THESIS DEFENSE

DEVICE AND IMAGE ANALYSIS ADVANCEMENTS TOWARDS PHOTOACOUSTIC AND ULTRASOUND TOMOGRAPHY-GUIDED PROSTATE BIOPSY

Brittani L. Bungart

February 11, 2019

Slides can be found online at http://phd-defense.brittanibungart.com.

Outline

INTRODUCTION

- Prostate cancer significance and background
- Identification of clinical need and engineering gaps

EX VIVO PROSTATE IMAGING STUDY FOR IDENTIFYING BIOPSY TARGETS

- Development of *ex vivo* PAT/US imaging system
- Image analysis to identify prostate biopsy targets using endogenous contrast PAT and US imaging

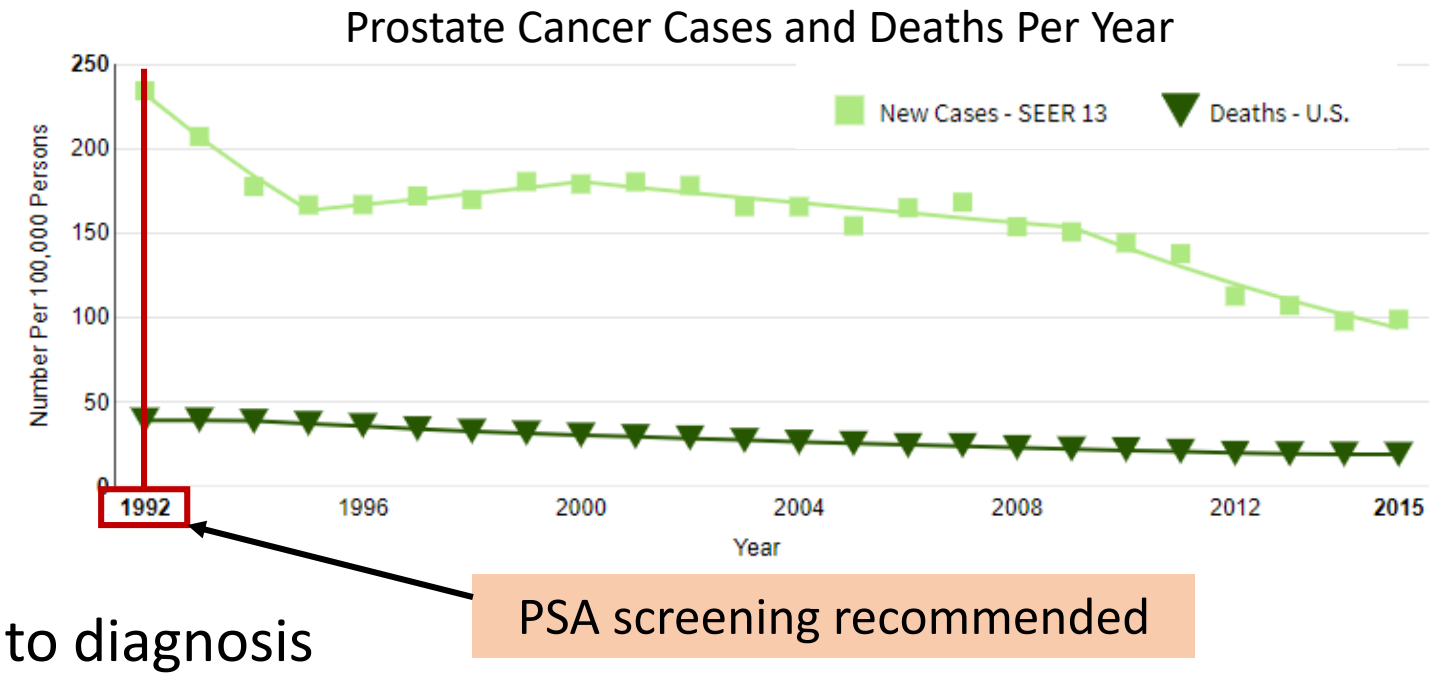
IN VIVO PAT/US IMAGING DEVICE DEVELOPMENT

- Background on illumination delivery
- Development of effective transurethral light delivery device

CONCLUSIONS AND FUTURE DIRECTIONS

Significance: Prostate Cancer

- Most common visceral cancer in men
- ~1 in 6 men develop prostate cancer in their lifetime
- 5 year survival rate = 98.2%
  Drops to 29% if metastasized prior to diagnosis
- ~1 in 32 men die from prostate cancer



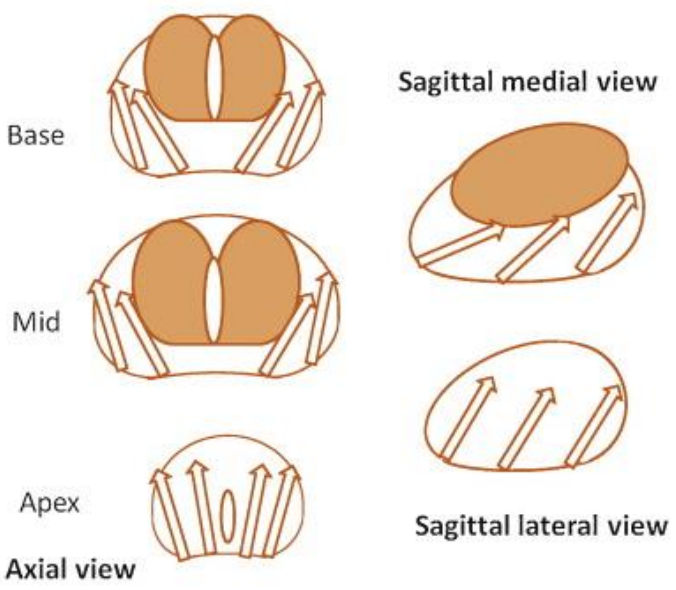
Overdiagnosis and overtreatment of prostate cancer is of major concern within the medical community.

SEER Cancer Statistics Review, 1975-2015 (2018).

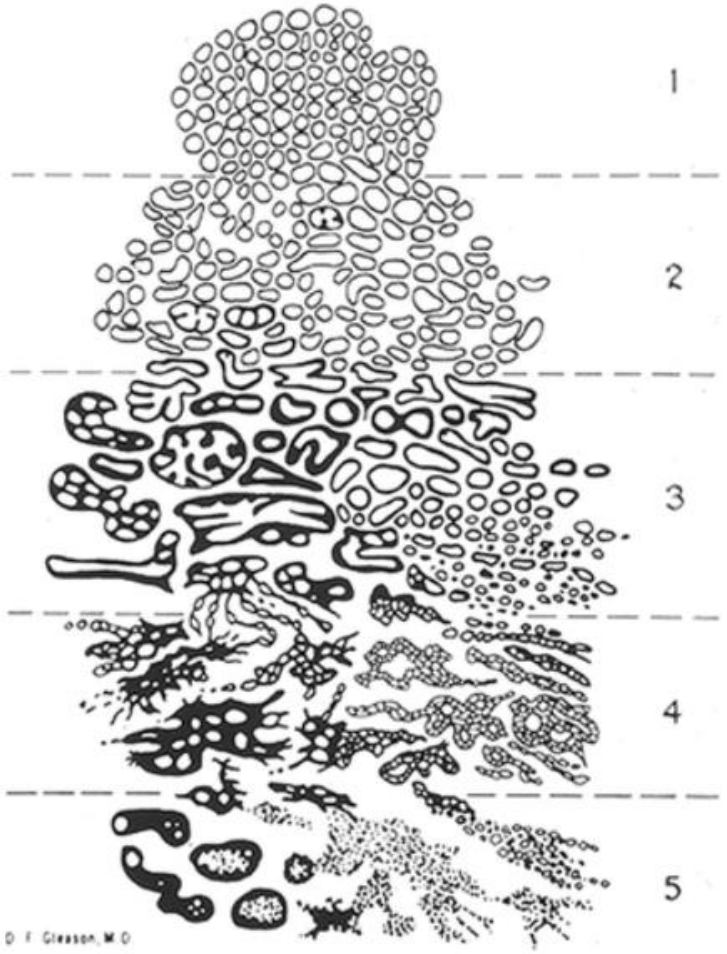
What Is the Most Important Component for Diagnosis?

Diagnostic confirmation:

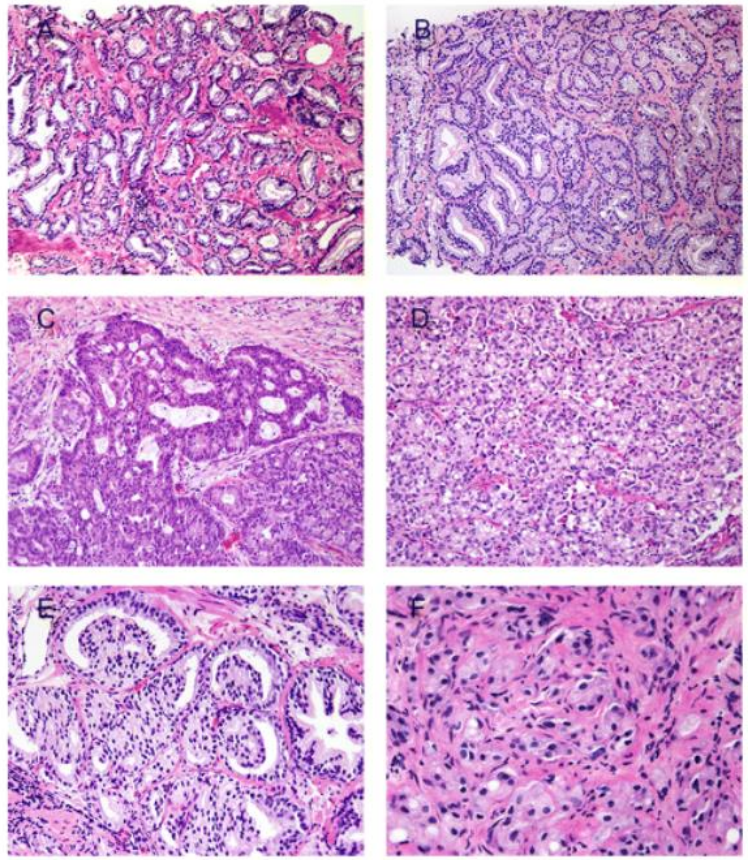
Tissue biopsy[1] with pathologic analysis.



Schematic of cores (arrows) taken during biopsy using prior clinical standard[2].



Gleason grading system[3].



Example Gleason Grades[3]. (**A**) 3+3 =6; (**B**) 3+4 = 7a; (**C**) 4+3 = 7b; (**D-F**) 4+4 = 8.

1. “Detection of Prostate Cancer: American Urological Association,” (accessed 11 February 2016).; 2. Diagn. Pathol. **11**(1), 25, Diagnostic Pathology (2016).; 3. Eur. Urol. **63**(2), 214–230 (2013).

