Welcome to CAP’s IVM Webinar Series sponsored by the In Vivo Microscopy Project Team

This webinar on “How IVM Could Improve Our Practice as Pathologists” is presented by Lida P. Hariri, MD, PhD.

Your host is Jill Kaufman, PhD. For comments about this webinar or suggestions for upcoming webinars, please contact Jill Kaufman at jkaufma@cap.org

THE WEBINAR WILL BEGIN MOMENTARILY. ENJOY!
How IVM Could Improve Our Practice as Pathologists

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February 27, 2014
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- Member of the IVM workgroup
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Disclosure

- Dr. Hariri has no relevant financial relationships with commercial interests to disclose
What is “In Vivo Microscopy (IVM)?”

Definition of IVM used by the CAP Workgroup:
A new field where microscopic images are obtained in real time from living patients

Ex vivo applications of IVM:
• … where microscopic images are obtained in real time from living cells or tissues
• Reagent-free, label-free or otherwise minimally processed specimen
Bridging the Radiology/Pathology Divide
What can IVM provide us as pathologists?

Our objectives

• Improve biopsy interpretation
  o Guide biopsy site selection
  o Additional virtual tissue volumes

• Assess tissue margins
  o Ex vivo in frozen section
  o In vivo to assess margins intraoperatively

• Assess tissues where it is unsafe to biopsy
  o i.e. coronary arteries, eye pathology
Examples of Imaging Modalities that provide IVM

- Optical coherence tomography
- Photoacoustic tomography
- Confocal and multiphoton microscopy
- Spectroscopy
  - Raman spectroscopy
  - Near infrared spectroscopy
Optical Coherence Tomography

- Cross-sectional (x-z) imaging of tissue structure
- Similar to low power microscopy (4x objective)
- < 10 µm axial resolution (z)
- Analogous to Ultrasound

- 10-30 µm transverse resolution (x)
- < 3 mm penetration depth
- Non-destructive
- No transducing medium
OCT Imaging Applications

- Retinal
- Coronary
- Gastrointestinal
  - Esophageal
  - Colonic
- Respiratory
- Ovarian
- Breast
- Renal
- Dermatology

Courtesy of Boris Povazay and Wolfgang Drexler. Medical University of Vienna. Austria.
Objective 1: Biopsy Guidance

IVM to improve biopsy interpretation

- Assess biopsy site selection during procedure to reduce sampling error and increase diagnostic yield
- Interpret volumetric imaging data sets as a form of “virtual” tissue to accompany physical tissue biopsies
Flexible imaging probe easily placed in standard 21-gauge TBNA needle

Needle-based OCT Probes


Wu Y et al. IEEE Selec Topics Quant Elec. 16(4). 2010
Vacuum-assisted OCT Needle Biopsy Probe

Forceps OCT biopsy probes

http://www.spectrascience.com/

Song C. BMOES. 4(7). 2013
OCT Endoscopy: Guided Biopsy for Barrett’s Esophagus

1. Volumetric OCT Acquisition

2. Image Assessment and Interpretation

3. Target selection

4. Laser Marking

5. Endoscopy with Biopsy Acquisition and Histopathologic Analysis of Biopsy Sites

OCT guided biopsy of lung nodules

A work in progress that exemplifies the need for pathologists and optical engineers to collaborate
Biopsy of Pulmonary Nodules

**Transthoracic needle aspiration:**
- High diagnostic yield
- Increased risk of pneumothorax

**Transbronchial needle aspiration:**
- Lower risk of pneumothorax
- Variable diagnostic yield

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http://library.bjmu.edu.cn

www.olympus.es
Currently Used Guidance Techniques

**Endobronchial Ultrasound**

**Electromagnetic Navigation:**

Diagnostic Yield is still low for lesions < 3.0 cm
Biopsy Triage!

To Pathology Lab

Courtesy of Dr. Kevin Leslie, Mayo Clinic, Scottsdale, AZ
Needle Biopsy of Lung Nodules

Target Lung Nodule

Miss Nodule
- Normal Airway
- Normal Parenchyma

Tumor: Diagnostic!

