Digital pathology and pathology informatics

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Disclosure

- I have no conflict of interest
Outline

• Introduction of digital pathology
• Digital pathology for primary diagnosis
  Component of digital pathology system for primary diagnosis
  Digital pathology workflow, SNUH
  Issues in implementation of digital pathology system
• Digital pathology for research
  Computational pathology: quantification, discrimination, prediction
  Reconstruction
• New technique for digital pathology
  Slide-free non-destructive pathology
What is digital pathology?


image-based information environment which is enabled by computer technology that allows for the management of information generated from a digital slide. Digital pathology is enabled in part by virtual microscopy, which is the practice of converting glass slides into digital slides that can be viewed, managed, shared and analyzed on a computer monitor. With the advent of Whole-Slide Imaging, the field of digital pathology has exploded and is currently regarded as one of the most promising avenues of diagnostic medicine in order to achieve even better, faster and cheaper diagnosis, prognosis and prediction of cancer and other important disease
What can we do with digital pathology?

What can we do with glass slide?

- **Education**
- **Research & bioindustry**
  - Prognosis factor
  - Classification
  - Biomarker development
  - Toxicology
  - Drug development: semi-quantitative grading consensus meeting

Segmentation, quantification, computation, prediction

- **Primary diagnosis**
- **Teleconference & -consult**
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• **New technique for digital pathology**
  Slide-free non-destructive pathology
Regulation of whole slide image for primary diagnosis

US Philips IntelliSite Pathology Solutions for primary pathology diagnosis

: 2000 surgical pathology cases (15,925 readings) : optical interpretation rate difference of 0.4% with a 95% confidence interval (−0.3–1.0) indicating noninferiority for digital versus optical reads
Fully digitalized pathology lab.

2018, 8.17, University Medical Center Utrecht, Netherland, Amsterdam

> 1,000 beds, >10,000 employes
20,000 /yr histopathology requests
156,000 slides/yr
15 pathologists, 10 residents

⇒ 6 scanner running

2018.8.16, Linkoping University Hospital, Linkoping, Sweden

30,000/yr histopathology requests
180,000 slides/yr
20 pathologists

⇒ 27 digital work stations
> 1,000,000 slides 440TB
Start in 2010, full digital in 2017
Components of digital pathology

- Slide scanner: image acquisition
- Image management: data, messages, integration in LIS
- Viewer software and image storage system
- Image evaluation and analysis system
- Hardware of users: user workstation and viewing monitor
Implementation of digital pathology & workflow, SNUH
Change of pathology workflow

1st step: Traditional paper-based workflow → paper-less workflow
Pathology PACS and HIS system: SNUH

- Digital Gross Photography system
- Sequencer PCR
- FISH/IF/EM images
- Slide scanner
- HIS system, upgrade 2016
  - Order
  - Patient information
  - Paper-less pathology report
  - Lab work-flow management
  - Slide tracking system
- Pathology image server (HUPAX, 2009, SNUH&Humintec)
- Hospital Information System
- Pathology PACS
- Template
HIS: main report

1. Order ancillary test
2. QA & QC
3. Statistics
HIS: Frozen report
HIS: Automatic text loading

1. Cytology > Heading, screening result
   - Negative

2. Immunohistochemistry / special study > antibody item

3. Gross examination, small tissue > gross text & heading
Reporting template, SNUH

Check-list electronic file > Excel-based

Text join
Copy & paste

Text report: semi-structured text
Pathology PACS: virtual slide

1. Previous slide review
2. Conference
3. Image analysis
4. Tumor marking
5. Research
6. Permanent storage
Change of pathology workflow

Submit → Gross (oral dic) → Glass slide → reading → Reporting (paper/typist) → Slide repository

Scanner 1: post-diagnosis

Scanner 2: pre-diagnostic

Virtual slide → Report [EMR] → Virtual slide for repository

Issues → Space, time, manpower → Storage → Diagnostic performance, TAT

2nd step: digitalization of glass slides for diagnosis, not for repository
Digital pathology project: SNUH, 2017-2018

Digital Gross Photography system
Sequencer PCR
FISH/IF/EM images
Slide scanner x2

EMR system, 2016
Order
Patient information
Paper-less pathology report
Lab work-flow management
Slide tracking system

Pathology image server
(HUPAX, 2009년 개발, SNUH&Humintec)
HP ProLiant DL380p (Gen8)
Storage: 55Tb (18Tb, backup)

Server/storage
2 servers
55Tb >> 220Tb

HUPAX upgrade & open to whole hospital
HUPAX web viewer
Pathologist workstation (2 sets)
Scanning

- **Objects**
  post-diagnostic: selected glasser for conference, key slides for molecular test
  pre-diagnosis: image analysis, hepatobiliary pancreas, urology, medical kidney, bone and soft tissue, skin, CNS, pediatric cases

- **Scan volume**
  File/data: 288,055 glass slides / 73Tb, 40% /total slides, 2018

- **Scan protocol and quality**
  cover slide mounting -> drying for 20min -> loading one rack (40 slides /rack)
  Rescan rates
  >5% [SNUH 6.3% -> 2%]
  stripe, focusing out
  histotechnical procedure: tissue fold, air bubbles, dirt on slides
  cannot find out tissue on autofocusing: limited tissue / too little, no positive stain
  automatic file loading to server by barcode system: no additional manual work for file management
  Slides can be seen within 1-3hr after loading
Pathology workstation