Problem Background

Two Major Reasons for Overdiagnosis/Overtreatment

- Prostate Specific Antigen (PSA)
  - 12-76% do not have prostate cancer
  - Elevation not specific to prostate cancer (transient and chronic causes)
    - Benign Prostatic Hyperplasia
    - Prostatitis
    - Others

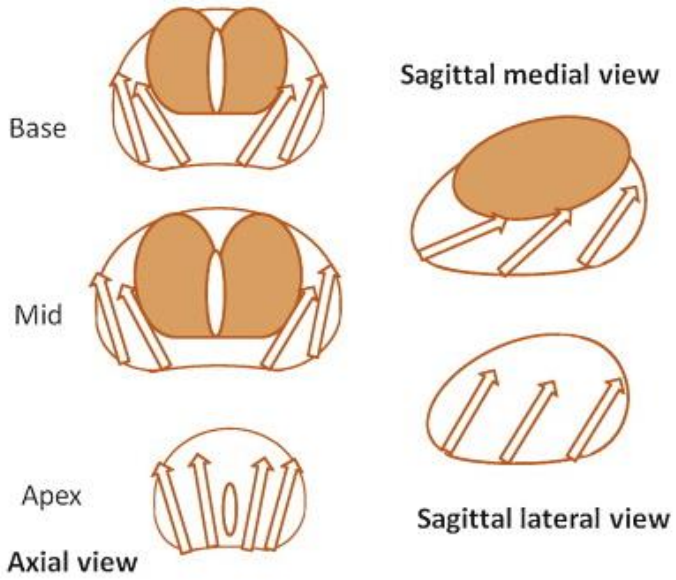
High false positive rate

- Transrectal Ultrasound-guided Core Biopsy
  - 12 random cores taken systematically
  - 12% repeat biopsy following negative result within 1 year
    - 38% within 5 years

High false negative rate

N. Engl. J. Med. 366:981–990, 2012.; *J. Natl. Cancer Inst.* 104:125–132, 2012.; *J. Natl. Cancer Inst.* 99:1395–1400, 2007.

Problem Background



Schematic of cores (arrows) taken during biopsy using prior clinical standard[2].

- Transrectal Ultrasound-guided Core Biopsy
- 12 random cores taken systematically
- 12% repeat biopsy following negative result within 1 year
  - 38% within 5 years

Untargeted sampling of <1 – 3% of prostate

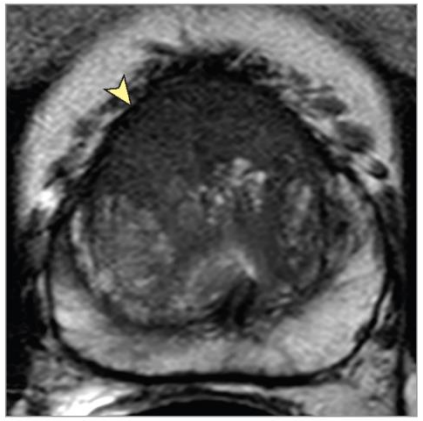
High false negative rate

N. Engl. J. Med. 366:981–990, 2012.; *J. Natl. Cancer Inst.* 104:125–132, 2012.; Welch, H. G., E. S. Fisher, D. J. Gottlieb, and M. J. Barry. *J. Natl. Cancer Inst.* 99:1395–1400, 2007.; Diagn. Pathol. **11**(1), 25, Diagnostic Pathology (2016).

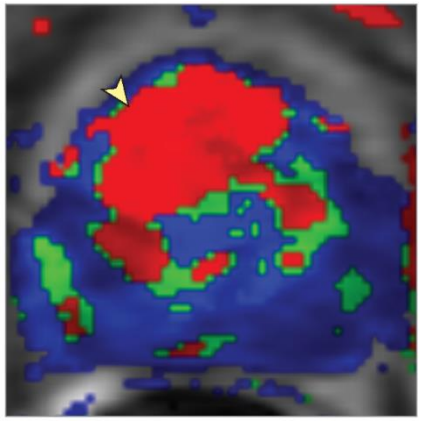
Recent Clinical Update: MRI Fusion Biopsy

Magnetic Resonance Imaging (MRI) machine

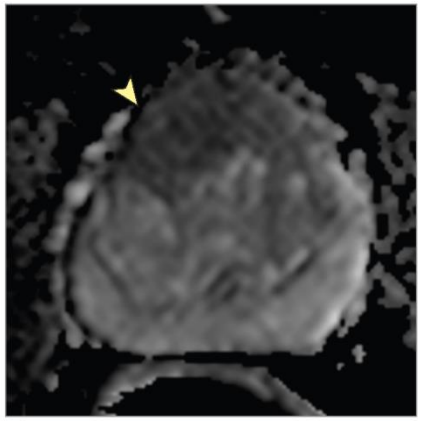
T2-weighted image



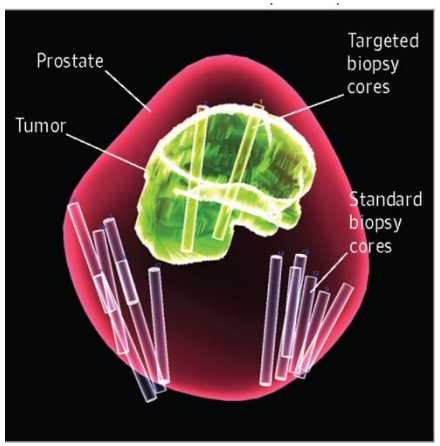
Dynamic C-E Image*



Diffusion Coef. Image



MRI read by Radiologist.
Outline targets



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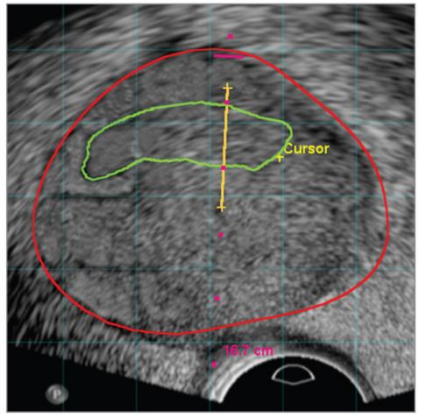
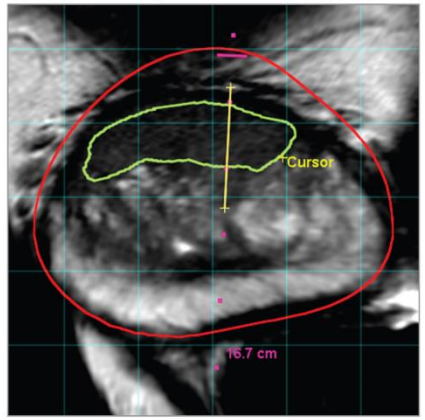


Ultrasound with “fused” MRI outlines.

+



MRI T2-weighted image. Target outlined in green. Red outline marks the prostate boundary.

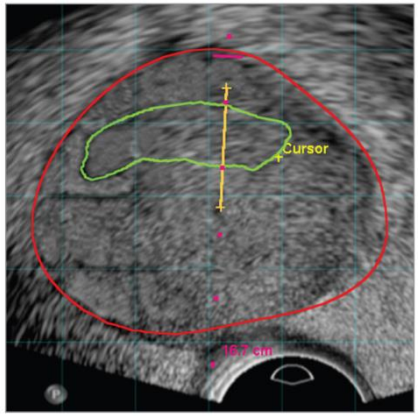
JAMA. 2015;313(4):390-397. doi:10.1001/jama.2014.17942

*Requires Gadolinium-based contrast agent.

Disadvantages of MRI-Fusion Biopsy

Transrectal Ultrasound

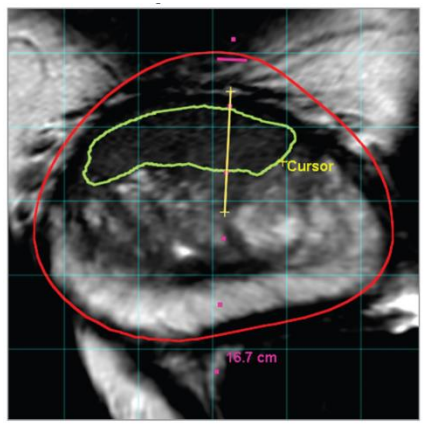
- Real-time imaging
- Patient awake



Ultrasound with "fused" MRI outlines.

MRI

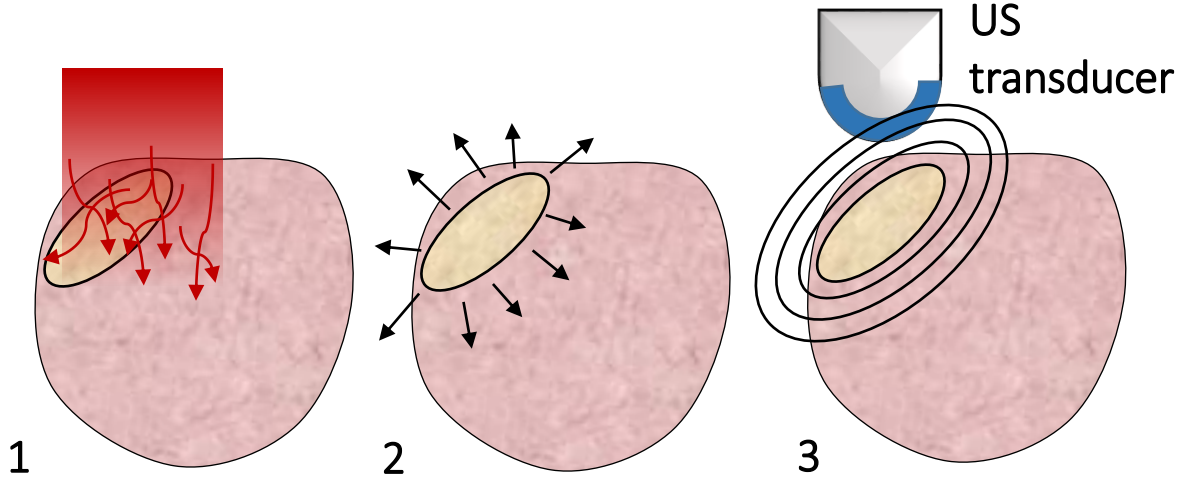
- Static image
- Separate appointment
- Patient in different position



MRI T2-weighted image.

