



In Vivo Microscopy: Applications in Pulmonary Pathology

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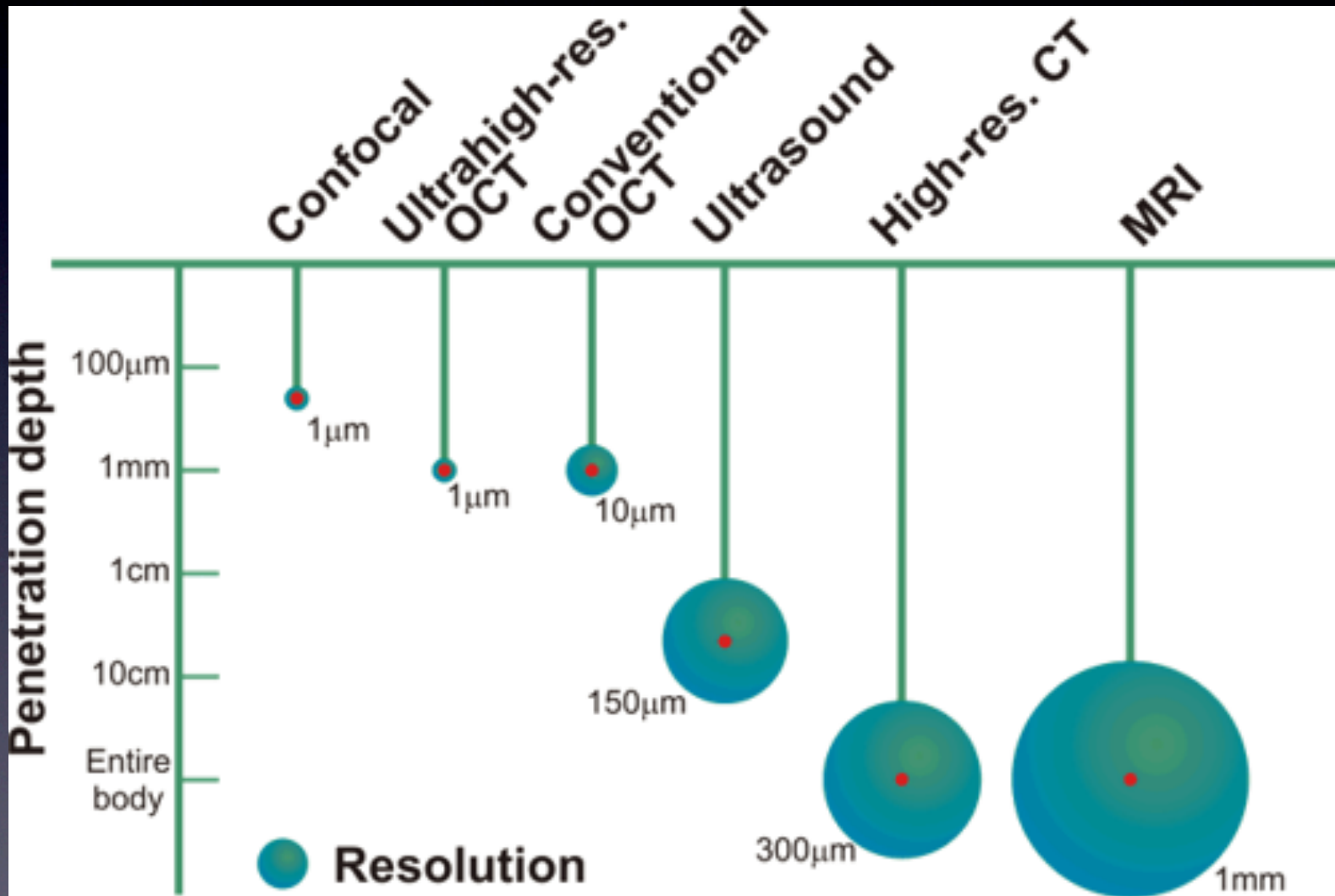
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Disclosures

No relevant financial relationships with commercial interests to disclose

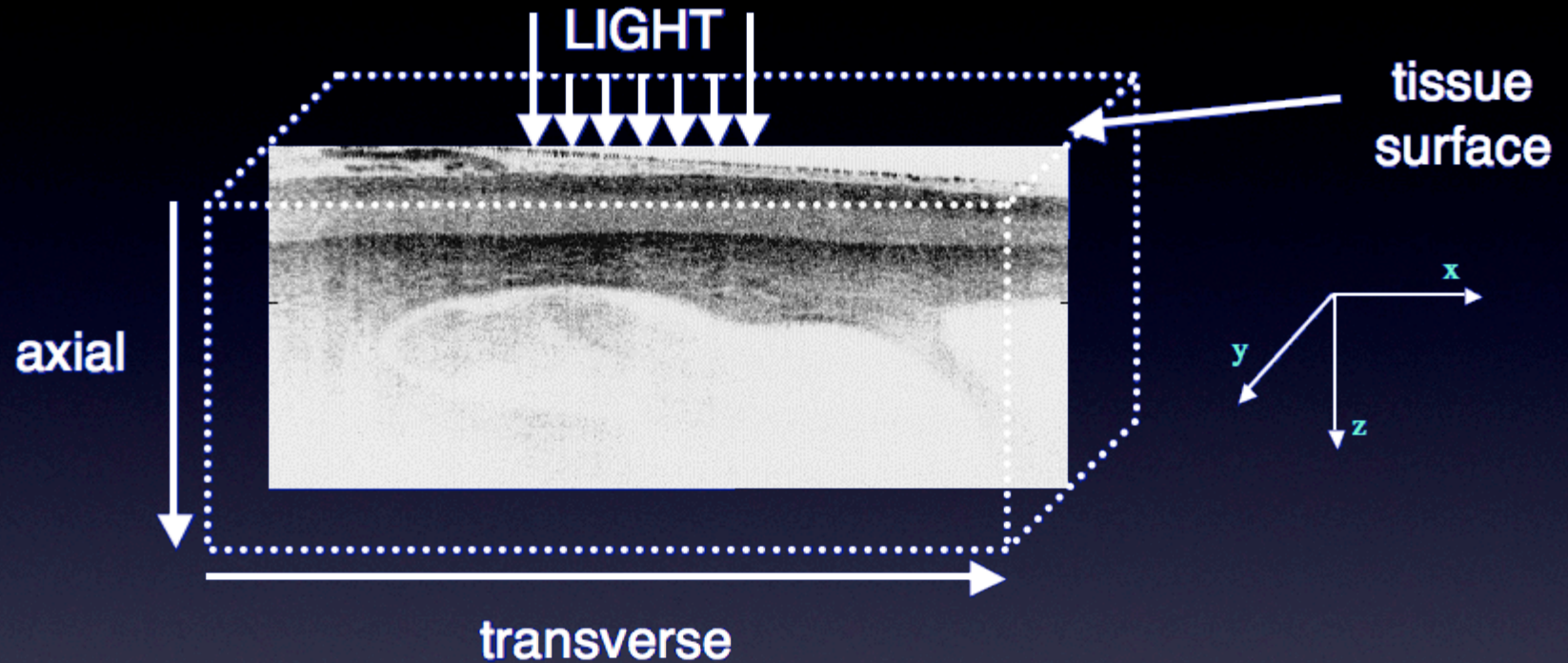
High Resolution Imaging: Bridging the Radiology/Pathology Divide



