Creation of a Pixel Pipeline and The Need for Image Analysis To Improve Workflow and Increase Adoption of Digital Pathology for Clinical Use

Andrew J. Evans
Disclosure of Relevant Financial Relationships

Dr. Evans declares he has no conflict(s) of interest to disclose.
Overview

- WSI telepathology at University Health Network
  - how we started
  - how we have expanded our use of the technology - based on whole slide imaging (WSI)
  - enabling sub-specialty pathology

- How image analysis would benefit a department in which WSI has been used for diagnostic work since 2006.
Do UHN pathologists still use microscopes?

• Yes
  • 80% is done with glass slides and a microscope
  • 20% of my service work is done by WSI

• WSI is used for clinical purposes on a regular basis by less than half of UHN pathologists
  • new applications are slowly coming online

• We are living the adoption challenges!
Value Proposition of Telepathology at UHN

- Full departmental consolidation at TGH in early 2006
- No regular on-site pathologist at TWH as of 2004

TWH Frozen Sections: Challenges

- Single pathologist traveling from TGH to TWH
  - Inefficient - traveling and waiting
  - Disruptive to regular workflow at TGH
    - delays in regular sign-out affecting other UHN patients
  - No consultation on difficult cases
    - potential to affect TWH surgical patients.
Image Analysis and Adoption of Digital Pathology
Facilitating Multi-Site Sub-Specialty Pathology

- Move slides?
- Move pathologists?
- Telepathology?

  ➢ Expanding list of clinical applications at UHN:
    - Frozen sections (2004-present)
    - Consultation - local and international
    - Supporting transplant pathology programs
    - Quality assurance
    - Primary diagnosis (2012 - present)
TWH Robotic System: November 2004-October 2006

- 350 frozen sections
- slow (~ 10 minutes/slide)
TWH Whole-Slide Imaging: October 2006-Present

- > 4000 frozen sections/3500 patients
- > 90% from neurosurgery
- 0-2% discrepancy rate
- 14-16 minute total turnaround time
- < 1-5% deferral rate
- 2 pathologists review all deferrals
Intra-Operative Consultations: Work Flow for Single Block Frozen Sections

10-12 minutes

1-3 minutes
Image Analysis and Adoption of Digital Pathology
Why Has This Worked at UHN?

- Started with a single clearly-defined application
  - neurosurgical frozen sections
- Uncomplicated frozen section work flow
- Long development period with due diligence
  - 18 months from initial meetings to go-live
  - time to build confidence and trust
- Implementation team
- Standard Operating Procedure (SOP)
Image Quality: The Importance of Good Histology

Poor slides = Poor image quality

20x scans – ask for 40x when necessary
Episodes of Mid-Case System Failure

- 11 episodes (0.2% of cases to date) requiring a pathologist to go to TWH
  - Small pale pieces of tissue (x2)
  - Excess mounting media (x1)
  - Burned out light bulb (x1)
  - Calibration errors (x5)
    - faded H&E test slides
    - aging light bulb

www.blog.ai.com/spotnews/2009
System Failure: Plan B

- Pathologist informs surgeon and goes to TWH if issue not resolved in 5 minutes.
- A second pathologist works with the TWH histotechnologist in case the issue is resolved.
Frozen Section Telepathology: Remote Sites
Timmins and District Hospital (TADH)

- General community hospital
- > 10,000 surgical pathology accessions/year
- UHN assumed medical leadership of TADH labs in 2006
- Pathologist staffing
  - 1 on-site at any given time
  - 1 week per month – no on-site pathologist
- 150 frozen sections per year
  - tissue identification/intra-operative staging
Kingston General Hospital (Queen’s University)

- Academic pathology department
- Neuropathology frozen sections (1-5 per week)
- 1 staff neuropathologist to cover all frozen sections
- Need for back-up during vacation, CME leave, etc
- UHN pathologists given limited consulting privileges
  - remote access to EPR/diagnostic imaging
  - remote access to KGH LIS
Transplant Telepathology at UHN

- Orthotopic liver transplant program
- ~ 600 post-transplant biopsies/year
  - 2 – 5 urgent biopsies/week (same day or next morning results)

**Practical Issues:**

- 2 liver pathologists
- both can be off-site at once - annual USCAP meeting
- need for continuity of highly-specialized reporting
Primary Diagnosis By WSI

- **First diagnosis made on scanned slide images** (H&E, special stains/immunohistochemistry)
- **Diagnostic information becomes part of the patient record**
- **Treatment decisions to be made** based on this information
Digital Pathology Guidelines

- American Telemedicine Association (2014)
- Royal College of Pathologists in Britain (2013)
- Canadian Association of Pathologists (2013)
- College of American Pathologists WSI Validation (2013)
- Others (Japan 2005)
Self-Validation Studies: What is Learned?