GAP: Real-time targeted prostate cancer biopsy

Photoacoustic Tomography Basic Principle



Factors that Influence Signal

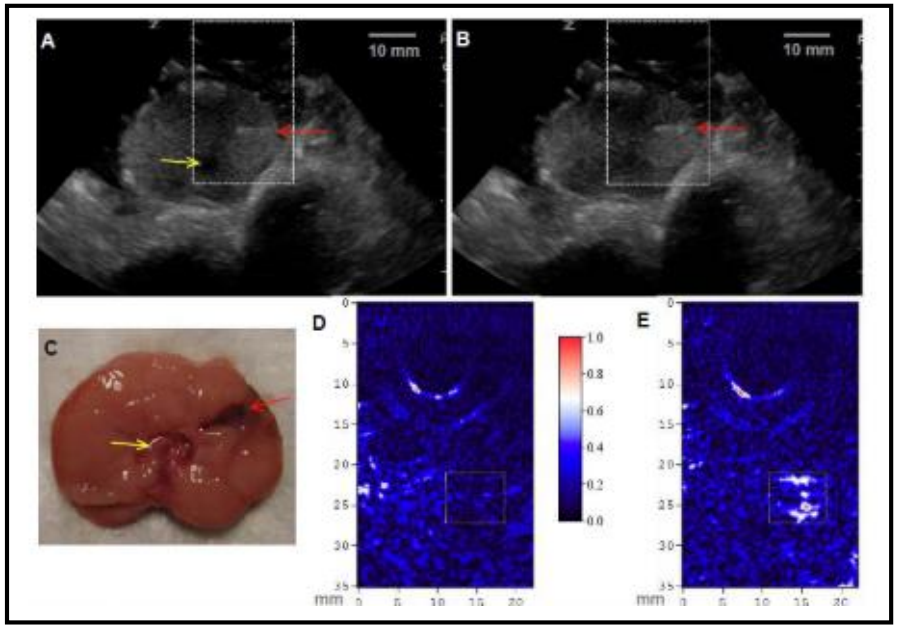
- Local light fluence (F)
- Absorber concentration ([A])
- Absorber coefficient of absorption (μ_a)
- Environment characteristics related to expansion, acoustic speed, and specific heat (Gruneisen parameter; Γ)

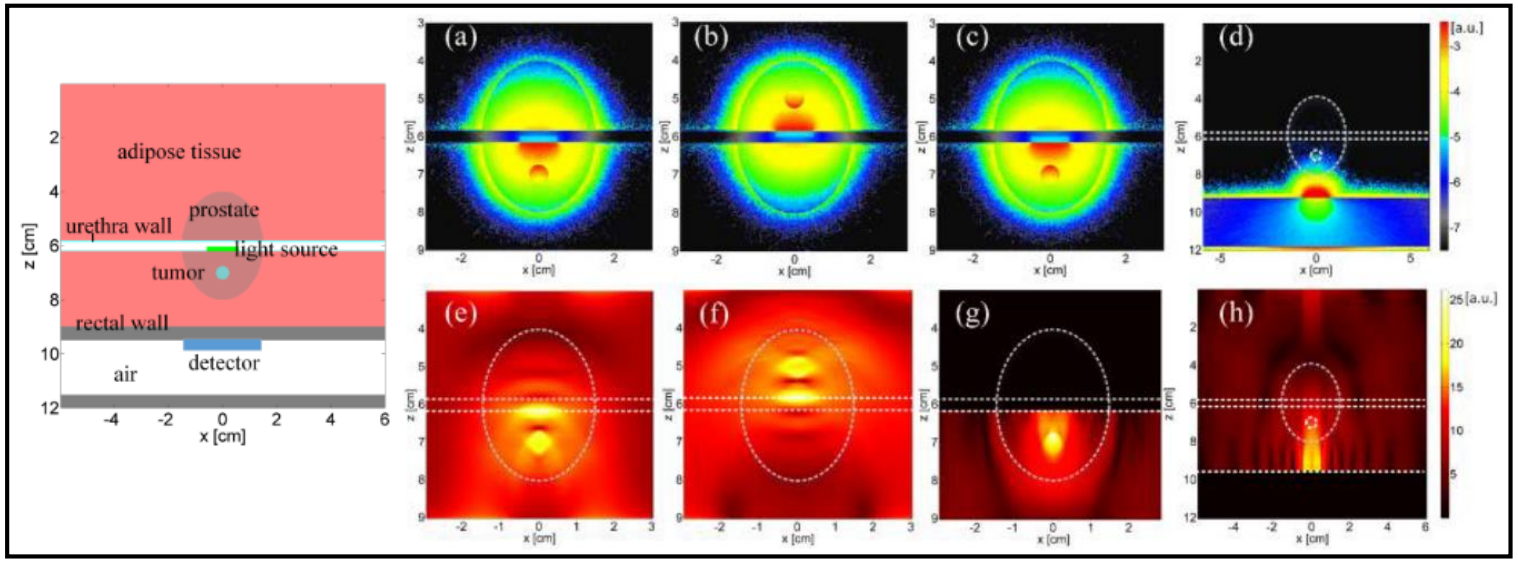
$$\text{PA signal} = \mu_a \Gamma F[A]$$

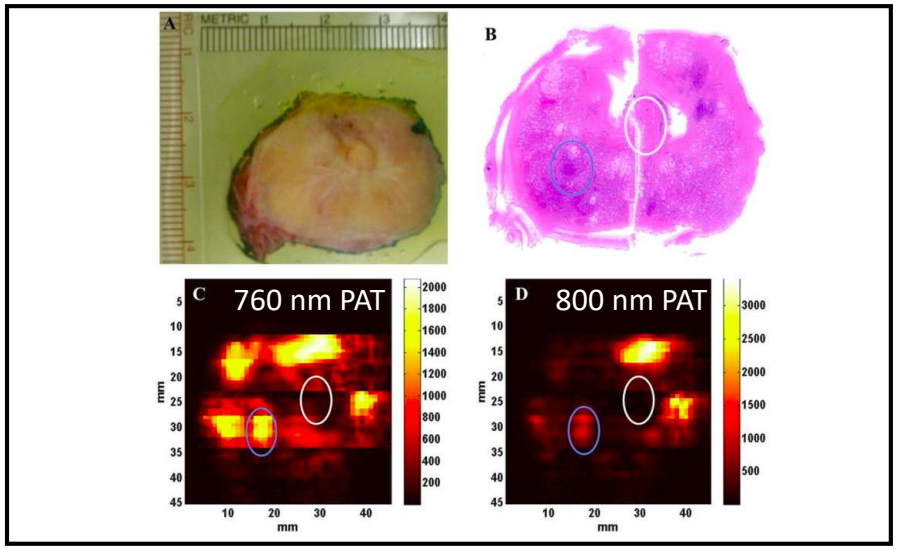
Signal collected by US transducers, which are used for current prostate biopsy.

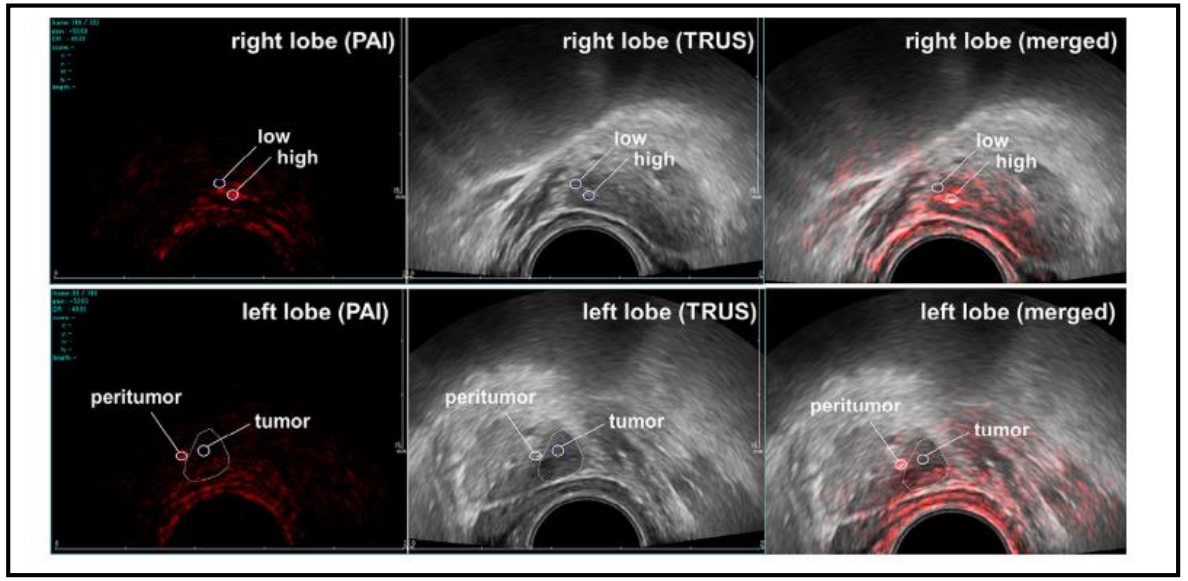
Biomedical Optics: Principles and Imaging. (2007) doi:10.1002/9780470177013.ch12.; Photoacoustics. 4 (2016) 11-21.; Nat. Methods. 13 (2016) 627-638.

Photoacoustic Tomography of Prostate





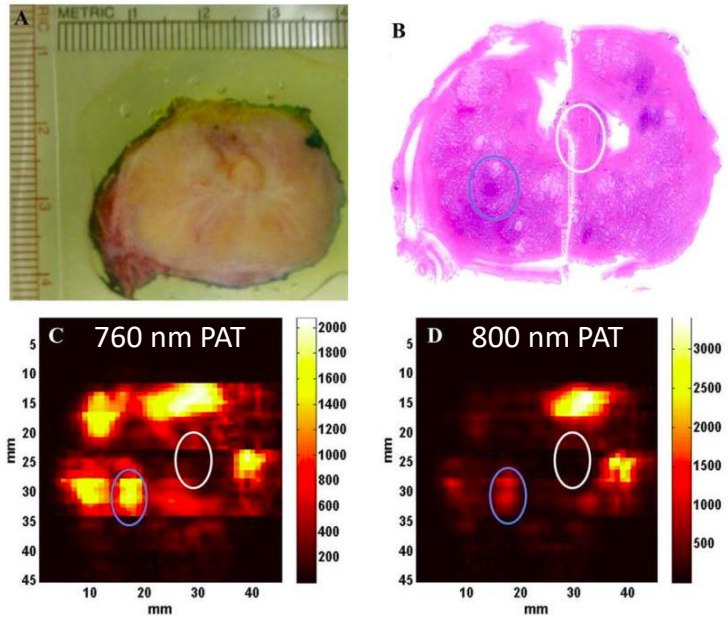




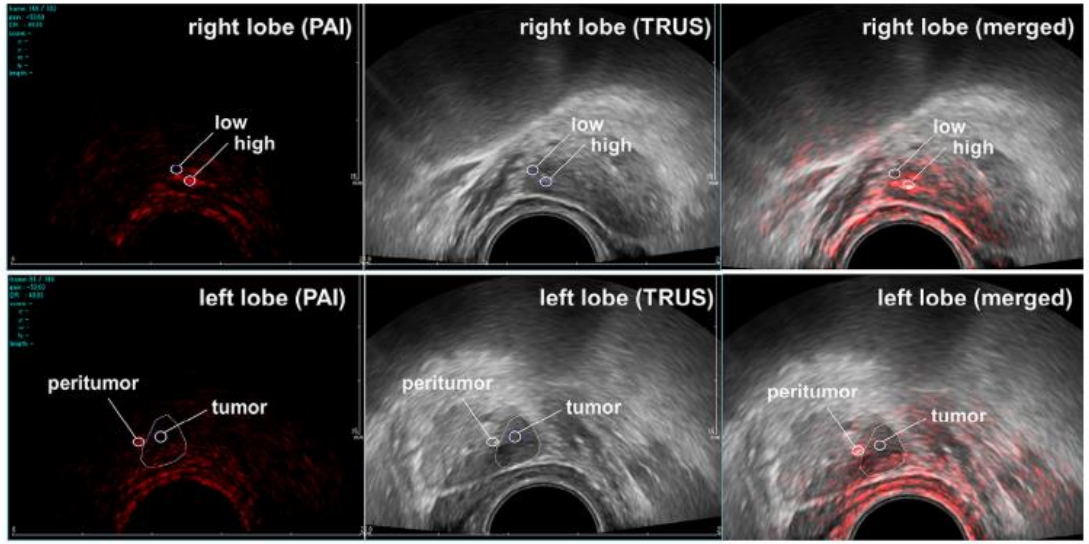
Biomed. Opt. Express 1, 1117–1126 (2010).; J Ultrasound Med. 2016 Oct; 35(10): 2165–2177.; Urology 108, 212–219 (2017).; IEEE Trans. Med. Imaging 35, 1780–1787 (2016).