Examples of Imaging Modalities that provide IVM

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

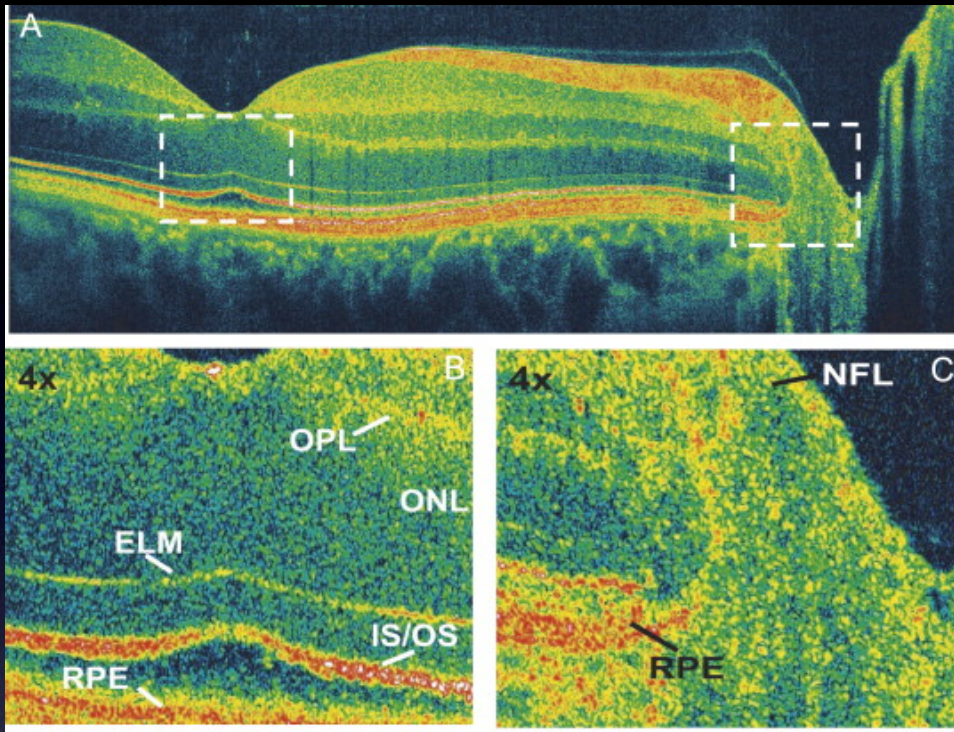
Optical Coherence Tomography



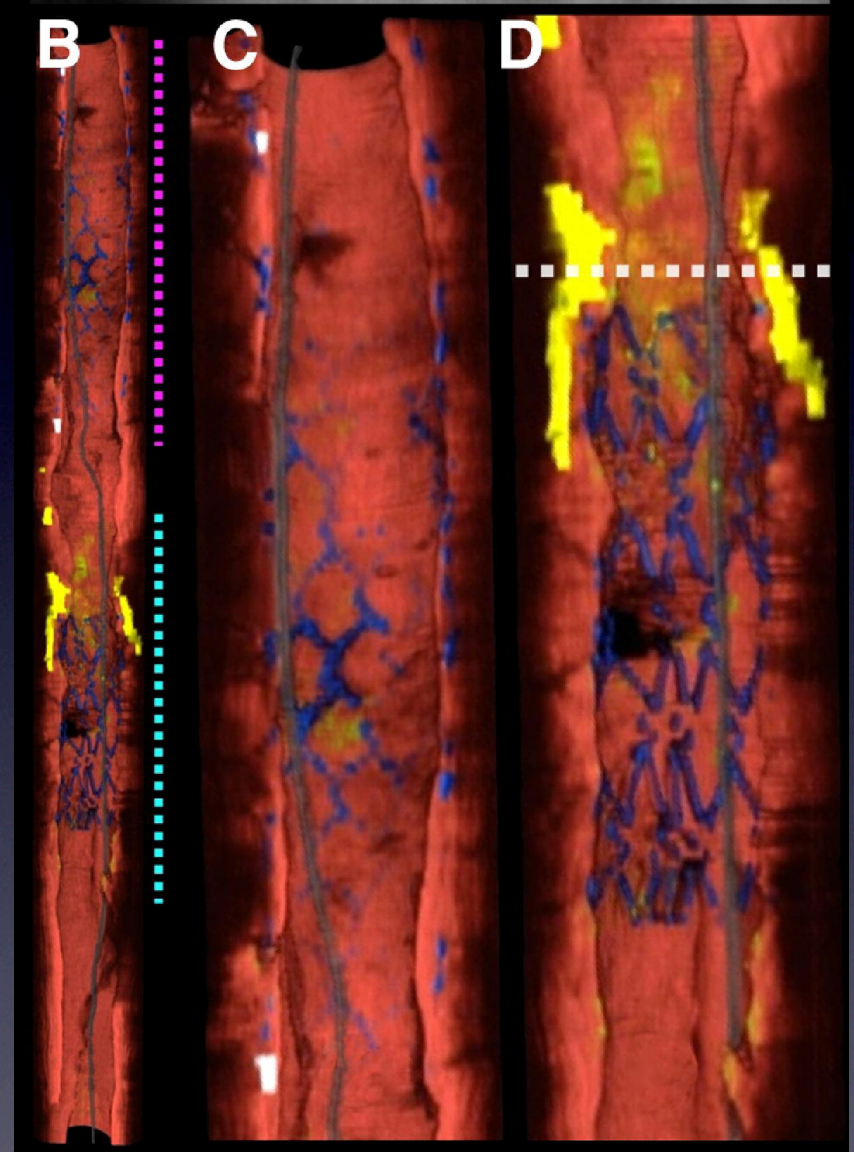
Analogous to Ultrasound

- Cross-sectional (x-z) imaging of tissue structure
- Similar to low power microscopy (2x-4x objective)
- $< 10 \mu\text{m}$ axial resolution (z)
- $10\text{--}30 \mu\text{m}$ transverse resolution (x)
- $< 3 \text{ mm}$ penetration depth
- Non-destructive
- No transducing medium

OCT Applications: Retinal and Intravascular



Drexler W et al. Progress in Retinal and Eye Research. 27(1). 2008



Tearney et al. JACC Cardiovasc Imaging. 1(6). 2008.



<http://buea.net/services-offered/retinal/>

High Resolution Imaging in Pulmonary Pathology

Pulmonary Nodules– Is it Cancer?