Hit Nodule
- Necrosis: Not Diagnostic
- Fibrosis: Not Diagnostic

Animations Courtesy of Dr. Alex Chee, University of Calgary
Needle Biopsy of Lung Nodules

Target Lung Nodule

Hit Nodule

Tumor: Diagnostic!

Necrosis: Not Diagnostic

Fibrosis: Not Diagnostic

Animation Courtesy of Dr. Alex Chee, University of Calgary
We need a high resolution imaging modality to:

Complement EBUS and ENB
Assess the needle position after placement
Give immediate feedback about placement site

So what is missing in biopsy guidance?
OCT Biopsy Guidance in Lung Nodules

Hariri LP et al. J Vis Exp. 71. 2013
Flexible imaging probe easily placed in standard 21-gauge TBNA needle

Needle-based OCT: Lung Parenchyma

Hariri LP et al. Chest. 144(4). 2013
Needle-based OCT: Lung Nodule

Hariri LP et al. Chest. 144(4). 2013
Differentiating nodules from parenchyma with OCT

High Sensitivity and Specificity (> 95%) for all readers: Pathologists, Pulmonologists, OCT Experts

Hariri LP et al. Chest. 144(4). 2013
Structural OCT can differentiate tumor from airway, parenchyma, and necrosis.

Cannot differentiate solid tumor from fibrosis

Polarization Sensitive OCT
Measures birefringence in organized tissues like collagen

SCC with dense established fibrosis
Adenocarcinoma with early fibrosis
Carcinoid tumor with no fibrosis

OCT Guided Biopsy of Lung Nodules: The Complete Picture

Target Lung Nodule

Miss Nodule
- Normal Airway
- Normal Parenchyma

Tumor: Diagnostic!

Hit Nodule
- Necrosis: Not Diagnostic
- Fibrosis: Not Diagnostic

Structural OFDI

Structural OFDI: Differentiate normal elements from tumor

PS-OFDI: Differentiate fibrosis from tumor
Biopsy Guidance: What this means for pathology

Performed by pulmonologist, but will aid pathologist

- Target lung nodules with needle-based OCT in vivo during bronchoscopic biopsy
- Use OCT to increase tumor yield for pathology
- Pathologist acts as consultant for difficult cases

Performed by pathologist

- Assess “virtual tissue volumes” as a complement to standard biopsy to aid diagnostics

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Large volume “virtual” tissue to accompany biopsy

1. OCT provides views of tissue microarchitecture comparable to low power (4x) microscopy

2. Tissue volumes are orders of magnitude larger than biopsy
3D Reconstruction: Cartilaginous Hamartoma
Objective 2: Tissue margins

IVM to assess tissue margins

- Ex vivo to assess margins in frozen section
- In vivo to assess margins intraoperatively
Full-Field OCT to assess lung carcinoma
Full-Field OCT
Full Field OCT: Normal Lung

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Jain M. J Path Inform. 4(26). 2013
Full Field OCT: Normal Lung
Full Field OCT: Lung Adenocarcinoma
Full-Field OCT in the frozen section lab

- FFOCT as an adjunct to frozens for intra-operative consultation
  - Surgical margin assessment
- FFOCT to assess adequacy of biopsy material in freshly excised tissue
- FFOCT in bio-banking to confirm tumor is present before cryopreservation
IVM to Assess Breast Excision Margins
Assessing Breast Excision Margins with OCT

Breast Excision Margins with OCT: Negative Margin

Breast Excision Margins with OCT: Positive Margins

<table>
<thead>
<tr>
<th></th>
<th>Histology (Positive)</th>
<th>Histology (Negative)</th>
<th>Total</th>
<th></th>
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<tbody>
<tr>
<td>OCT (Positive)</td>
<td>9 (TP)</td>
<td>2 (FP)</td>
<td>11</td>
<td>PPV = 82%</td>
</tr>
<tr>
<td>OCT (Negative)</td>
<td>0 (FN)</td>
<td>9 (TN)</td>
<td>9</td>
<td>NPV = 100%</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>11</td>
<td>20</td>
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</tbody>
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Sensitivity = 100%  Specificity = 82%