Remaining Engineering Design Needs

Aim 1: Identify tumors without manual selection in images acquired in a more clinically-relevant manner.



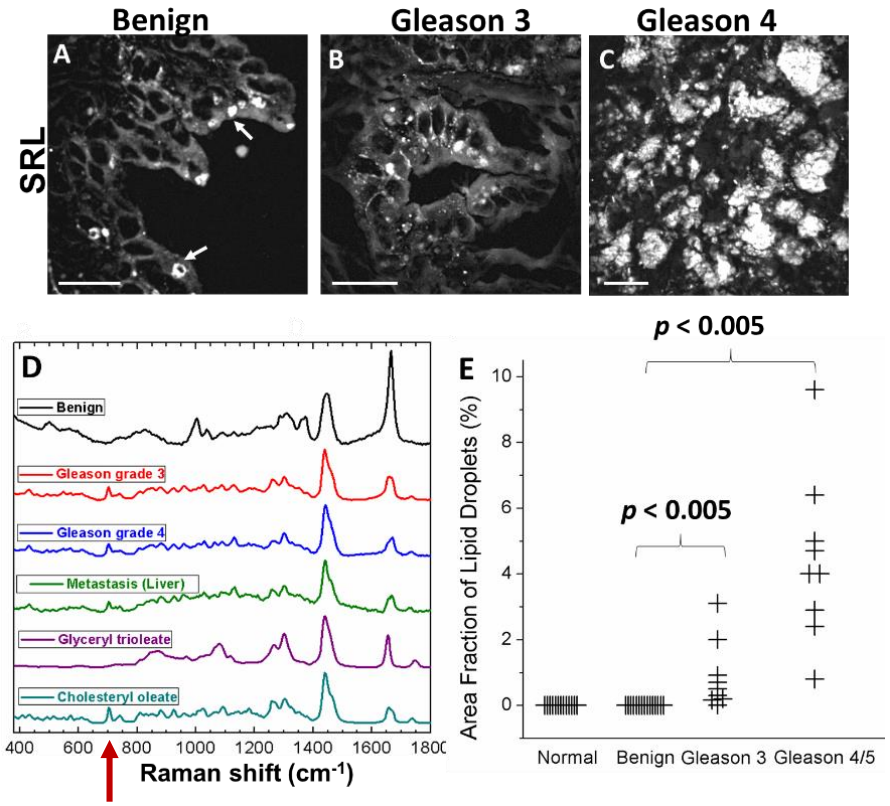
Aim 2: Improve light delivery to enable anterior prostate PAT imaging.



J Ultrasound Med. 2016 Oct; 35(10): 2165–2177.; Urology 108, 212–219 (2017).

Biomarker for Photoacoustic Tomography

Cholesteryl Ester - a potential marker of prostate cancer aggressiveness



Vibrational Photoacoustic Tomography – Ji-Xin Cheng Lab pioneered lipid as contrast

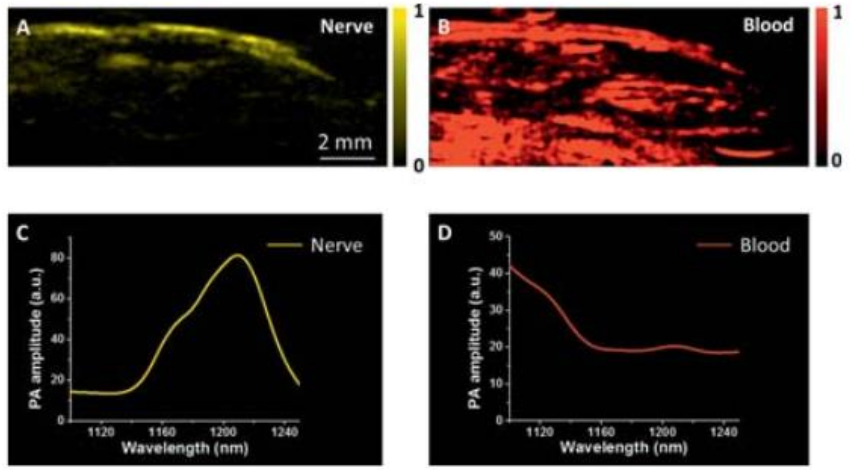
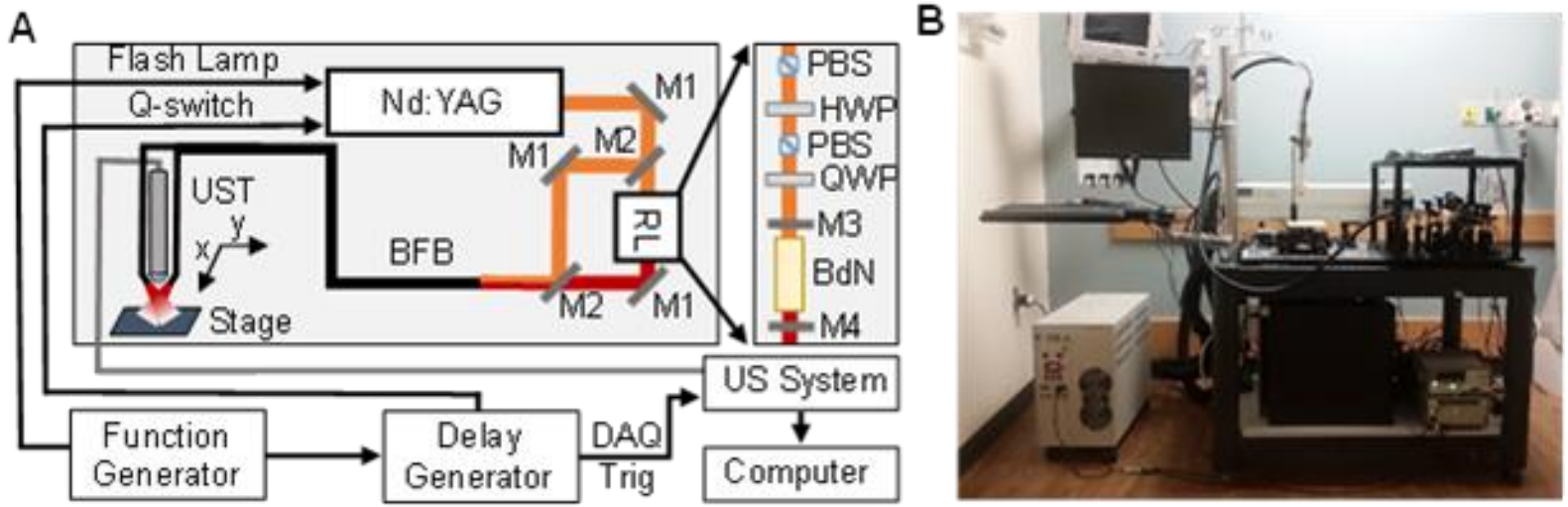


Figure 5 Multivariate curve resolution (MCR) method was used to distinguish femoral nerve from femoral artery. (**A**) MCR map of mouse femoral nerve. (**B**) MCR map of mouse femoral artery. (**C**) PA spectrum of mouse femoral nerve generated by MCR analysis. (**D**) PA spectrum of mouse blood generated by MCR analysis.

Cell Metab. 19, 393–406 (2014).; Journal of Biophotonics, 9, No. 1–2, 124–128 (2016).