- WSI can be used for making accurate and complete diagnoses
- What needs to be optimized in the histopathology laboratory to facilitate digital sign out
- Limitations
  - cases that require re-scanning
  - cases to scan at 40X
  - cases requiring deferral to glass slide review

5%
Lakeridge Health-UHN
- Transition of Lakeridge to sub-specialty reporting 2011-2012 including a common LIS
- 5-8 on-site pathologists
Primary Diagnosis Telepathology (Live as of November 2012)

- regional cancer center
- 25,000 surgical cases per year
- 300-400 slides per day sent to UHN

WSI is an enabler:
1. Cost
2. Delayed TAT
3. Risks
   - lost/broken slides
Phased Implementation Strategy

• Start with most experienced users
  • GU, endocrine, liver, head and neck
  • placentas, miscellaneous orthopaedic cases
• Attempt to scan all cases for these groups
• Review digital slides and sign out
  • request glass slides whenever it is required to sign out a given case
WSI: Primary Diagnosis

- October 2012 - present
- 9,700 cases (52,000 slides) scanned for primary diagnosis
## Spectrum of GU Cases

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Description</th>
<th>No. Cases</th>
<th>No. Slides</th>
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<td>Partial penectomy</td>
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<td>Grand Total</td>
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**Total Cases:** 2012: 725, 2013: 1036, 2014: 1764, Grand Total: 38,3632
Difficult or unusual cases especially where there is a high likelihood a case will be sent out for glass slide review by another pathologist.

“It’s slower than glass and I’m too busy” - if the pathologist has a large volume of cases to report

Performing diagnostic activities that are currently difficult or cannot be performed using WSI:
- counting mitoses per high power field basis
- identifying micro calcifications on breast biopsies by polarized light microscopy

Suboptimal image quality in an area of potential diagnostic importance - a minor reason for deferral
Example of a Case Deferred to Glass

47 year-old male, 6 cm right inguinal mass, “lipoma”
- Worrisome cellularity with mitoses (some atypical)
- Spindle cell lipoma/mammary-type myofibroblastoma
- De-differentiated liposarcoma
- Required IHC and molecular work-up (MDM2 FISH) not available at Lakeridge Health Oshawa
Growing Pains So Far

1. IT infrastructure/bandwidth
2. Viewer stability and reduced viewing speeds
3. Scanner issues
4. WSI-LIS interface and barcode issues
   - all cases are primarily accessed via the LIS
   - no flexibility for organizing electronic worklists
5. Mixed glass slide-WSI workflow
Hybrid Glass Slide - WSI Workflow

- Culture change – learning to use the Pathologist's Console
- Need to sort WSI from glass cases within the LIS
- Special stains – when are they ready for review?
- Glass slides sent when pathologist is looking for scanned slides
Summary of Clinical Use of WSI at UHN

• We have used computer screens the same way we use microscopes.
  ➢ visual interpretation of H&E morphology
  ➢ visual interpretation of immunohistochemistry

• Our WSI system works for those who use it - improvements on several fronts are needed to increase adoption

• Enter the need for a “pixel pipeline” with image analysis!
“Image Analysis” To Date

Measurement Tools:
- Linear extent
- Distance from margins
- Depth of invasion
- Surface area
Pixel Pipelines

• Graphics card components that process pixel information to accelerate image processing tasks.

• Sequence of steps from digitizing a slide to final diagnosis with complete and robust prognostic information

• Doing what human eyes cannot do with WSI, glass slides or a microscope
  ➢ “It’s slower than glass and I’m too busy”
  ➢ “Digital pathology is the future of pathology - and always will be”
Image Analysis: Software Tools To Help Pathologists (Not Replace Us)

• **Intended goals:**
  - allow the pathologist to act as the final interpreter
    - not field selection technologist
  - more robust biomarker quantitation
    - oncologists and patients like reports with hard numbers

• **Use cases we have discussed at UHN**
Ki-67/MIB-1

**Clinical Applications**
- neuroendocrine tumors
- neuropathology - adjunct for grading gliomas and meningiomas
- lymphoma

**Translational Research Applications**
- breast cancer - additional prognostic information over grading?
- prostate cancer - active surveillance patient selection?
Ki-67 Labeling Index

- Visual inspection/hot-spot detection
  - time consuming and error prone

Hot spot detection for breast cancer in Ki-67 stained slides: Image dependent filtering approach