Currently Used Biopsy Guidance Techniques in the Lung

Endobronchial Ultrasound

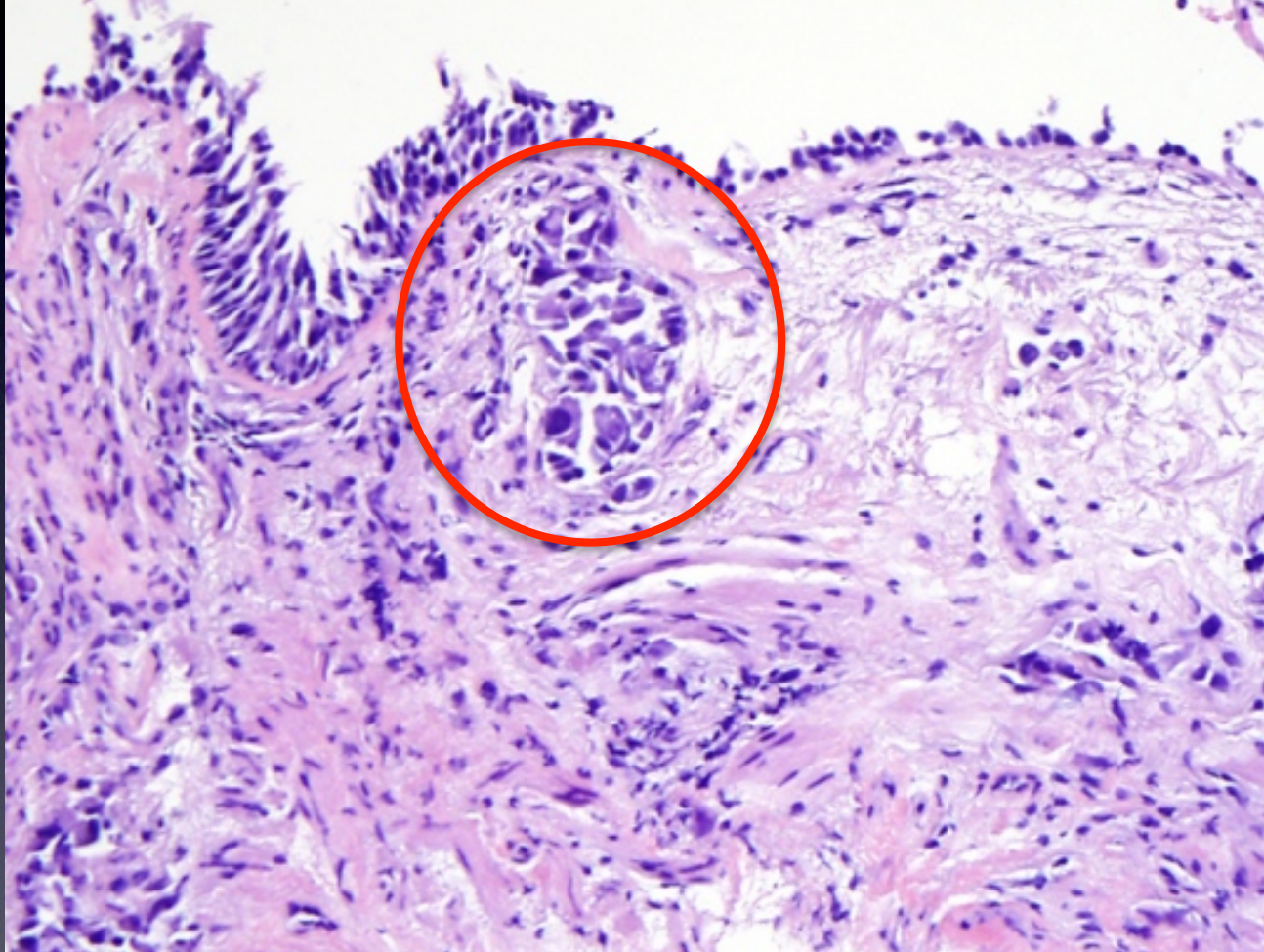


Electromagnetic Navigation

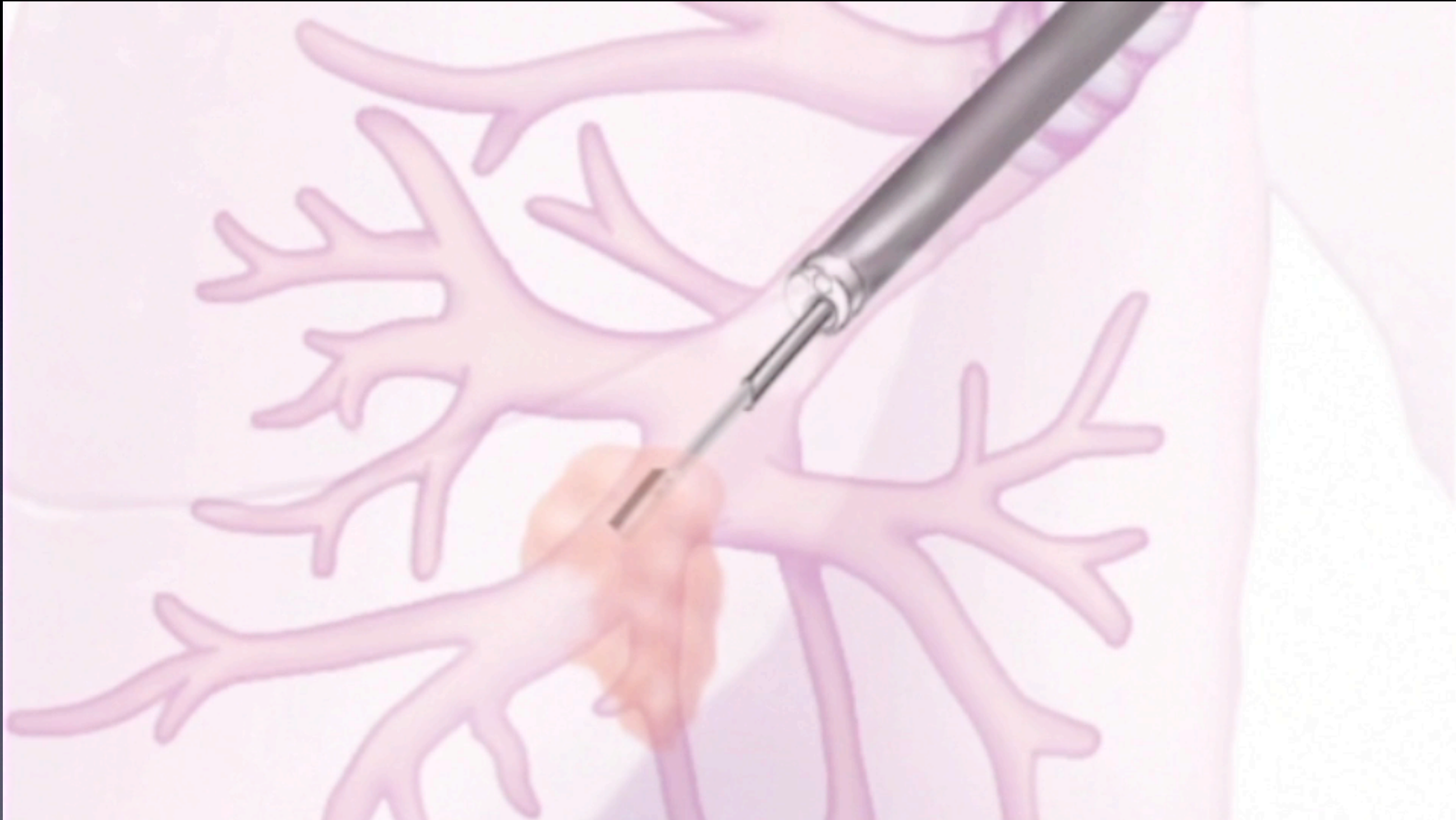


**Diagnostic Yield is still
low for lesions < 3.0 cm**

Lung Nodule Biopsies



OCT to Guide Bronchoscopic Biopsy



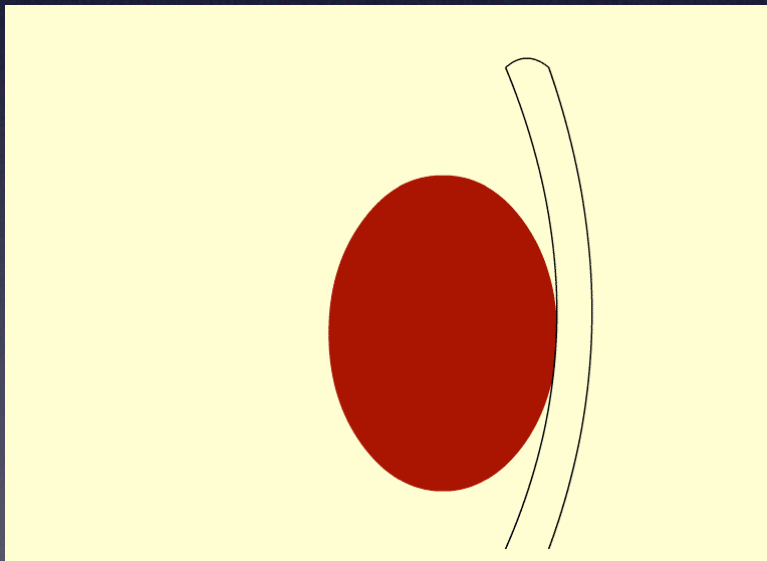
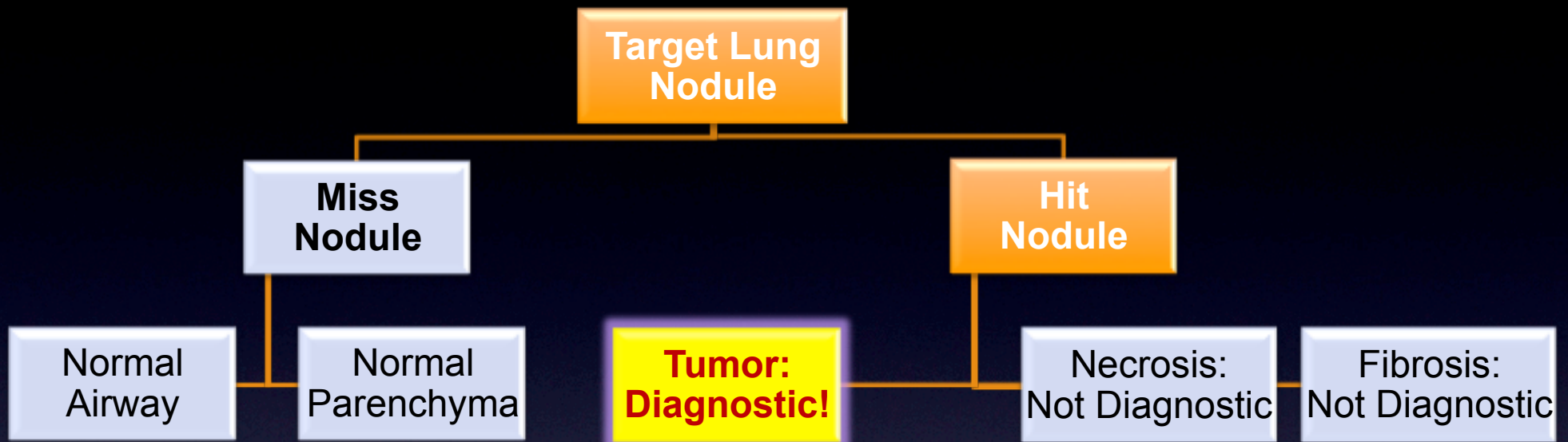
Needle-based OCT probe

Flexible OCT imaging probe easily placed within standard 21-gauge TBNA needle

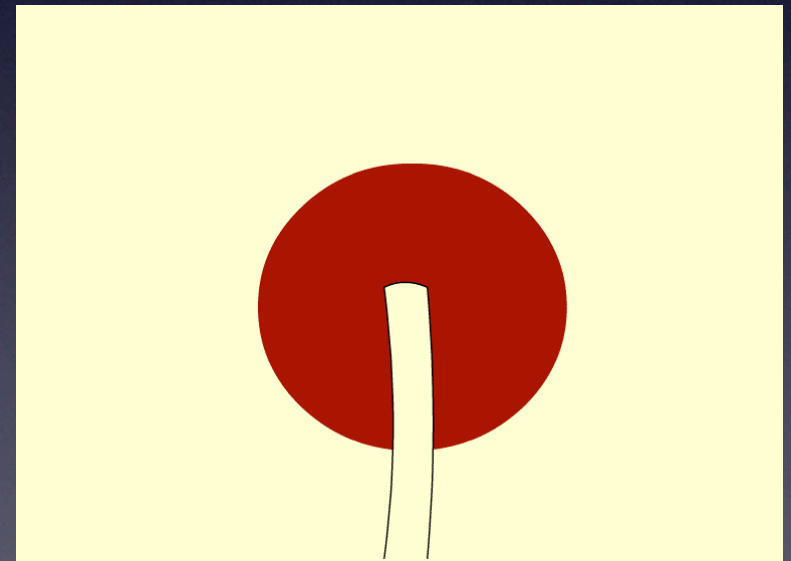
Image and biopsy with same needle



Bronchoscopic Biopsy



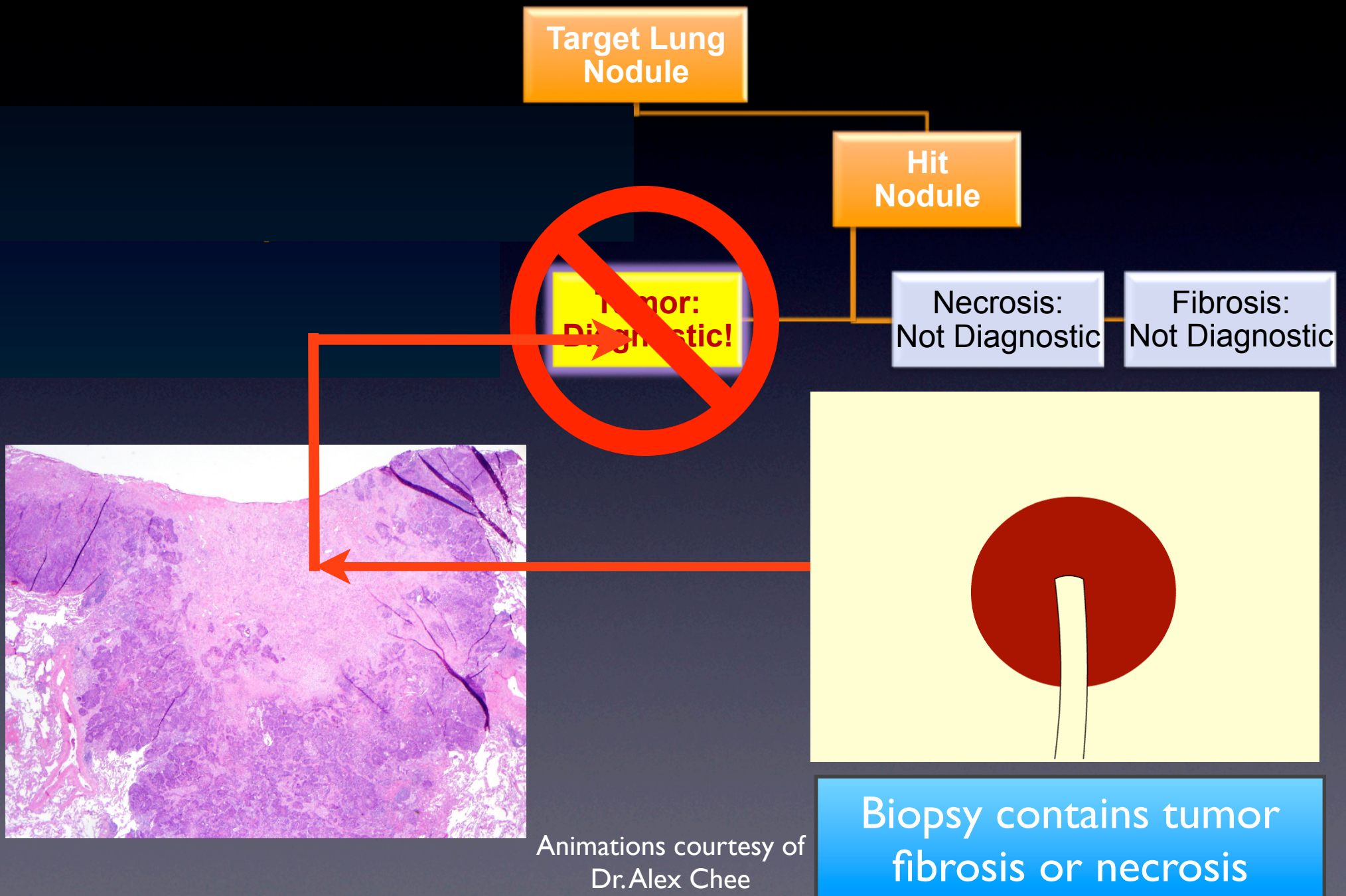
Biopsy contains bronchial wall or lung parenchyma