Photoacoustic Tomography System at IU Hospital

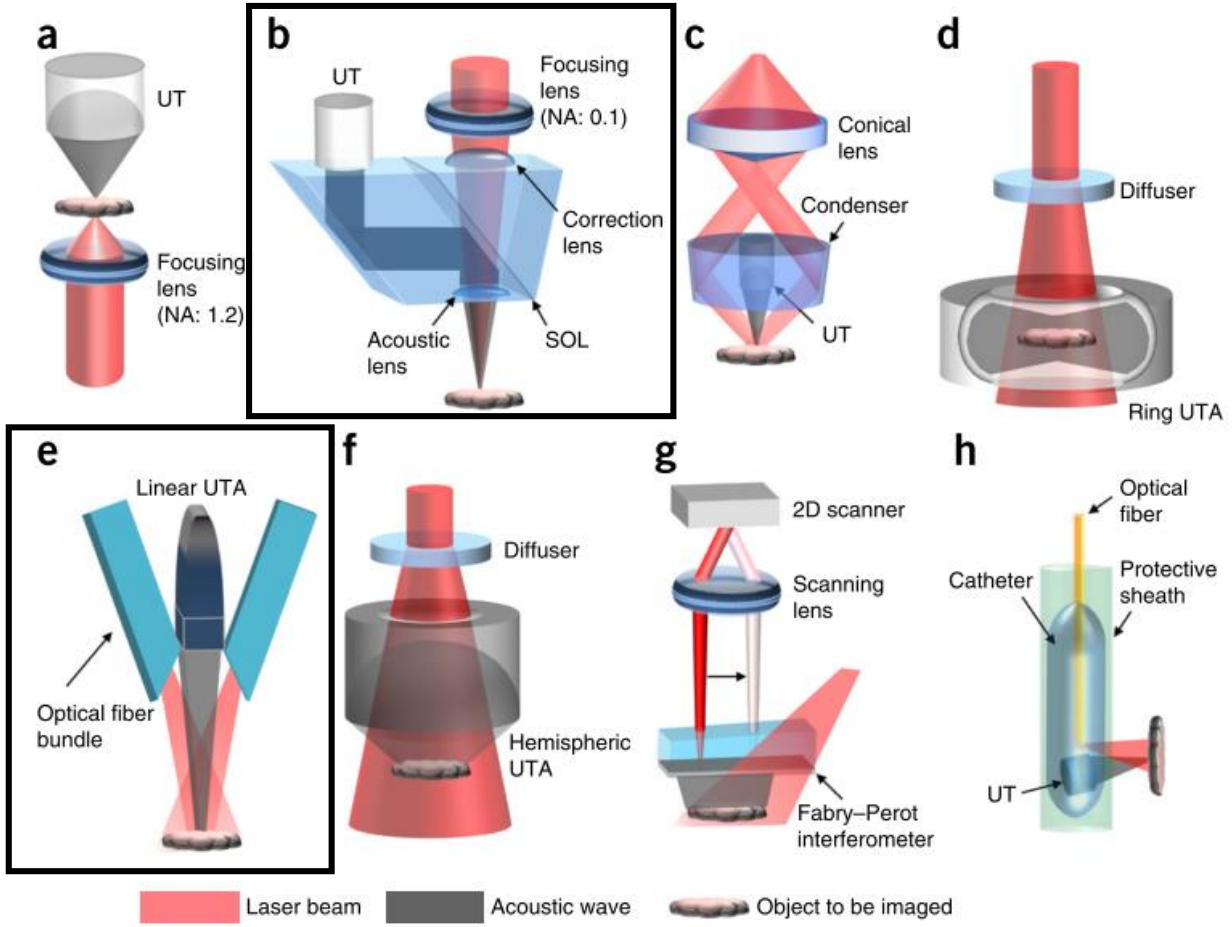


Ultrasound frequency range: 4.6 – 9 MHz

Wavelength outputs: 1064 & 1197 nm

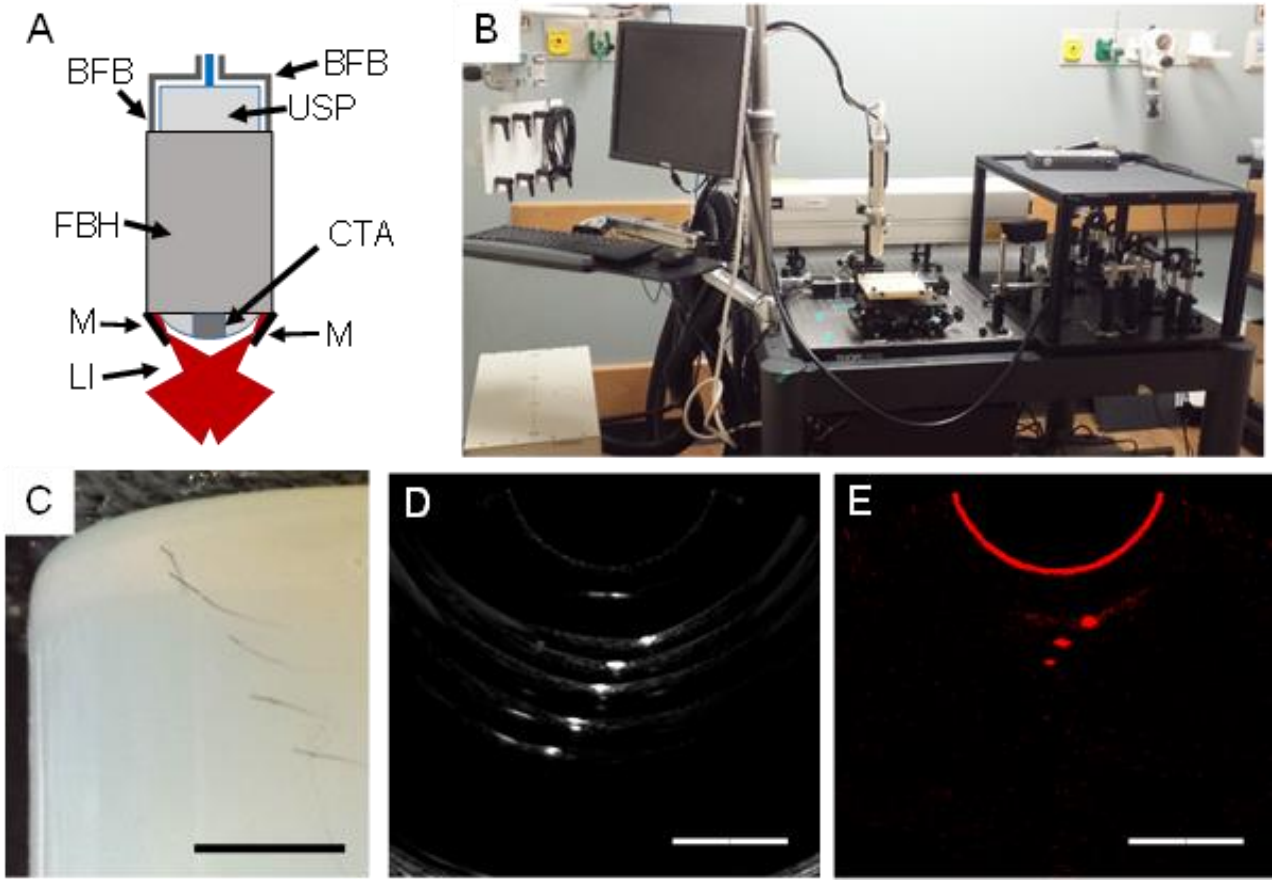
M1: 45 degree reflective mirror; M2: flip-mounted 45 degree reflective mirror; M3: resonator end mirror; M4: output coupler; PBS: polarizing beam splitter; HWP: half wave plate; QWP: quarter wave plate; BdN: barium dinitrite crystal; BFB: bifurcated fiber bundle; UST: ultrasound transducer; DAQ: data acquisition system.

PAT/US Probe for Ex Vivo Prostate Imaging



Nat. Methods 13:627–638, 2016.

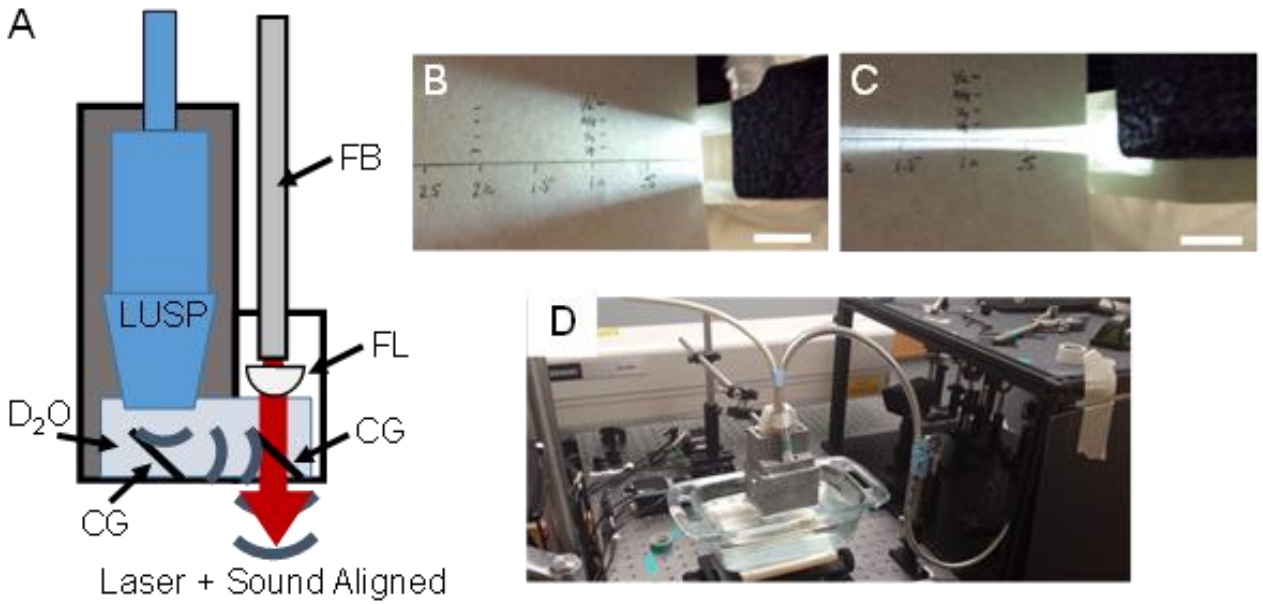
Bifurcated PAT/US Probe V1 for Ex Vivo Prostate Imaging