M Khalid Khan Niazi\(^a\), Erin Downs-Kelly\(^b\), Metin N. Gurcan\(^a\)
\(^a\)Department of Biomedical Informatics, The Ohio State University, Columbus, Ohio, USA
\(^b\)Department of Anatomic Pathology, Cleveland Clinic, Ohio, USA

\[
\begin{align*}
t &= \text{integer} \left( \max \left( \frac{-2b + \sqrt{(2b)^2 - 4ac}}{2a}, \right. \\
& \left. \frac{-2b - \sqrt{(2b)^2 - 4ac}}{2a} \right) \right) \\
&= \text{integer} \left( \max \left( \frac{-2b + \sqrt{4b^2 - 4ac}}{2a}, \right. \\
& \left. \frac{-2b - \sqrt{4b^2 - 4ac}}{2a} \right) \right) \\
&= \text{integer} \left( \max \left( \frac{-b + \sqrt{b^2 - 4ac}}{a}, \right. \\
& \left. \frac{-b - \sqrt{b^2 - 4ac}}{a} \right) \right)
\end{align*}
\]
Mitotic Figure Counting: H&E

Potential confounders for visual counting:
- thick sections
- over-staining
- apoptotic bodies
Mitotic Rate in Melanoma

Prognostic Value of Immunostaining and Computer-assisted Image Analysis

Christopher S. Hale, MD,* Meng Qian, MS,† Michelle W. Ma, MD,‡§ Patrick Scanlon,‡§ Russell S. Berman, MD,†† Richard L. Shapiro, MD,‡† Anna C. Pavlick, DO,‡§†† Yongzhao Shao, PhD,‡‡‡ David Polsky, MD, PhD,*‡‡ Iman Osman, MD,‡‡‡ and Farbod Darvishian, MD*‡

40 year-old female - needle biopsy of incidentally-found left renal mass

Immunohistochemistry panel: CD10, CD117, CK 7, AMACR, CAIX
Multiplex Immunofluorescence

- Biopsy with limited lesional tissue
- Requires an immunohistochemistry panel (5-10 stains)
- Lesional tissue is exhausted from the block
- Can the panel be run on one single paraffin section?
  - hyperplexing (60 or more markers)

A Single Slide Multiplex Assay for the Evaluation of Classical Hodgkin Lymphoma

Denise Hollman-Hewgie, MS, MBA,* Michael Lazare, BS,* Alex Bordwell, BS,* Emily Zebadua, MSc,* Pinky Tripathi, MBA,* Alexander S. Ross, PhD,* Deanna Fisher, BS,* Alisha Adams, B.A,* Derek Bowman, BS,* Dennis P. O’Malley, MD,† and Lawrence M. Weiss, MD*†

Interactive digital slides with heat maps: a novel method to improve the reproducibility of Gleason grading

Lars Egevad · Ferran Algaba · Daniel M. Berney · Liliane Boccon-Gibod · Eva Compérat · Andrew J. Evans · Rainer Grobholz · Glen Kristiansen · Cord Langner · Gina Lockwood · Antonio Lopez-Beltran · Rodolfo Montironi · Pedro Oliveira · Matthias Schwenkglenks · Ben Vainer · Murali Varma · Vincent Verger · Philippe Camparo

<table>
<thead>
<tr>
<th>Decision support tools for Gleason grading in prostate cancer</th>
<th>Table 1 Fifteen consensus cases with at least 67% agreement for Gleason score categories</th>
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<td>23</td>
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</tbody>
</table>

Number of votes for most commonly assigned grade shown in bold.
Pathologist Time & Motion Study: Glass Slide Review (Stratman et al)

Slide Review: 36.0%
Reporting: 34.6%
Other: 16.0%

Workflow Opportunities:
- Organizing Cases: 24.1% (0:10:25)
- Querying for Cases: 18.5% (0:07:59)
- Waiting for Delivery: 11.2% (0:04:49)
- Searching for Cases: 9.4% (0:04:04)
- Transporting Cases: 9.2% (0:03:58)
- Other: 17.0% (0:07:21)
Concept of “pCAD”

- Automated, systematic slide review, pre-annotated slides
- Construct a report as slides are reviewed
- Reduce the time spent on non-diagnostic work
Deep learning for digital pathology image analysis: A comprehensive tutorial with selected use cases

Andrew Janowczyk, Anant Madabhushi

Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH 44106, USA

Need for adequately-powered training sets (large number of exemplars)

Machine learning with iterative improvement
How To Make The Pixel Pipeline a Reality

• Do it yourself (?)

• Partner with companies who focus on:
  ➢ streamlining workflow in digital pathology - complete digitization
  ➢ dependable IT support - continuous system monitoring
  ➢ managing large volumes of digital data
  ➢ development of clinically relevant algorithms
  ➢ creative business models
Summary

• WSI telepathology at University Health Network
  ➢ enabling sub-specialty pathology
  ➢ how we started
  ➢ how we have expanded our use of the technology

• How image analysis would help pathologists who have been using WSI for diagnostic work since 2006.
Acknowledgements

• Pathologists
  - Dr. Sylvia Asa - vision of bringing telepathology to UHN
  - Colleagues who worked to move digital pathology forward

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  - Peter Woo
  - Dr. Zoya Volynskaya
  - Celcilia Lagmay-Traya

• Lakeridge Health Oshawa Staff
  - Alan Wolff