Biopsy contains tumor fibrosis or necrosis

Animations courtesy of Dr. Alex Chee

Transbronchial Needle Aspiration



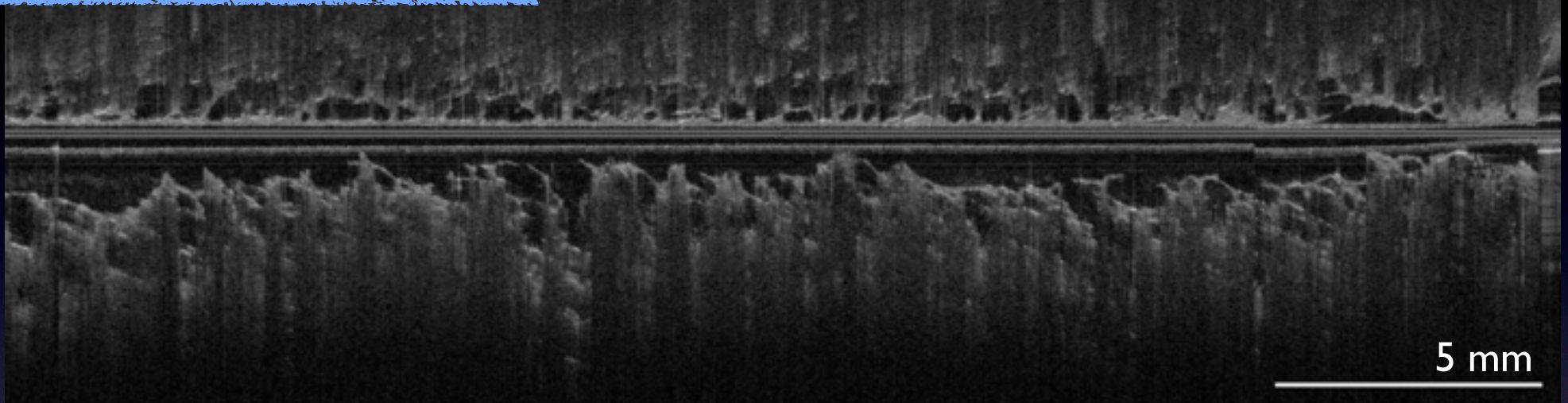
OCT Criteria for Nodule and Lung Parenchyma

- Develop OCT criteria for peripheral nodule and lung parenchyma in ex vivo lung resection specimens
- Validate OCT criteria in a blinded assessment with 6 independent readers
 - Two pathologists, pulmonologists, and OCT experts
 - 15 minute training on criteria
 - Validation Set: 109 ex vivo samples
 - Include a variety of pathology for nodules and parenchyma

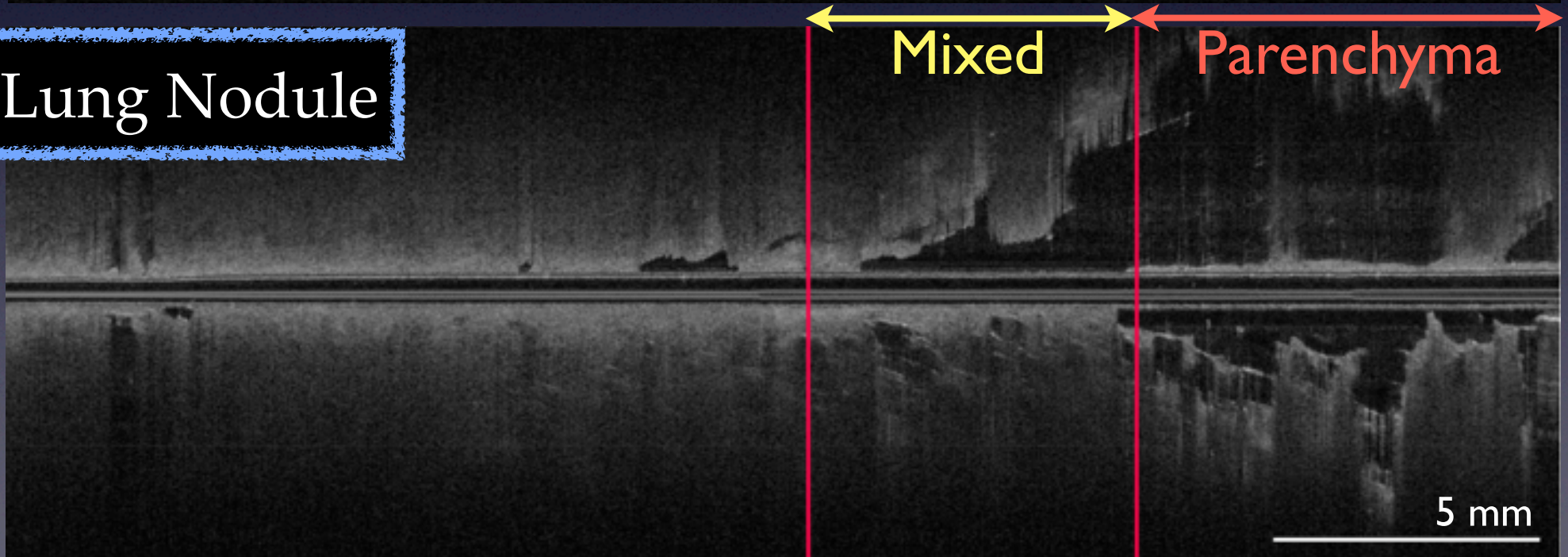
Assess: Nodule or Parenchyma

Needle-based OCT

Lung Parenchyma



Lung Nodule



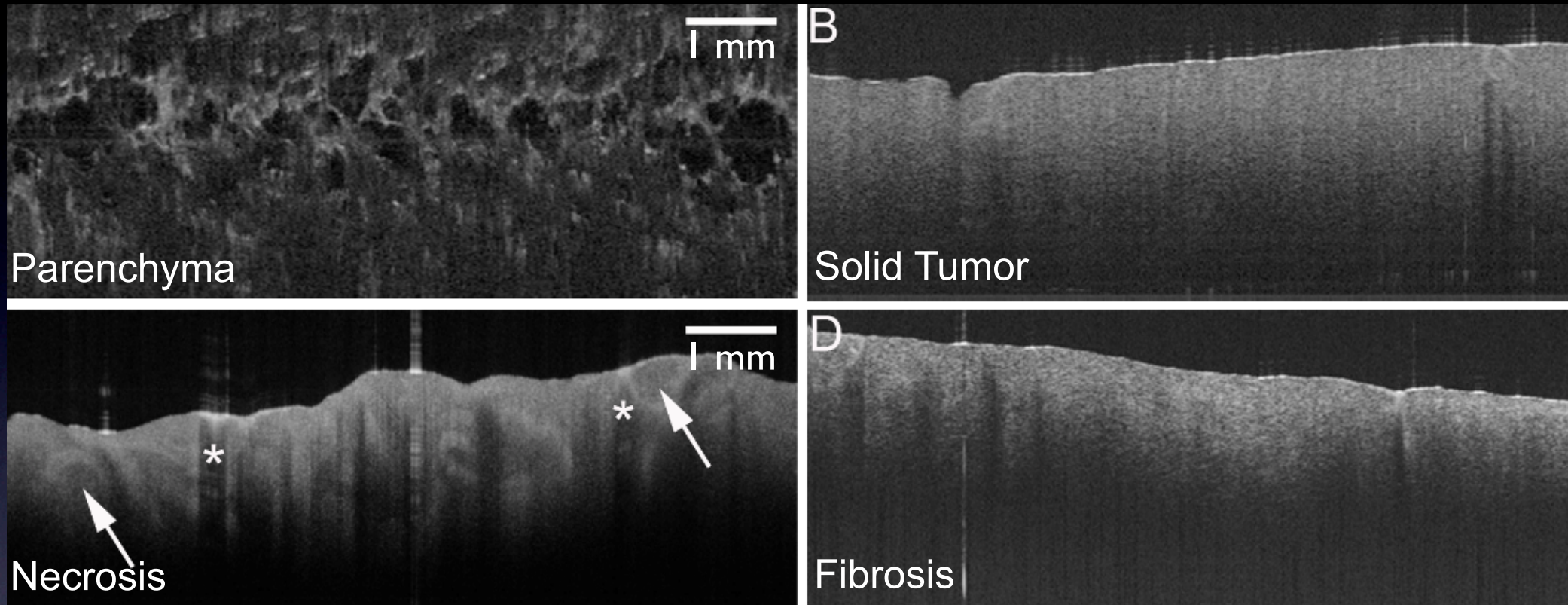
How did everyone do?

Sensitivity and Specificity

	OFDI Experts	Pathologists	Pulmonologists
Sensitivity	99.1 ± 1.3	93.5 ± 6.6	93.5 ± 6.6
Specificity	99.1 ± 1.3	98.2 ± 2.6	97.3 ± 3.9
Accuracy	99.1 ± 1.3	95.9 ± 1.9	95.4 ± 1.3
	All OFDI Readers		
Sensitivity	95.4 ± 5.1		
Specificity	98.2 ± 2.3		
Accuracy	96.8 ± 2.1		

*High sensitivity and specificity (> 95%) for all readers
OCT can aid in determining if biopsy needle is in the nodule or
adjacent parenchyma*

