WHOLE SLIDE IMAGING - CURRENT STANDARDS

• A number of companies are producing increasingly capable automated, high-speed whole slide imagers.

• A typical imaging robot today can run in batch mode (reading barcodes on slides) and can capture and compress an image of a slide with a 1.5x1.5 cm tissue section in approximately six minutes with spatial sampling periods of between 0.3 to 0.5 microns/pixel.

• The “High Speed Whole Slide Imaging Robot” industry is becoming highly diverse with a wide range of optics, detectors, slide handling devices and software resulting in an increasing range of capabilities and costs.
ScanScope CS System
http://www.aperio.com

NanoZoomer Digital Pathology (NDP) System
http://sales.hamamatsu.com

MedScan Digital Slide System
http://www.trestlecorp.com
Clinical Evaluations – WSI

- **Several Types:**
  - QA through WSI --- Completed
  - (Ho et al, 2006).
  - Special Stain Distribution -- Ongoing
  - Primary Diagnosis Study – Completed (Gilbertson et al, 2006).
  - Frozen Section Study -- Ongoing
Clinical Evaluations of WSI

• Clinical (diagnostic) validation of WSI systems is extremely important because their image capture is automated, their focusing mechanisms are novel, and the size of the datasets they generate mandates the use of lossy compression.

• Validation studies are also an important way for pathologists to guide the development of the technology.

• There is little question that digitization itself is not a barrier to pathology diagnosis.

• For many years pathology practices have provided remote diagnostic services using robotic real-time, near real-time and even static image-based telepathology.
Clinical Evaluations of WSI

• In these traditional telepathology applications, however, pathologists directly control the image formation (focus) and capture process.

• This is not the case with high-speed WSI systems in which image formation and capture are automated.

• Given the large number of slides generated by pathology laboratories, one of the most essential features of a clinical WSI system is slide capture speed (or throughput).

• Fortunately, modern WSI devices are becoming very fast, with current devices ranging from 2 to 8 minutes per slide. To achieve this speed, systems employ a unique focusing strategy.
Quality Assurance Studies

Error rates in anatomic pathology have been estimated to be between 1% and 5% of all cases, with 1% of these cases resulting in significant clinical events.

Quality assurance in anatomic pathology typically is performed by case over-reads of 5-10% of signed-out cases.

The College of American Pathologists mandates the performance of quality assurance, but does not specify the methods with which to perform quality assurance.

Current practices allow for case over-reads with knowledge of both sign-out pathologist and sign-out diagnosis along with the originating facility, all potential sources of bias.
PROJECT TEAM

• A project manager and a principal faculty investigator, responsible for the management, integration and overall execution of the project;

• Evaluators with the University of Pittsburgh Center for Biomedical Informatics, responsible for IRB approvals, data management and focus group interviews;

• The Quality Assurance Division of the Department of Pathology, responsible for case selection and the formal resolution of any diagnostic discrepancies discovered during the study;

• An honest broker, responsible for de-identifying case material; and
• An imaging team, responsible for whole slide image capture, storage and presentation.
The quality assurance study was a retrospective, comparative study in which 24 full genitourinary pathology cases were selected randomly by the quality assurance division using standard quality assurance protocols.

Cases were de-identified and slides imaged to 0.46 um/pixel using an Aperio T2 commercial whole slide imager (Aperio Technologies, Vista CA).

For each case, study pathologists were randomized to either a traditional glass slide review approach or a review based on digital slides so that each case got two independent reviews, one with glass slide and one with digital slides.

At the end of the study, diagnostic discrepancies were evaluated by a pathology consensus committee.
• The 24 cases represented 47 surgical parts and 391 individual slides.

• There were nine prostate biopsies (representing 29 parts) and five bladder biopsies (representing 6 parts).
• Other cases included transurethral resections, prostectomies, nephrectomies, vasectomies, and a scrotal lesion.

• The slides included 29 special stains, two frozen sections and two touch preps.

• Approximately half the cases had a diagnosis of cancer or in situ neoplasia in the signed out diagnostic line.
<table>
<thead>
<tr>
<th>Case Type</th>
<th>Number of Cases</th>
<th>Number of Parts</th>
<th>Number of Slides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate biopsy</td>
<td>9</td>
<td>29</td>
<td>214</td>
</tr>
<tr>
<td>Bladder biopsy</td>
<td>5</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>TURP</td>
<td>3</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>2</td>
<td>4</td>
<td>98</td>
</tr>
<tr>
<td>Nepthrectomy</td>
<td>2</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>2</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Excision of a scrotal lesion</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>47</td>
<td>391</td>
</tr>
</tbody>
</table>
Over the 24 cases in the study

the glass QA assessment (review) resulted in 22 cases of agreement (with the signed out report), one case of moderate, clinically insignificant disagreement (Case 16), and one case of mild, clinically insignificant disagreement (Case 21).