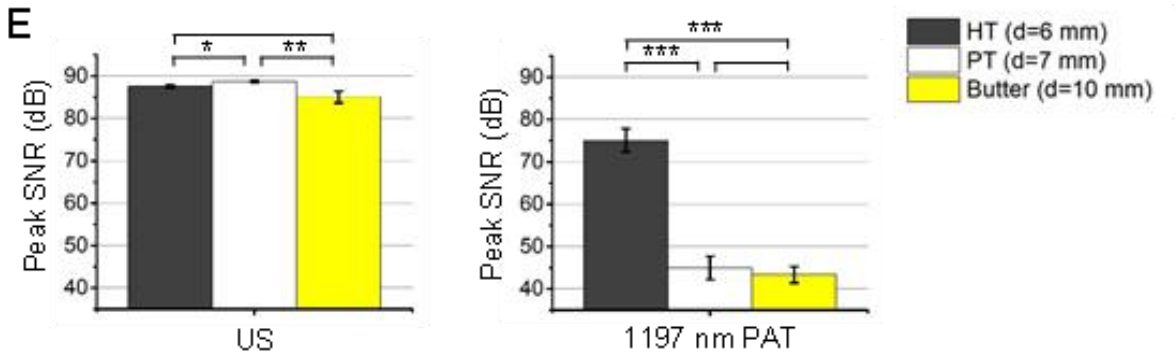


Pros: Compact design

Cons: Focus too close to US

Colinear PAT/US Probe for Ex Vivo Prostate Imaging

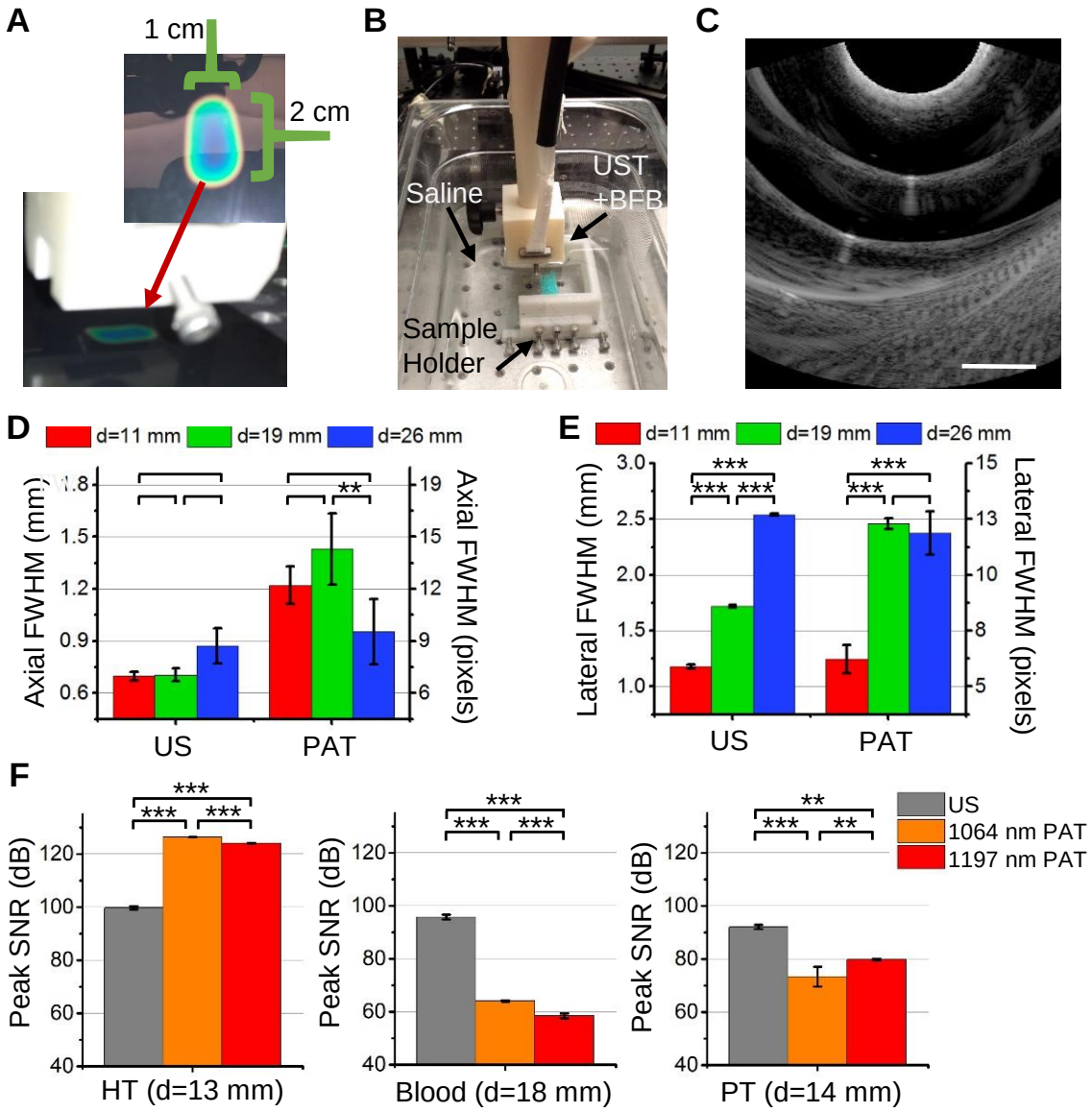




<u>Pros:</u> Aligned light and acoustic path

<u>Cons:</u> Bulky design; Complex; Lower SNR

Bifurcated PAT/US Probe V2 for Ex Vivo Prostate Imaging



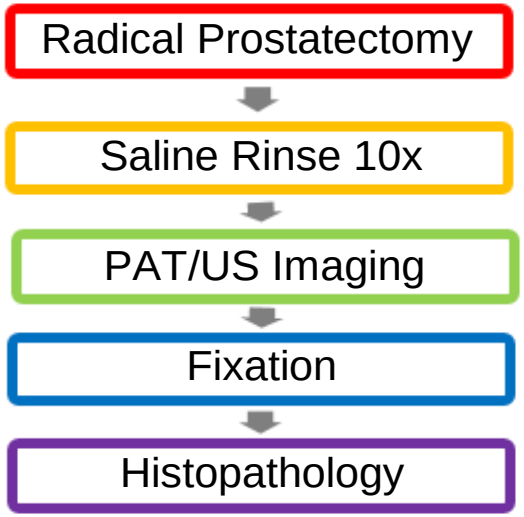
Pros: Simple design; Deeper PAT imaging

Cons: Too bulky for *in vivo*

Use this design for *ex vivo* human prostate imaging.

Human Prostate Handling and Imaging

A



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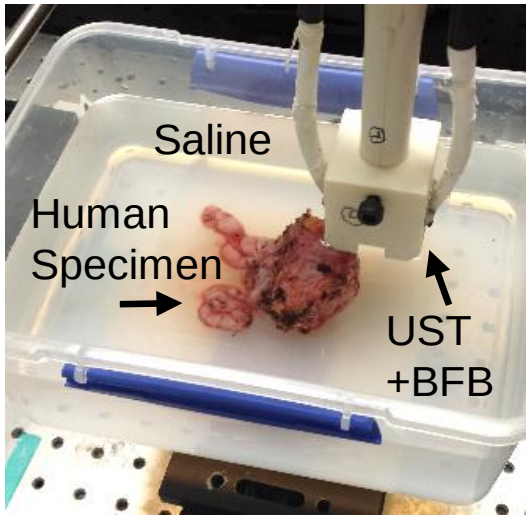
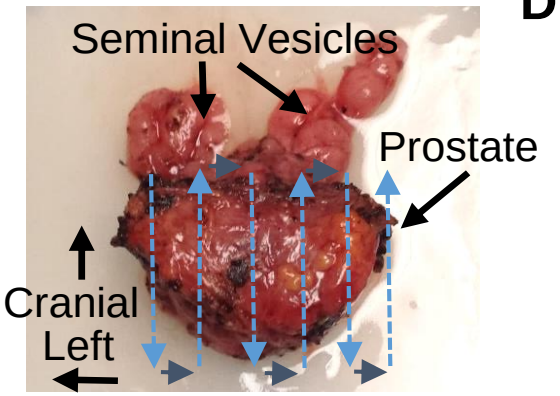
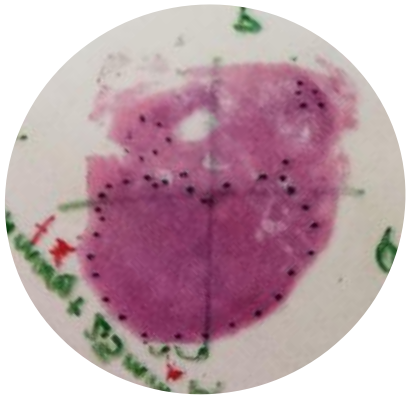