- VS monitor: 4096x2160 resolution medical imaging display
- HIS monitor
- Secondary monitor for ancillary images
- 4096x2160 resolution medical imaging display
- HUPAX web viewer
- 3D mouse: navigation of VS
- PC: Intel i7-7700k, GTX1080, 8G RAM
Primary diagnosis by WSI, SNUH
Diagnostic performance: SNUH

- Consecutive 235 건

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- Discordant rates: 9% (20/235)
  - Activity: 8
  - Dysplasia grade: 1
  - H. pylori: 8
  - H. pylori, Activity: 3
  - active inflammation: neutrophil
  - dysplasia grade: low grade > high grade
  - Helicobacter pylori: x20 > x400
  - No missed case: malignancy, reactive atypia

- x20 / x40 (medical kidney)
- Concordant rate: 91%
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Quantification (I) : Biomarker

Usage: biomarker evaluation eg. Hormone receptor, HER2, proliferation index, PD-L1

Limitation:
- automatic tumor cell identification among various cells
- Artifact: tissue, staining
  ➔ Need manual correction
Segmentation by QuPath (free software)
Manual removal of nontumor cells or artifact
→ 4.24% 75/1770, Neuroendocrine tumor, G2 : tumor grading
Quantification (II): multiplex IHC

Multiplexed immunohistochemistry, imaging, and quantitation: A review, with an assessment of Tyramide signal amplification, multispectral imaging and multiplex analysis

Edward C. Stack, Chichung Wang, Kristin A. Roman, Clifford C. Hoyt*

PerkinElmer, Inc., Waltham, MA 02451, USA
Quantification (II): multiplex IHC

multiplex IHC in CRC patients

Novel technique for evaluation of cancer immunity

- Brief process of multiplex IHC method
- Stacking of multiplex virtual slide image
- Gain each marker’s intensity value for all annotated cells

- PD-L1

Red=FOXP3
Green=PD-1
Blue=PD-L1

Courtesy by YJ Kwak, Department of pathology, Seoul National university Hospital presented in the 7-th annual fall meeting of the Korean society of pathologists
Quantitative nucleic features are effective for discrimination of intraductal proliferative lesions of the breast

Masatoshi Yamada, Akira Saito, Yoichiro Yamamoto, Eric Cosatto, Atsushi Kurata, Toshitaka Nagao, Aiko Tatsuki, Masahiko Kurada

Table 2: Nuclear morphological parameters

Table 4b: Accuracy table

Discrimination (I) : quantitative image feature

- Discrimination by digitalized image feature >
  

- Extract quantitative image feature : 790 items

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- Quantitative image features cannot be understood or perceived by pathologist
Discrimination (II) : Deep learning

More sensitive than pathologist, but some false positive result
- Lack of other disease pattern
- **Assisting pathologist, not primary role**
Find new prognostic groups

Predicting cancer outcomes from histology and genomics using convolutional networks

Pooya Mobadersany, Safora Yousefi, Mohamed Amgad, David A. Gutman, Jill S. Barnholtz-Sloan, Jose E. Velazquez Vega, Daniel J. Brat, and Lee A. D. Cooper

*Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA 30322; †Department of Neurology, Emory University School of Medicine, Atlanta, GA 30322; ‡CAAC Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH 44106; §Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322; ¶Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611; ††Wisconsin Cancer Institute, Emory University, Atlanta, GA 30322; and ‡‡Department of Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, GA 30322

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A
1. Sample HPFs for training patient
   - Outcome: 1077 days, deceased
   - Training slides and regions of interest
   - SCNN model training

2. Model training
   - Output: prognostic model
   - Randomized transformations

B
1. Sample HPFs for test patient
   - Outcome?
   - Testing slides and regions

2. Calculate median risks in each region
   - Predicted risks (one region)
   - Sorted median risks

3. Calculate patient risk

TCGA-DB-S273 (IDH-mut astrocytoma)

TCGA-S9-A7JQ (IDH-mut astrocytoma)

TCGA-TM-AM4G (Oligodendroglioma)
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Slide-free non-destructive pathology

Light-sheet microscopy for slide-free non-destructive pathology of large clinical specimens

Adam K. Glaser{a}, Nicholas P. Reder{b}, Ye Chen{c}, Erin F. McCarty{d}, Chengbo Yin{e}, Linpeng Wei{f}, Yu Wang{g}, Lawrence D. True{h} and Jonathan T. C. Liu{i}

For the 1.7 million patients per year in the US who receive a new cancer diagnosis, treatment decisions are largely based on histological and nuclear morphology. Histological, the gold standard of clinical pathology, involves slicing tissues from

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**Figure 1** Open-top light-sheet microscope for clinical pathology. a. An illumination light sheet enters the bottom surface of a tissue sample at an oblique 45° angle (purple). The specimen is placed on a modular glass-slide sample holder, which is inserted into a two-axis translation stage and scanned in a
Closing

- Virtual slide: replaceable system of light microscopy: practical problems remained
- Numerous research algorithms vs few clinical use: standardization of images
- Future of digital pathology
  To save pathologist’s time
    - find tumor, mitosis, micro-organism
      - quantification, measurement, reporting
  To help pathologist’s decision
    - segmentation and classification of cell and tissue
      - support diagnosis, grading, pattern recognition
  To find new histologic feature or subtype
    - survival, genetic information