With WSI reviews, there were 21 cases of complete agreement (with the original report), and three cases of mild, clinically irrelevant disagreements (Cases 10, 19, 29).
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Case Type</th>
<th>Disagreement</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 10</td>
<td>Prostate needle biopsy</td>
<td>WSI review: Gleason 3+4=7</td>
<td>Agreement with the signed out report</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signed out report: Gleason 3+3=6</td>
<td></td>
</tr>
<tr>
<td>Case 16</td>
<td>Prostate needle biopsy</td>
<td>Glass review: foci of carcinoma</td>
<td>Moderate, clinically insignificant disagreement with signed out report</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signed out report: no foci of cancer in the core in question</td>
<td></td>
</tr>
<tr>
<td>Case 19</td>
<td>Radical prostatectomy</td>
<td>WSI review: high grade PIN</td>
<td>Mild, clinically insignificant disagreement with the signed out report</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signed out report: no mention of high grade PIN</td>
<td></td>
</tr>
<tr>
<td>Case 21</td>
<td>Prostate needle biopsy</td>
<td>Glass review: no evidence of atypia</td>
<td>Agreement with the signed out report</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signed out report: foci of atypia</td>
<td></td>
</tr>
<tr>
<td>Case 29</td>
<td>TURP</td>
<td>WSI review: spelling error in report</td>
<td>Spelling error, not clinically significant</td>
</tr>
</tbody>
</table>
The overall distribution of perceived case complexity (as reported by the pathologists) was virtually identical between glass and WSI examination. Average reported case complexity was 1.79 for glass examination and 1.71 for WSI examination (1 = low, 2 = medium, 3 = high), indicating that the WSI modality did not cause the cases to be perceived as more complex.
Whole slide imaging over-reads, on average, took longer to complete than glass over-reads. The main discrepancy was a set of eight cases that took over 45 minutes to evaluate with the imaging system. Significantly however, seven of the long WSI over-reads were among the first ten cases in the study, possibly indicating a learning curve.
Figure 3: Case 10: focus of disputed Gleason grading

Case 10, area of the whole slide image, moderate magnification: The image shows a small focus of prostatic adenocarcinoma. The area in question is in the upper left where several glands appear to fuse together, creating a small area that the pathologist reviewing the case with WSI considered a focus of higher Gleason grade (grade 4), with an overall grade of Gleason score 3+4 = 7.
Case 16, area of whole slide image, moderate magnification: The area in question is in the center of the field. These five to six small glands with an infiltrative growth pattern are suspicious for invasive adenocarcinoma under the microscope but appear less worrisome on the whole slide image. The original signed out report mentioned high grade PIN, but not invasive cancer, in this part of the case. This case had established areas of adenocarcinoma on additional cores.
LESSONS FROM THE QA STUDY

• In summary, current WSI technology is worthy of more extensive evaluation in surgical pathology QA.

• It provides a potential mechanism to share QA between facilities, with the caveat that image quality (and image calibration) is very, very good, but not yet perfect.

• Operating WSI as a clinical service (QA) within a working medical center will require more than an imaging robot.

• In summary, current WSI systems seem capable of providing a useful level of surgical pathology review across a distributed health system and they will only get better. Much work needs to be done however especially in slide navigation, presentation speed and data integration for WSI to research full potential in the clinical space.
Primary histologic diagnosis using automated whole slide imaging: a validation study

John R Gilbertson¹,⁵, Jonhan Ho¹, Leslie Anthony¹, Drazen M Jukic ³, ⁴, Yukako Yagi¹, Anil V Parwani³*

¹Center for Pathology Informatics, University of Pittsburgh Medical Center, Pittsburgh, PA, 15232, USA
Primary Diagnosis Trial

1. Case Selected
2. Case Recreated In the LIS
3. Case sent to Pathologist
4. Original Slides Imaged
5. Re-cuts or Special Stains Ordered/Cut/Imaged
6. Case Signed Out
• Biopsy or tumor resections cases are randomly selected by the QA office

• Study cases are re-created in the LIS with the clinical history and gross description data only

• Cases are sent to the study pathologist’s queue, he examines the case, orders recuts/special stains or signs the case out in the LIS

• If recuts/special stains are ordered, they are made (or pulled from the archive if the original pathologist had made them) and imaged
WSI Consensus Meeting

Consensus Report Written

Compare with

Signed Out Report
• The original signed out report is examined by the group.

• If there are differences between the WSI consensus and the Original Signed Out report, the case is examined under the microscope and the reasons for the differences examined.
Primary Diagnosis Trial

In 17 of 25 cases there were no discrepancies between the study pathologist reports. In 8 of the remaining cases, there were 12 discrepancies, including 3 in which image quality could be at least partially implicated. When the WSI consensus diagnoses were compared with the original sign-out diagnoses, no significant discrepancies were found.
• Type 1 discrepancies: These represent situations in which a pathologist misdiagnosed a fairly straightforward, well-imaged lesion.
Case 52 was a seborrheic keratosis. One study pathologist diagnosed actinic keratosis citing the mild atypia in the epithelium. Consensus was that the correct diagnosis was seborrheic keratosis.
**Type 2 discrepancies**: In these situations, a pathologist did not look at (and therefore did not report on) an area containing a clear, well-imaged lesion.
Figure 7, Case 38, granulomatous inflammation
A clear granuloma missed by two pathologists as they steadfastly searched for neoplasia in the epithelium
**Type 3 discrepancies:**

In these situations, the pathologists agreed on what they saw but disagreed on how to report it.