C



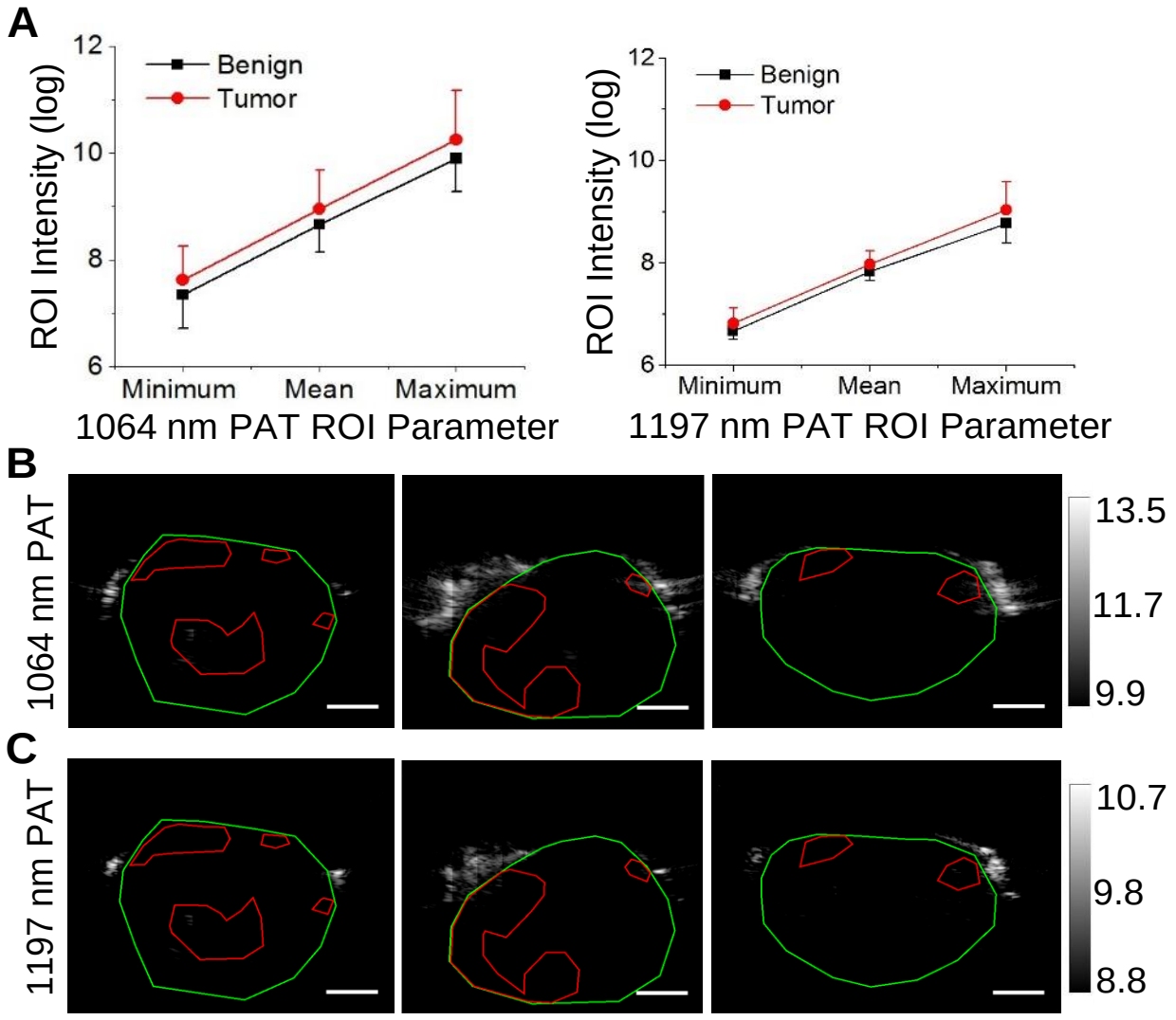
D



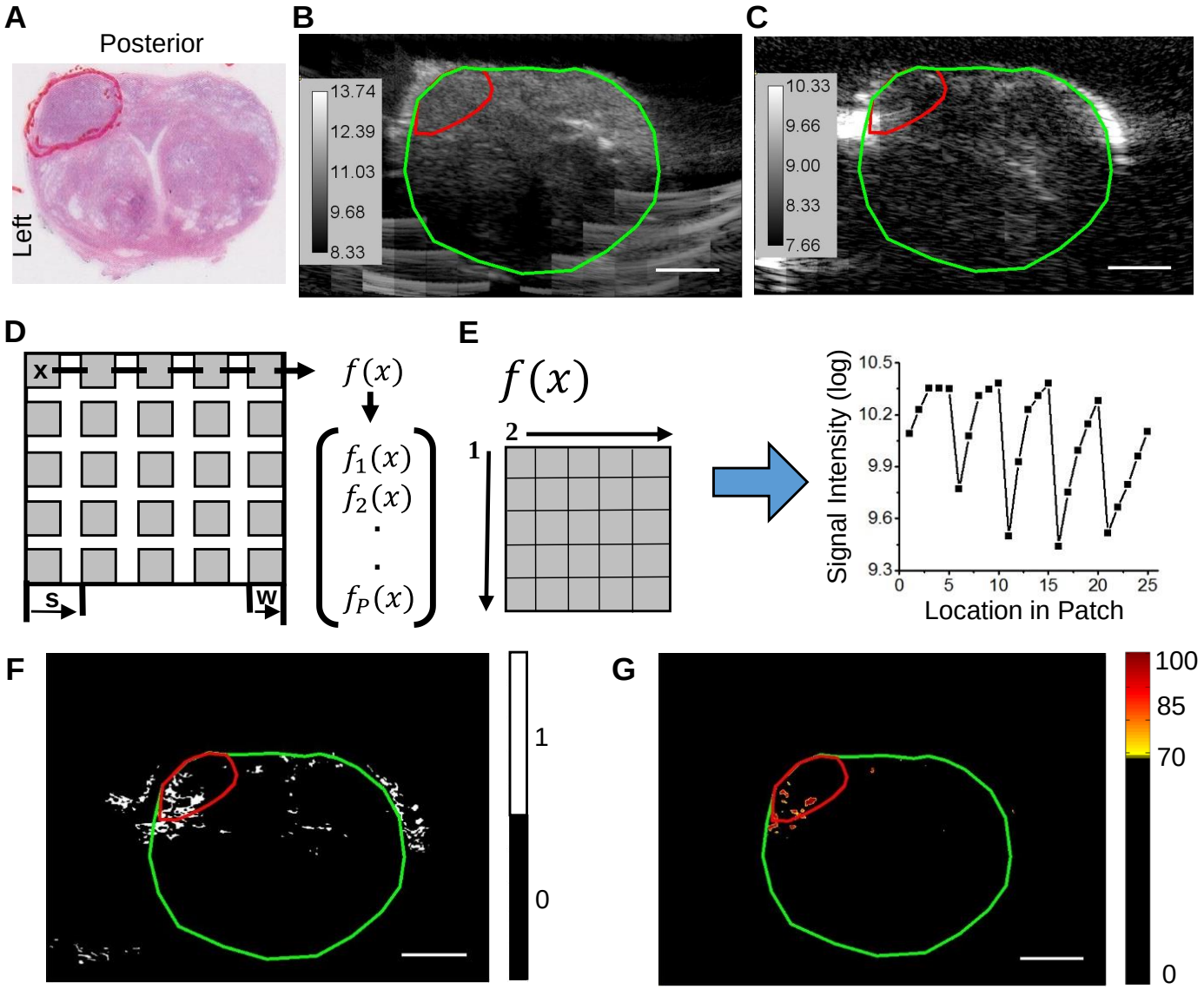
Acquire: 1197 AND 1064 nm PA and US data

Imaging plane: **AXIAL** (to match pathology)

Intensity Thresholding-based Analysis Ineffective



Texture-based K-means Clustering Feature Learning



Aistats 2011 215–223 (2011).

Texture Analysis Underlying Theory

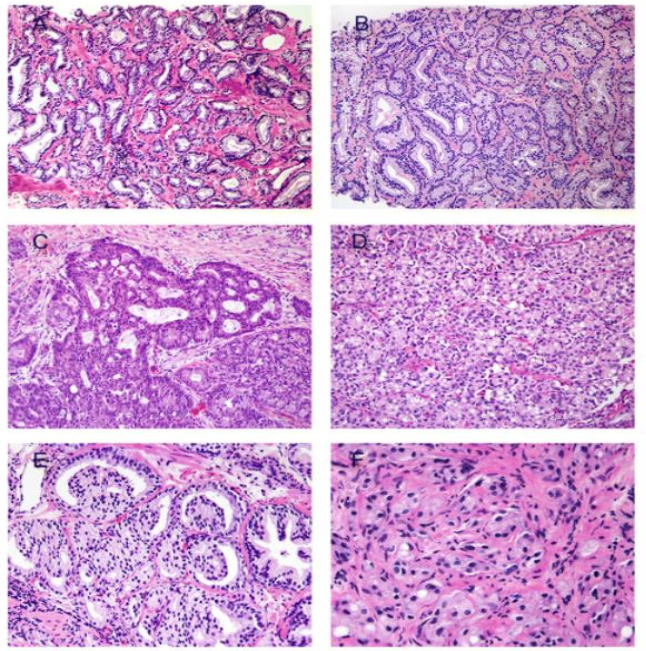
Prostate cancer is strongly associated with neovascularization.

- NOT specific to prostate cancer though…BPH also exhibits

Morphology KEY with unique changes in gland structure.

Analysis based on premise of different vasculature topology and not density (intensity).

Gleason grading system



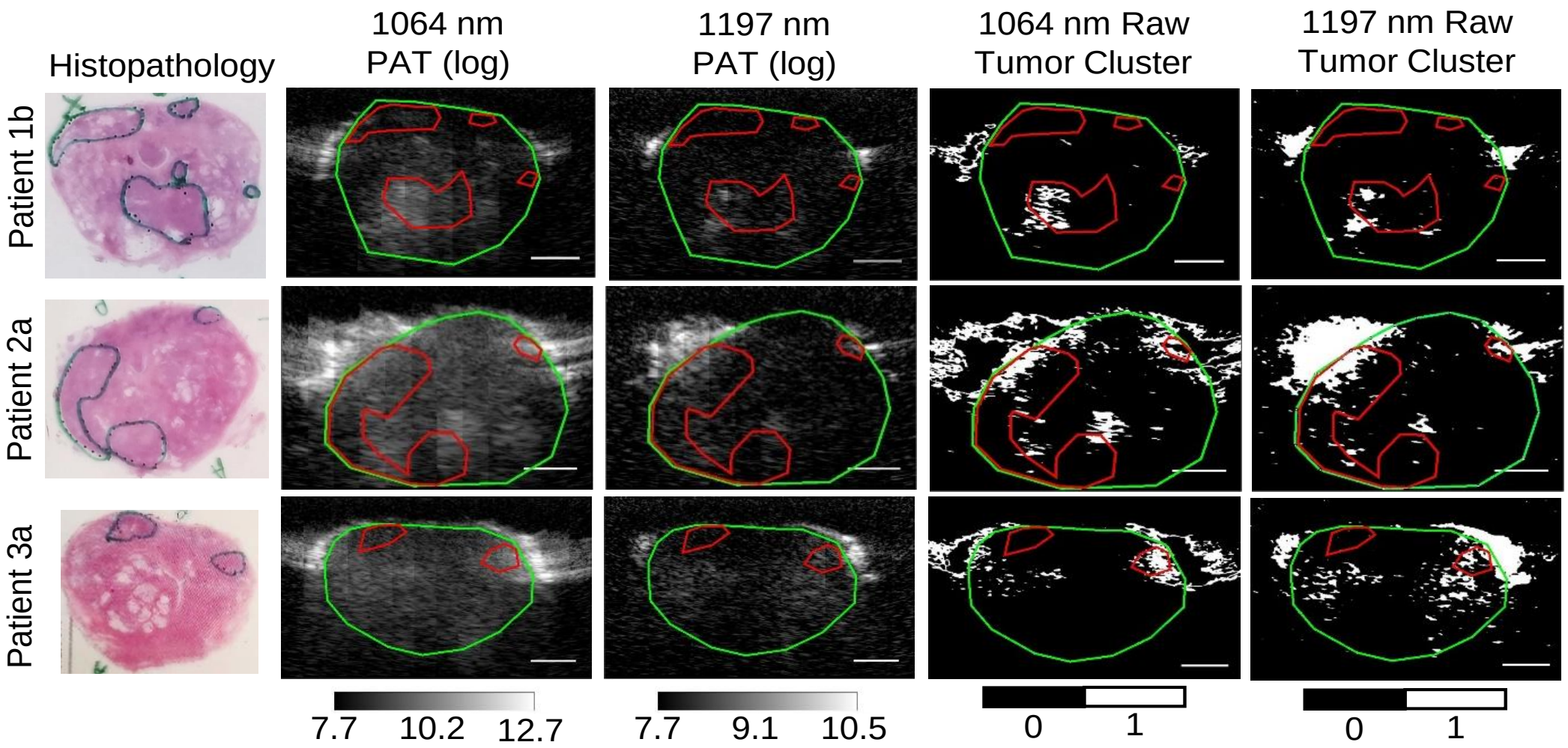
Example Gleason Scores.

BJU Int. 110, 794–808 (2012).; Eur. Urol. 63(2), 214–230 (2013).

Dataset Characteristics

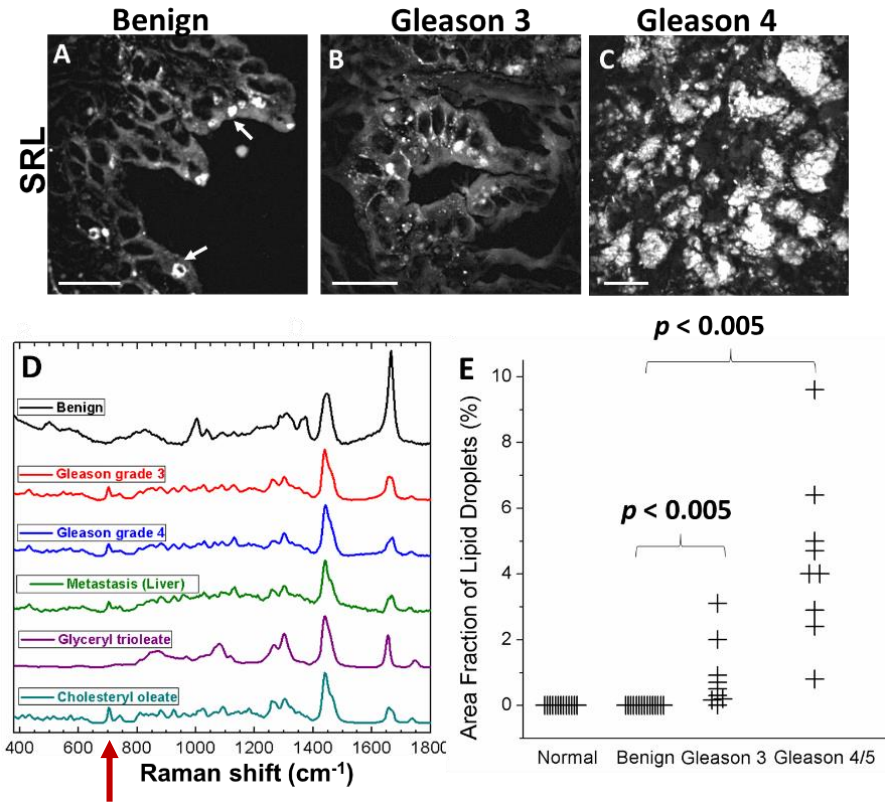
Training Dataset (prostates=6)	
Age	61 +/- 9
Prostate Volume (cm^2)	82.3 +/- 26.0
Primary Lesion Largest Dimension (cm)	2.79+/- 1.1
Secondary Lesion Largest Dimension (cm)	1.0 +/- 0.4
Gleason 6	1
Gleason 7a	3
Gleason 7b	2
Gleason 8-10	0
Testing Dataset (prostates=3)	
Age	72 +/- 7
Prostate Volume (cm^2)	96.4 +/- 23.3
Primary Lesion Largest Dimension (cm)	1.9 +/- 1.0
Secondary Lesion Largest Dimension (cm)	1.2 +/- 0.6
Gleason 6	0
Gleason 7a	2
Gleason 7b	1
Gleason 8-10	0