Intraop margin assessment with OCT: Clinical Trial

- Multi-center, randomized blinded clinical trial
- Intraoperative imaging in partial mastectomy:
  - Excised breast margins
  - In vivo surgical cavity
- Compare surgical re-excision rates between standard of care partial mastectomy and intraoperative imaging with partial mastectomy

Objective 3: Tissue that cannot be biopsied

IVM to assess tissues where it is unsafe to biopsy

i.e. coronary arteries, eye pathology
IVM in Coronary Artery Pathology
IVM in the Coronary Arteries

Witnessed Plaque Rupture with OCT

IVM in Retinal Pathology
IVM in Retinal Pathology

Drexler W and Fujimoto J. Progress in Retinal and Eye Research. 27(1). 2008
IVM in Retinal Pathology: 3D retinal visualization

IVM in Retinal Pathology: Commercial System

http://buea.net/services-offered/retina/
Ultra-High Resolution OCT
Micro-OCT: Atherosclerotic Plaque

Optical Coherence Microcopy_ Normal Kidney

Lee HC, et al. Biomedical Optics Express. 4(8). 2013
The Role of the Pathologist

- OCT provides high resolution architectural images similar to histopathology

- Pathologists already have strengths in
  - Interpreting high magnification/resolution microscopy
  - Pattern recognition
  - Understanding of pathology entities
    - Histological features
    - Differential diagnosis

Pathologists are well suited to interpret high resolution imaging as an adjunct to histopathology
“Will IVM replace traditional pathology?”

**No**

- Sensitivity/specificity in tested applications not 100%
- Resolution not high enough
- You are there, take a biopsy!
  - Histology is the gold standard
  - Differential diagnosis in many scenarios is vast
  - Molecular testing
“IVM seems like a clinician’s tool—why should I care about it?”

1) We are the end beneficiaries of IVM:

- IVM has a lot of potential to increase the quality of our tissue samples
  - Guided biopsy sampling- Barrett’s esophagus
  - Increased tumor yield- Lung nodule biopsy

- Our expertise as pathologists is needed to help identify applications where IVM can make big impacts
“IVM seems like a clinician’s tool—why should I care about it?”

2) IVM assessments will become more complex:

- IVM is pretty new and so far, its assessments are straightforward
  - Tumor versus non-tumor elements
  - Diagnosis where there are few options

- As IVM applications develop, the complexity of interpreting IVM images will also develop
  - Will require knowledge pathologists already have: histologic features, differential diagnosis, etc

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“IVM seems like a clinician’s tool—why should I care about it?”

3) IVM needs a defined expert:

• For example, many clinicians can assess CT scans but that does not make them experts in radiology
• Similarly, many clinicians may use and interpret IVM
• IVM is in essence a form of microscopy, and as such pathologists are the obvious choice as IVM experts
Scenarios of IVM in Pathology

**Ex vivo**

Assess adequacy of tissue biopsy - Increase Tumor Yield

Intraoperative consult - Part of frozen section assessment

Guide tissue sampling in the grossing room
Scenarios of IVM in Pathology

**In vivo**

Real-time diagnosis in endoscopy or interventional suite
- Pathologist present during procedure
- At remote site using viewing workstation

**As Part of Sign-out**

Pathologist views images off-line after procedure

Interprets images as a complement to standard histology (particularly in tissue biopsy)
How can we get involved as pathologists?

Pathologist inherently have the skills needed to become IVM experts, but we have to take the reigns.

- Identify clinical scenarios where IVM can make impacts
- Participate in ex vivo and in vivo validation studies
- Be key players in instituting and interpreting high resolution imaging as part of our pathology practice

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MGH Thoracic Surgery

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  o October 23 at 11 am Central
  o Richard M. Levenson, MD, FCAP

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Printed Versions Now Available

• created to assist pathologists who are considering providing or developing in vivo microscopy skills and services within the next 24 months

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Genomic Analysis (large panels, exome, genome)
Digital Pathology

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Thank you for attending our webinar “How IVM Could Improve Our Practice as Pathologists” by Lida Hariri, MD, PhD, FCAP.

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