Tumor Versus Non-diagnostic Contaminants

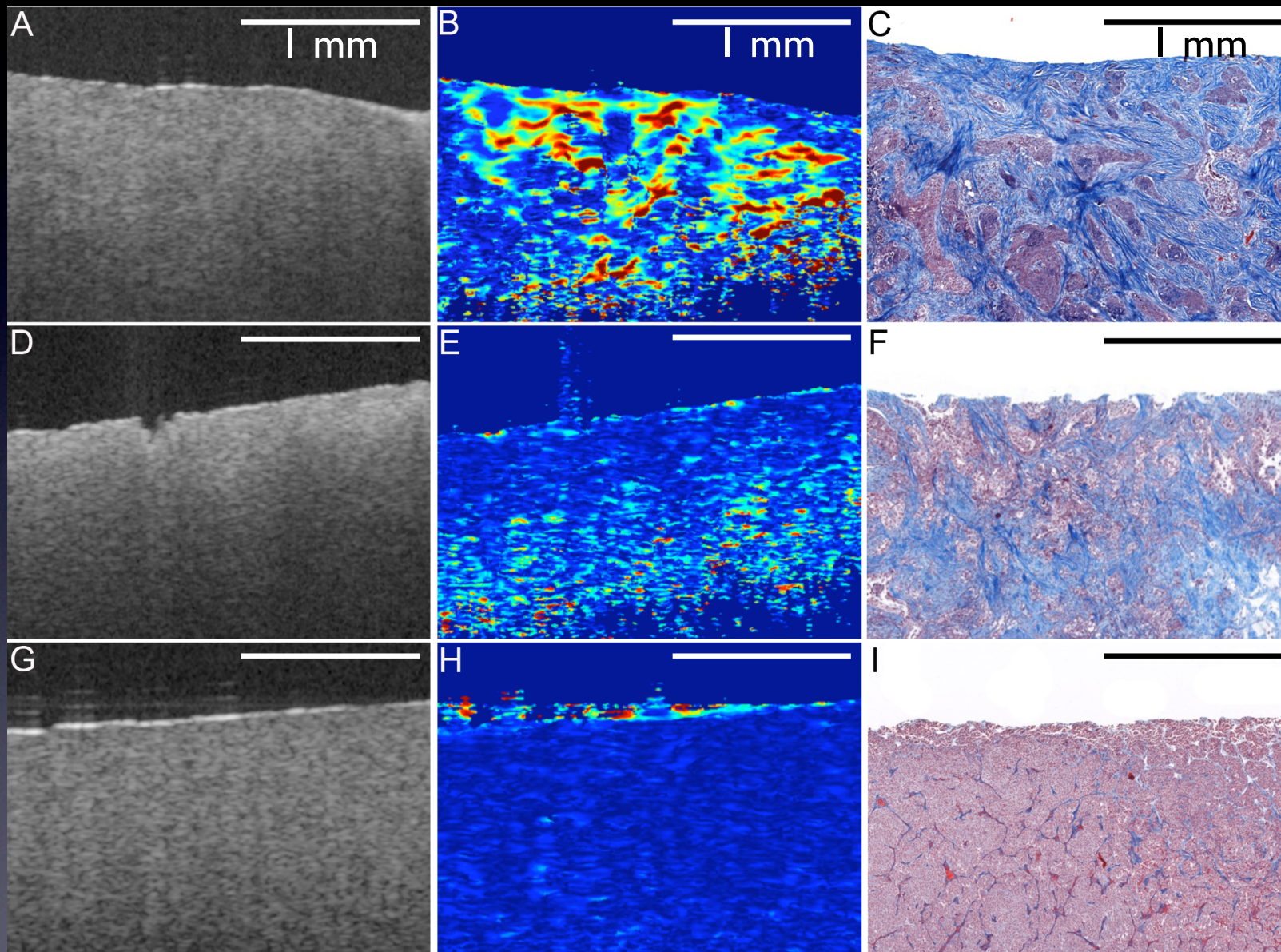


Structural OCT can differentiate tumor from:

- Airway
- Parenchyma
- Necrosis

Cannot differentiate solid tumor from fibrosis

Polarization Sensitive OCT visualizes fibrosis

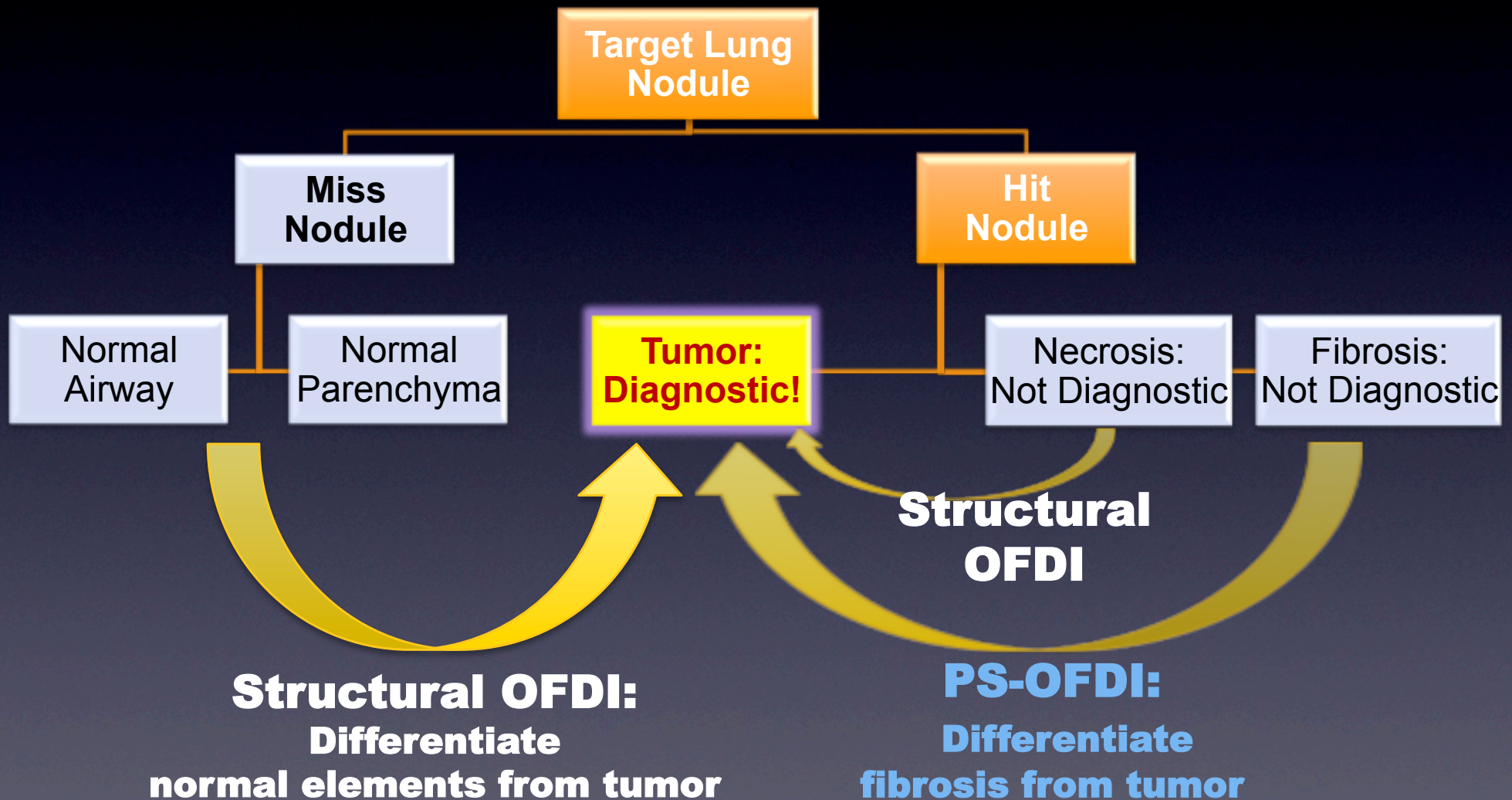


SCC with dense
established
fibrosis

Adenocarcinoma
with early
fibrosis

Carcinoid tumor
with no fibrosis

OCT Guidance in Bronchial Biopsy: The Complete Picture



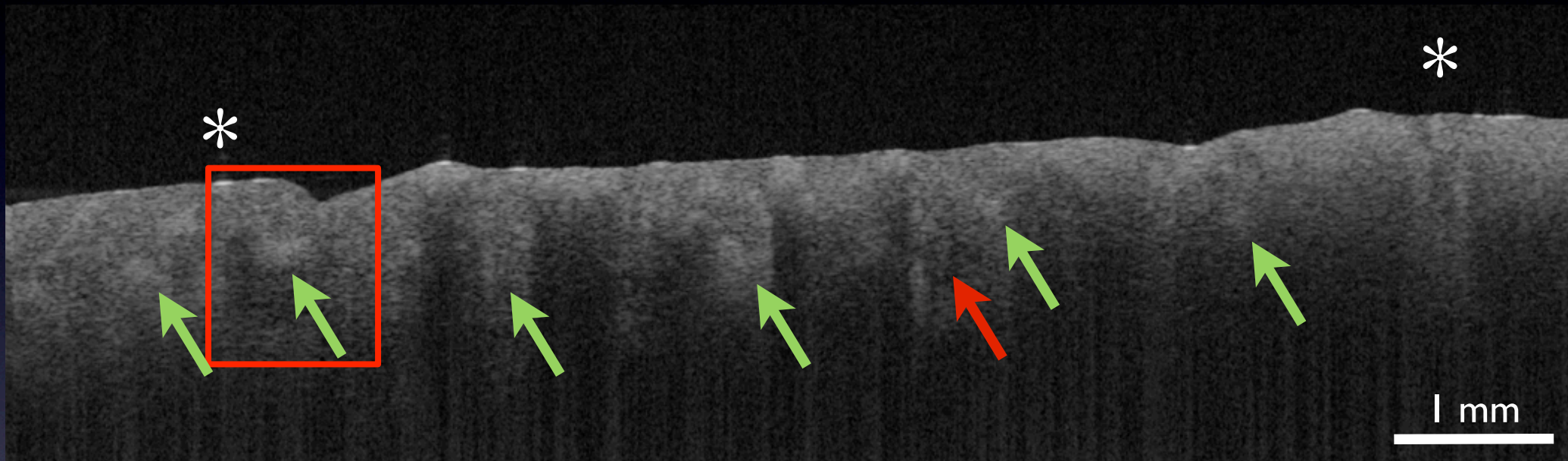
Can OCT aid in diagnosing lung CA?

Potential to replace biopsy?

In this study:

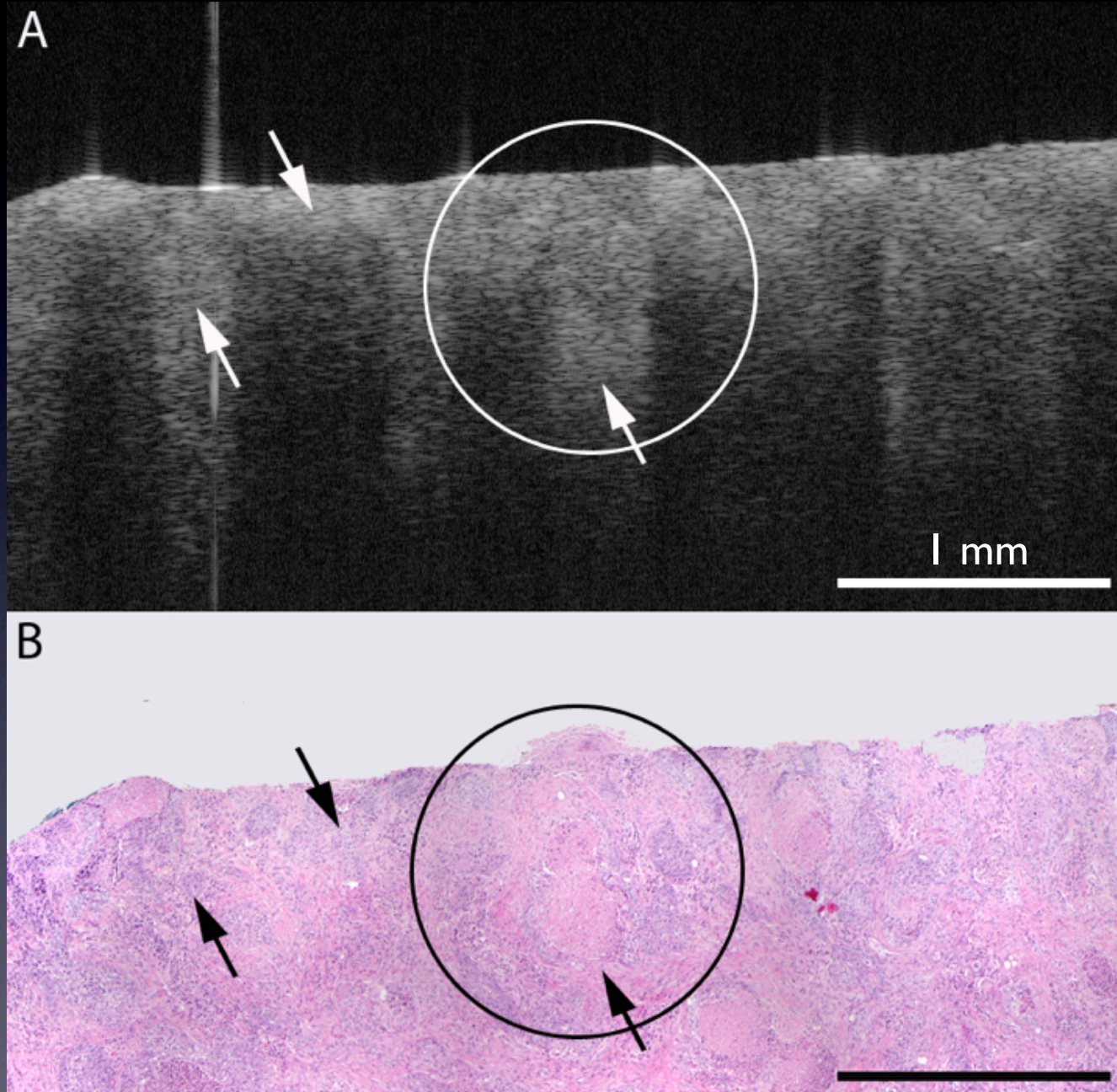
- Develop/validate OCT criteria for common lung carcinomas
- Three blinded readers are trained on OCT criteria and assess 78 tumor samples from ex vivo resection specimens
 - 36 AdenoCA, 23 SCC, 19 poorly differentiated carcinoma

Squamous Cell Carcinoma



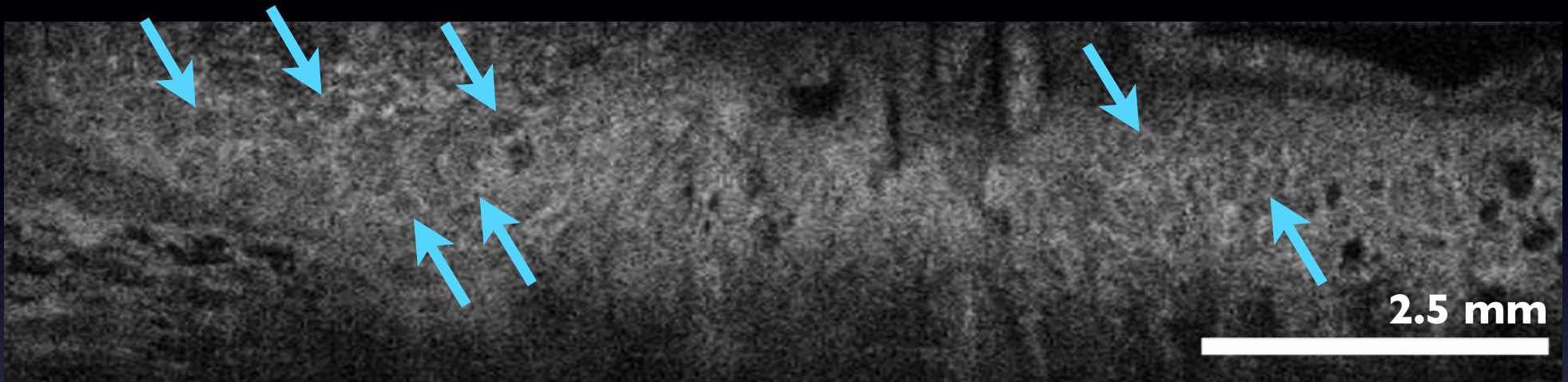
- A. Signal intense (bright) nests, round/irregularly shaped (Green Arrows)
- B. May have variably sized, irregularly-shaped signal poor areas of necrosis
Either admixed with nests (Red Box) or in center of nests (Red Arrow)

Squamous Cell Carcinoma



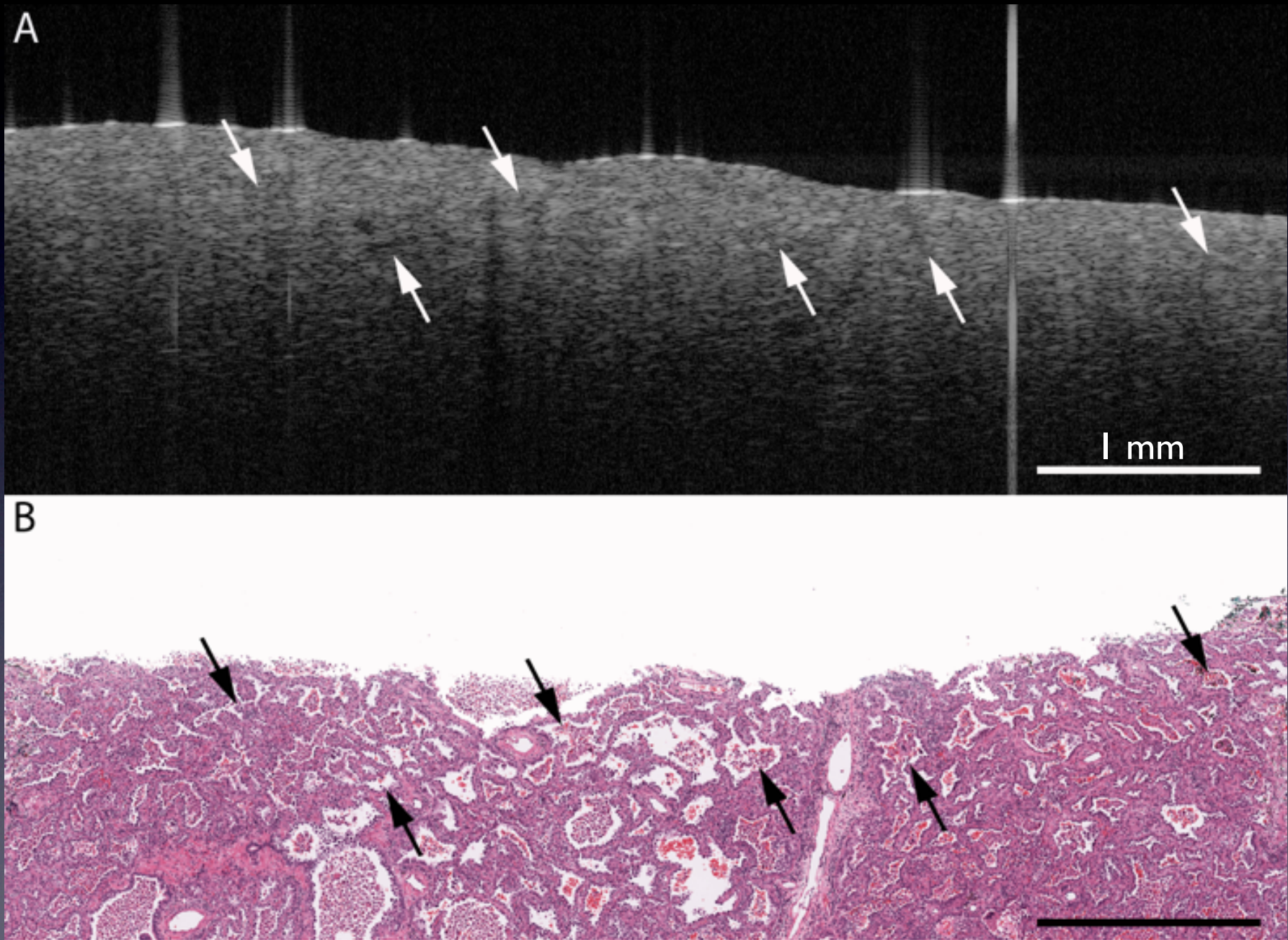
Hariri LP et al. Annals ATS. 2015

Adenocarcinoma



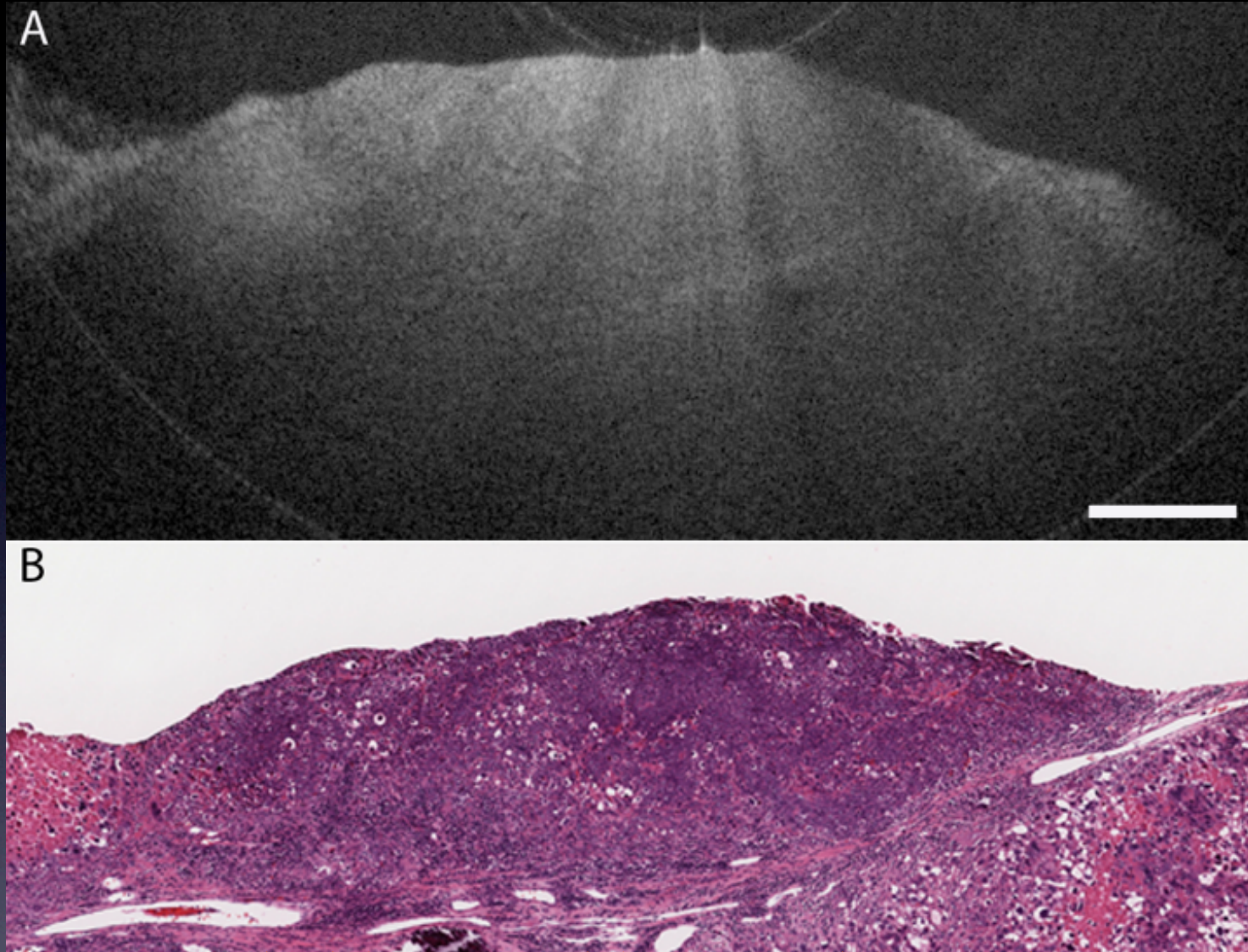
- A. Round or angulated signal poor structures (Blue Arrows)
Typically small, but may vary in size
- B. Lack of signal intense (bright) nests