To qualify as a type 3 discrepancy, there needed to be convincing evidence that image quality did not contribute to the differences in judgment.
Figure 11, Case 37, bladder biopsy with urothelial carcinoma
An overview of the specimen, the diagnostic question was high grade versus low grade
Type 4 discrepancies:

In these cases, image quality was implicated (at least partially) in the disagreements between pathologists.
The study pathologists disagreed about this focus. Opinions ranged from benign to suspicious to outright cancer. Special stains were non-contributory. After discussion, it was agreed that cancer could not be definitively diagnosed. This turned out to be consistent with the signed report. The area is slightly out of focus.
<table>
<thead>
<tr>
<th>Case</th>
<th>Part</th>
<th>Specimen</th>
<th>At Issue</th>
<th>Discrepancy Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>1</td>
<td>Bladder Biopsy</td>
<td>Tumor Grade*</td>
<td>Type 3</td>
</tr>
<tr>
<td>38</td>
<td>1</td>
<td>Bladder Biopsy</td>
<td>Dysplasia v Benign Granulomatous Inflammation?</td>
<td>Type 4*</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Bladder Biopsy</td>
<td>Granulomatous Inflammation?</td>
<td>Type 2</td>
</tr>
<tr>
<td>40</td>
<td>1</td>
<td>Bladder Biopsy</td>
<td>Tumor Grade Superficial Invasion?</td>
<td>Type 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Type 3</td>
</tr>
<tr>
<td>45</td>
<td>1</td>
<td>Bladder Biopsy</td>
<td>Muscle Invasion?</td>
<td>Type 1</td>
</tr>
<tr>
<td>50</td>
<td>2</td>
<td>Skin Biopsy</td>
<td>Atypical Melanocytic Lesion: Invasion?</td>
<td>Type 4*</td>
</tr>
<tr>
<td>52</td>
<td>1</td>
<td>Skin Biopsy</td>
<td>Actinic Keratosis versus Seborrheic Keratosis with HPV infection</td>
<td>Type 3</td>
</tr>
<tr>
<td>54</td>
<td>1</td>
<td>Bladder Biopsy</td>
<td>AK versus Artifact</td>
<td>Type 3</td>
</tr>
<tr>
<td>55</td>
<td>1</td>
<td>Skin Biopsy</td>
<td>Junctional versus Compound Nevus</td>
<td>Type 2</td>
</tr>
<tr>
<td>57</td>
<td>2</td>
<td>Prostate Bx</td>
<td>Atypical Glands (Cancer v HGPIN)</td>
<td>Type 4*</td>
</tr>
</tbody>
</table>
Each pathologist rated each whole slide image as “Excellent” (“Flawless – superb color and sharpness/focus”), “Diagnostic” (“Minimal distortion – quality is high enough to render a diagnosis”) or “Poor” (“Extreme distortion – quality makes diagnosis difficult or impossible”). No whole slide image was rated “poor” by more than one pathologist. Six of seven times, the reason for a “poor” rating was that “key areas were out of focus”. 
Each pathologist rated each case for “Complexity”. Complexity involved aspects of diagnostic difficulty, case management (i.e. the need for recuts or special stains), and reporting issues (i.e. the need for a diagnostic comment). The study appeared to include a balanced set of cases with “high”, “medium”, and “low” complexity.
For each case, the pathologists rated their confidence in their diagnosis. Despite the relative novelty of WSI, diagnostic confidence was high. Out of 72 responses, there were only 3 instances of “low” diagnostic confidence (involving cases 30, 35 and 51). These cases did not involve instances of “poor” image quality and did not result in diagnostic discrepancies between pathologists.
Ratings provided an impression of pathologists’ satisfaction with system performance (stability, response times and ease of use). The data is not quantitatively significant, but system performance was felt to be excellent to good in most cases.
Though useful, this data was very hard to interpret as it included not only “monitor time” but also time required to write the report, order stains and, in some cases, work directly with histology lab to identify and orient blocks.
The results indicated that the image information contained in current whole slide images is sufficient for pathologists to make reliable diagnostic decisions and compose complex diagnostic reports.

However, virtually every slide had focal areas in which image quality (focus and dynamic range) was less than perfect. In some cases, there was evidence of over-compression and regions made “soft” by less than perfect focus.

Pathologists expected systems will continue to get better, image quality and speed will continue to improve, but that further validation studies would be needed to guide development of this promising technology.
Summary

• Microscopes cannot be replaced….
• Digital imaging is increasingly being used in pathology…
• Digital technology is on the move
• Many areas of pathology including education, clinical pathology, anatomic pathology and informatics are creating and utilizing digital imaging applications.
• Pathologists’ current routines will change and be impacted by digital imaging.
• We need to be in the forefront to embrace and evaluate this technology and make it work for us!!!
IN THE NOT SO NEAR FUTURE!!!!

“I will be referring you to a telepathologist”