Adenocarcinoma



Hariri LP et al. Annals ATS. 2015

Poorly Differentiated Carcinoma



- A. Lack of round/angulated signal poor structures
- B. Lack of signal intense (bright) nests

Results: OCT in lung CA diagnostics

	AdenoCA	SCC	PDC
Sensitivity	80.3% (66-92%)	83.3% (70-100%)	85.7% (81-95%)
Specificity	88.6% (81-98%)	87% (75-97%)	97.6% (93-100%)
Accuracy	82.6% (74-95%)		

Conclusions: OCT in lung CA diagnostics

Overall average accuracy was 82% with > 80% sensitivity and specificity
Wide range suggests potential for improvement with further training
OCT Expert achieved >95% accuracy

Take Home Message

OCT has potential to complement, but not replace, tissue biopsy

Guide intramass tissue sampling towards areas of diagnostic material

Specificity for PDC high so readers identified when features were present

Identify tumor regions with better differentiation during biopsy

Need to validate findings in clinical in vivo study

“Will IVM replace traditional pathology?”

No

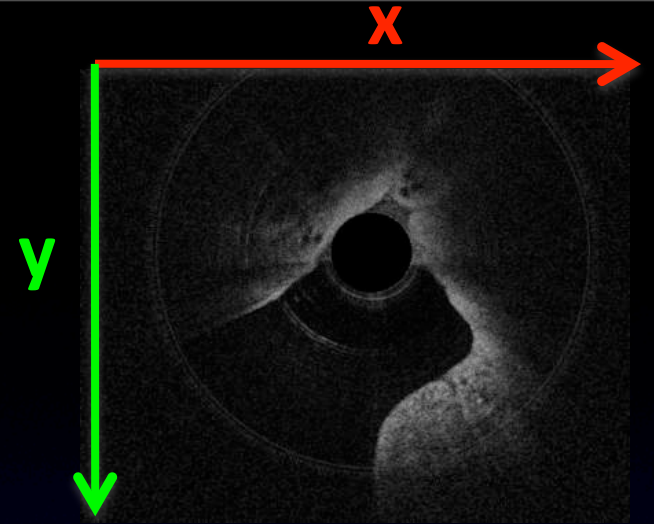
- Sensitivity/specificity not high enough
- Resolution not high enough
- Differential diagnosis in many scenarios is vast
- You are there, take a biopsy!
- Molecular testing requires physical tissue

Future Directions in Lung Cancer

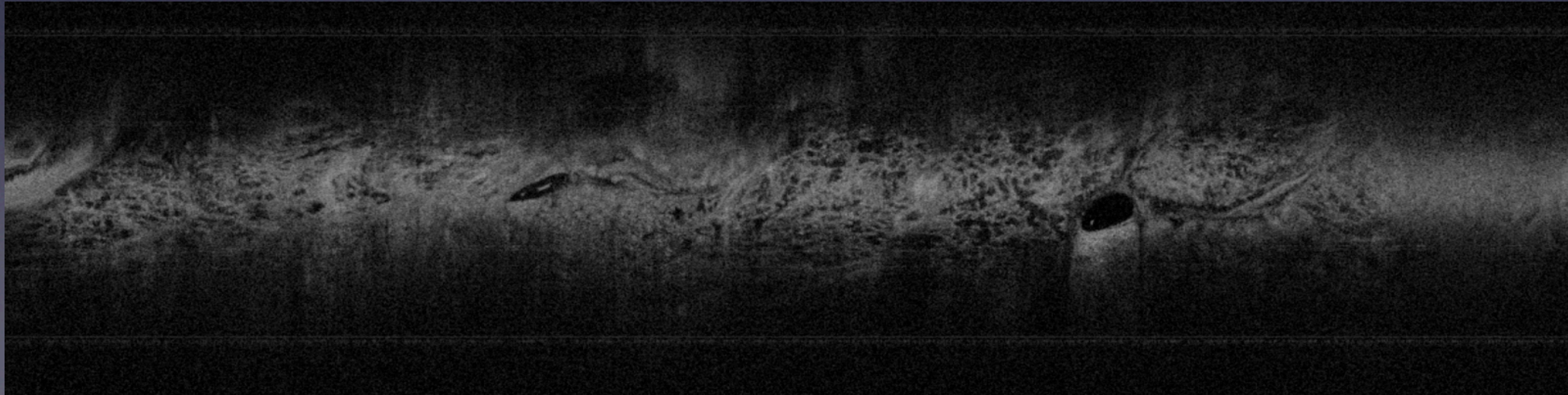
- In vivo study to assess diagnostic yields of transbronchial biopsy with and without OCT guidance
- Assess diagnostic capability of OCT+biopsy vs biopsy alone
- Can optical imaging provide “virtual tissue” with additional diagnostic information when added to traditional biopsy?

Large Volume Virtual Datasets To Complement Small Biopsy

Adenocarcinoma

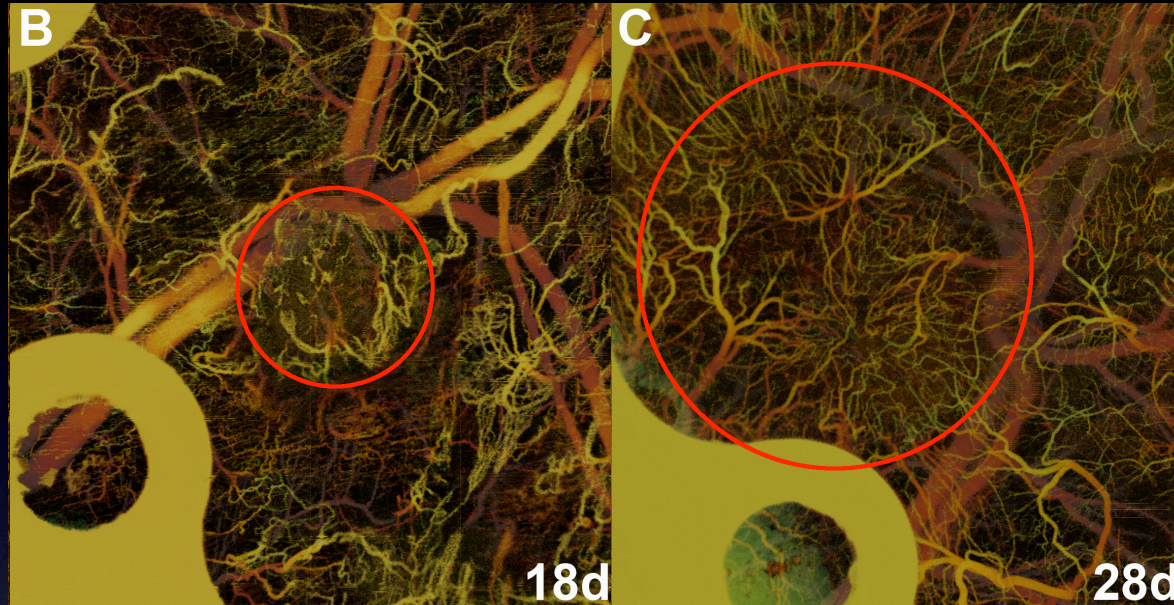


← Z = 6.1 cm →

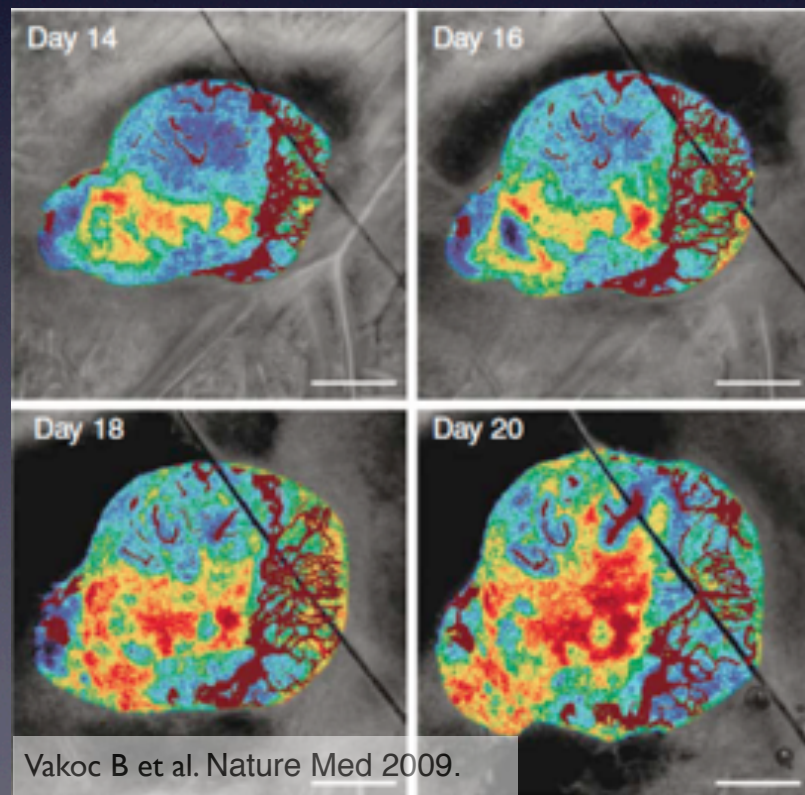


High Resolution Imaging in Pulmonary Pathology: Snapshots of New Upcoming Things

Higher Precision Tumor Measurements Over Therapy

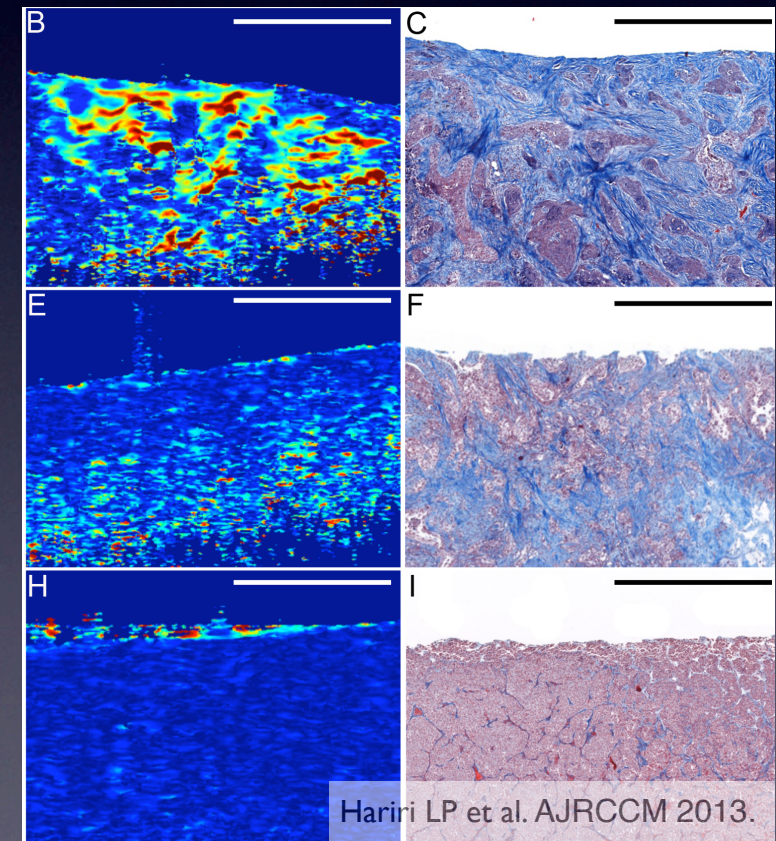


OCT visualizes tumor angiogenesis over time



Vakoc B et al. Nature Med 2009.

Optical scattering properties delineate necrotic (red-yellow) and viable (blue-green) tumor regions

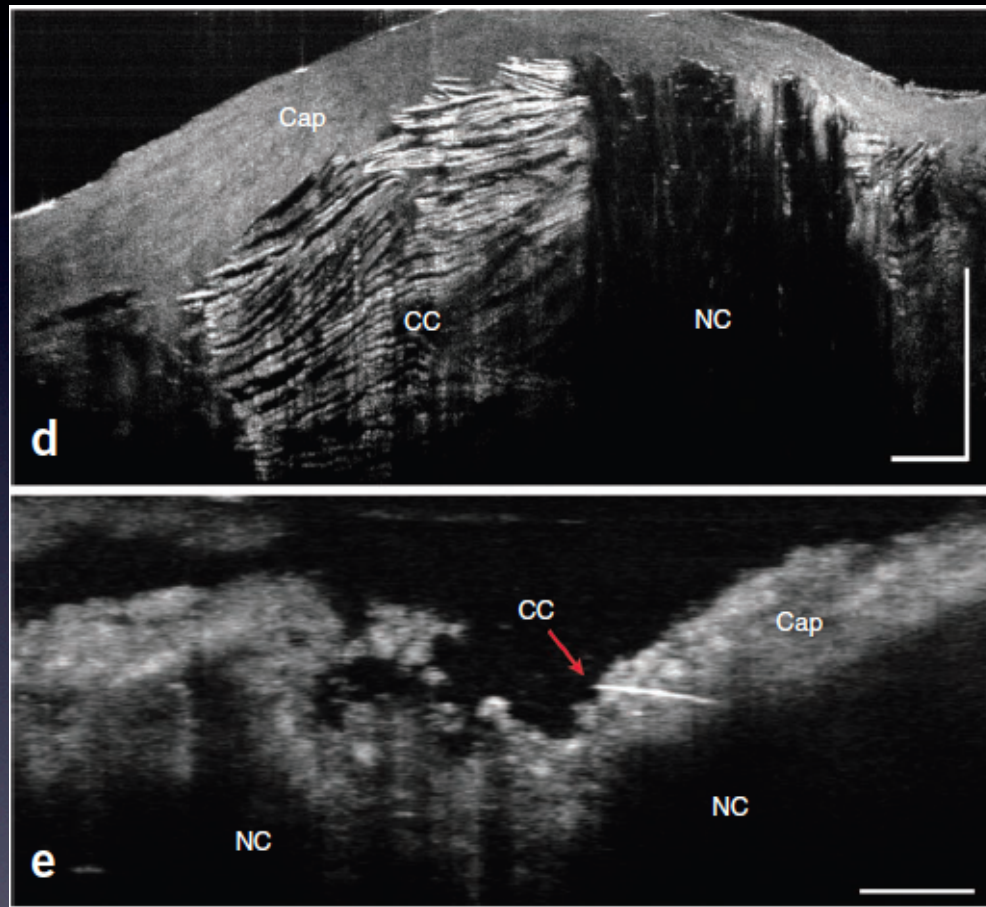


Hariri LP et al. AJRCCM 2013.

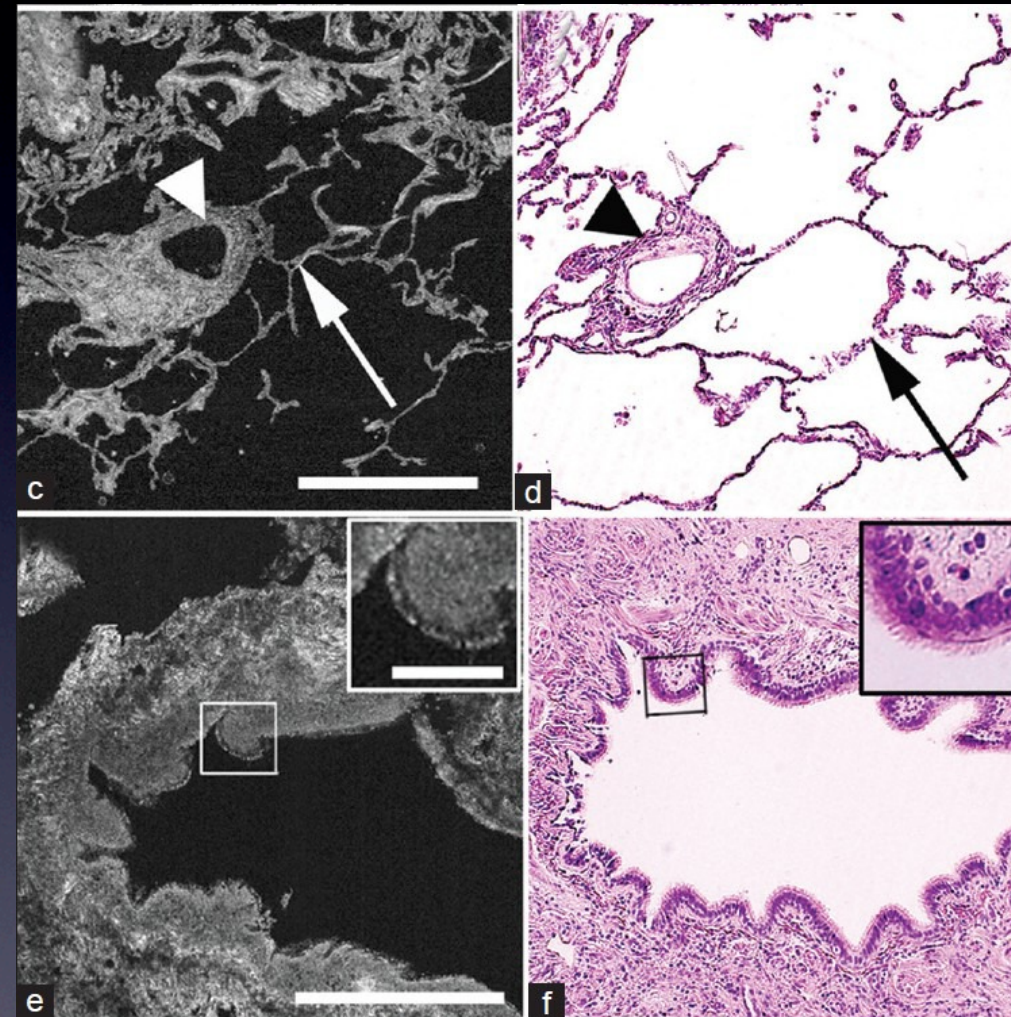
PS-OCT identifies regions of fibrotic stroma in tumor

Moving towards even higher resolution in OCT

So far just ex vivo....



Atherosclerotic Plaque



Normal Lung

In vivo microscopy needs a defined expert:

Pathologists

- In radiology, many clinicians can assess CT scans but that does not make them radiologists
- 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

IVM needs a defined expert: Pathologists

**Pathologist inherently have the skills needed
to become IVM experts,
but we need to gain experience to accomplish this**

- **Collaborate in IVM studies**
- **Identify clinical scenarios where IVM can make impacts, especially in pathology**
- **Participate in ex vivo and in vivo validation studies**

Acknowledgements

Suter Optical Imaging Laboratory

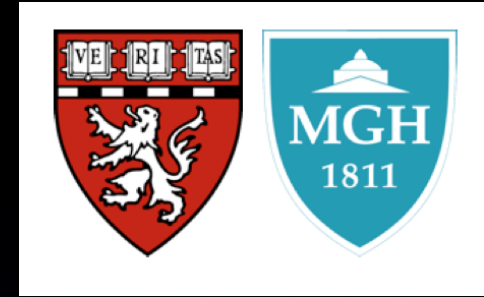
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