1197 nm PAT Does Not Provide Unique Information

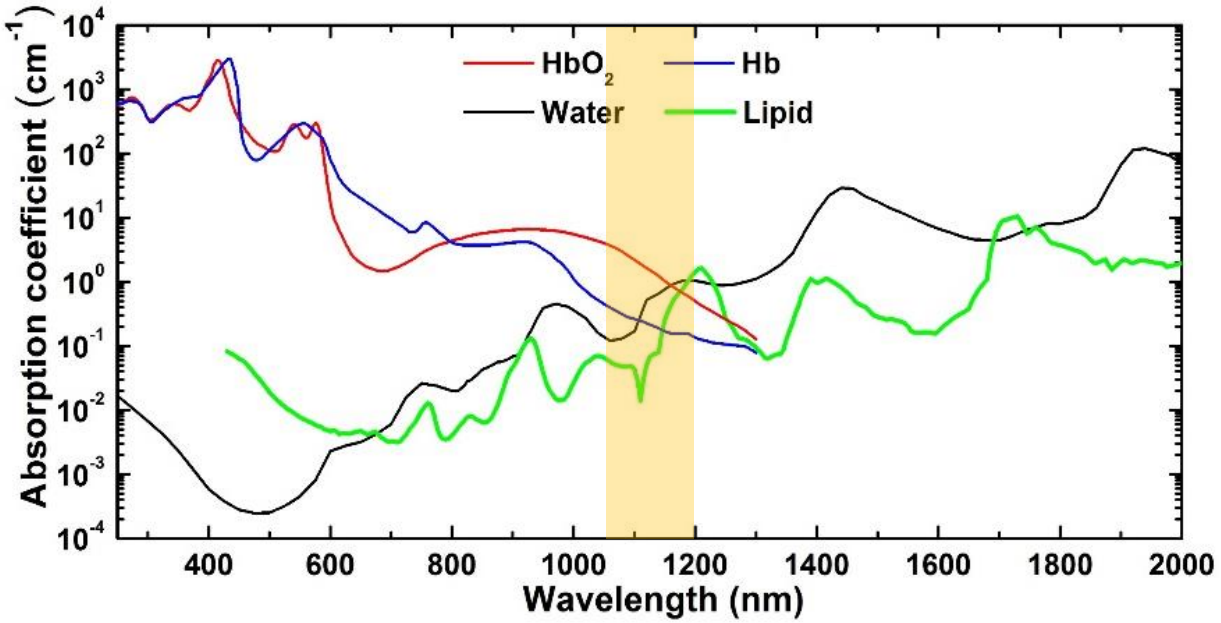


1197 nm PAT Does Not Provide Unique Information

Cholesteryl Ester - a potential marker of prostate cancer aggressiveness

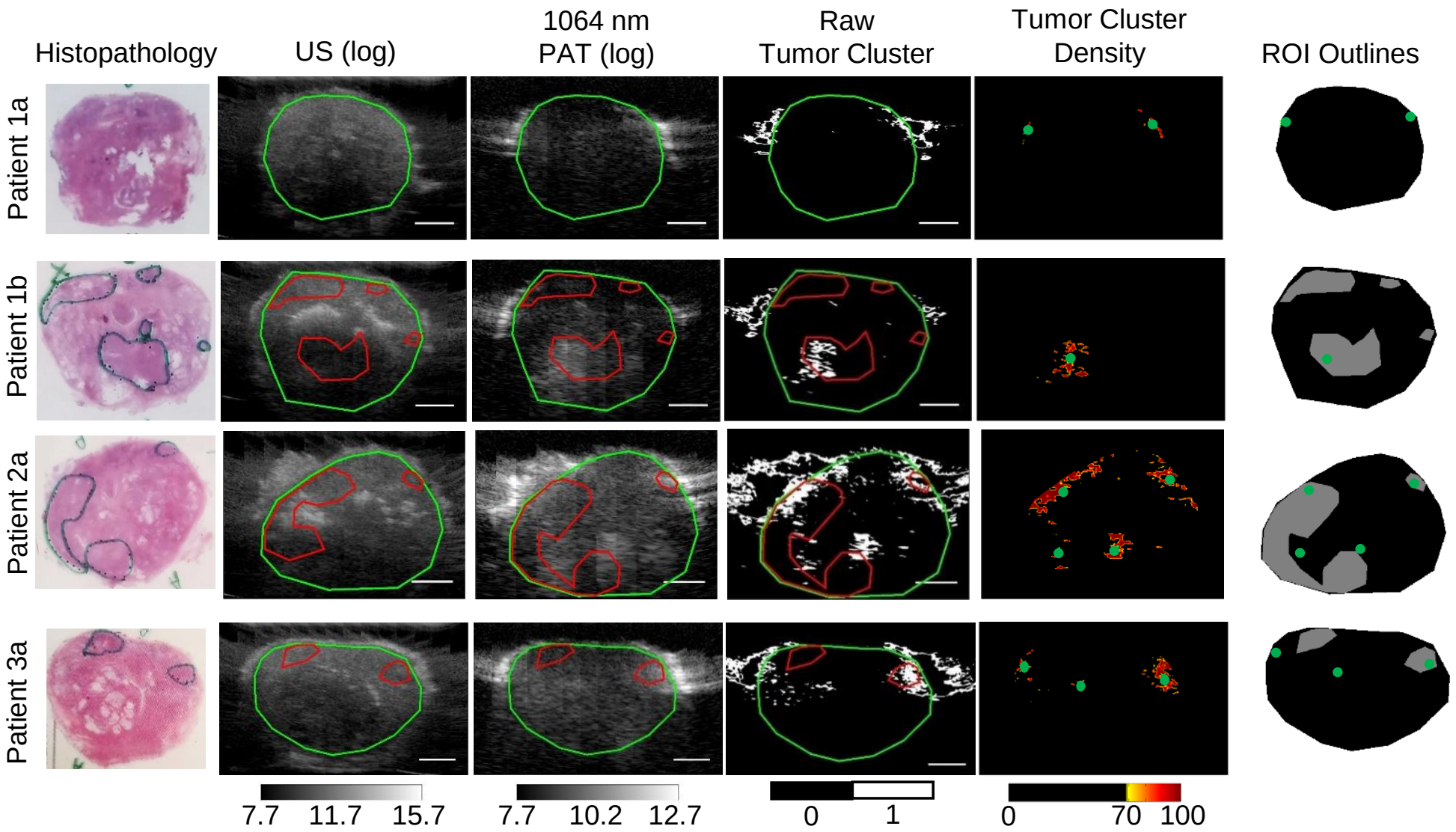


PA signal = $\mu_a \Gamma F[A]$



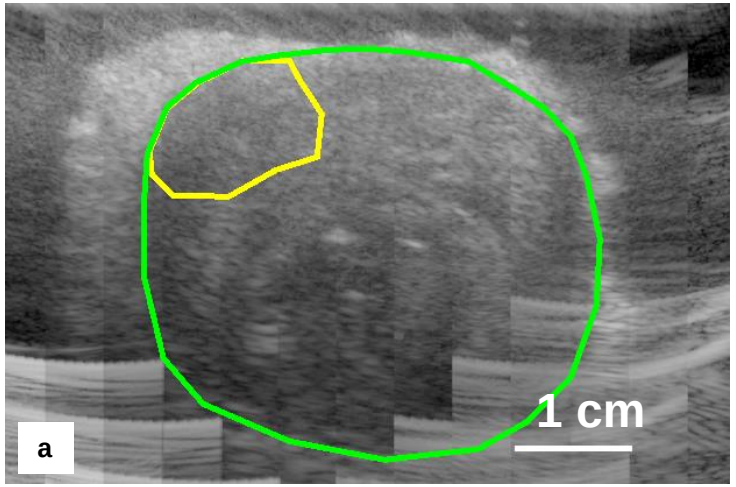
Cell Metab. 19, 393–406 (2014).; Photoacoustics 4:11–21, 2016.

Prostate Biopsy Targets Identified in Testing Dataset

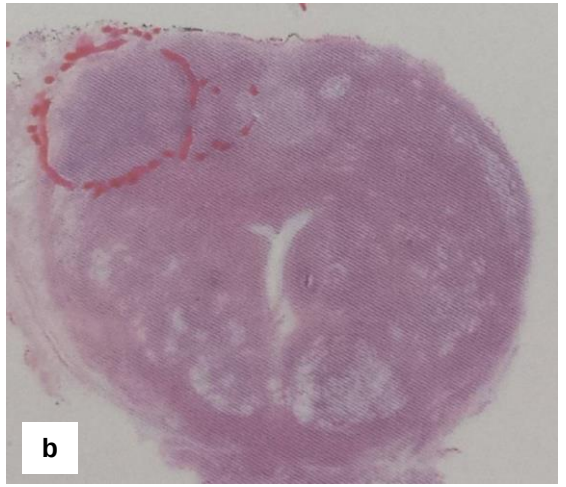


Need Improved Light Fluence to Anterior Prostate

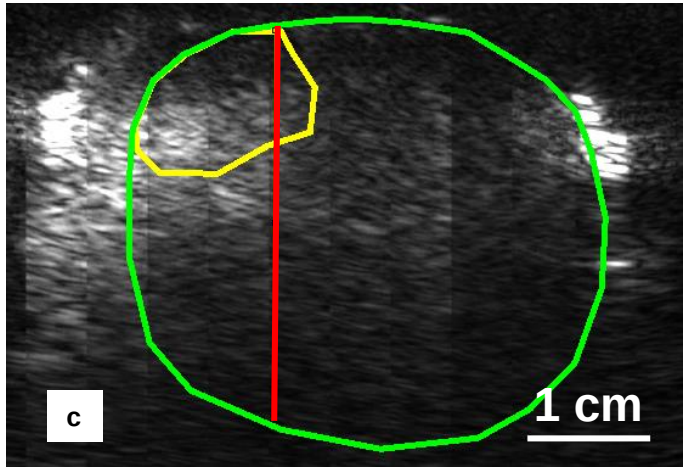
US

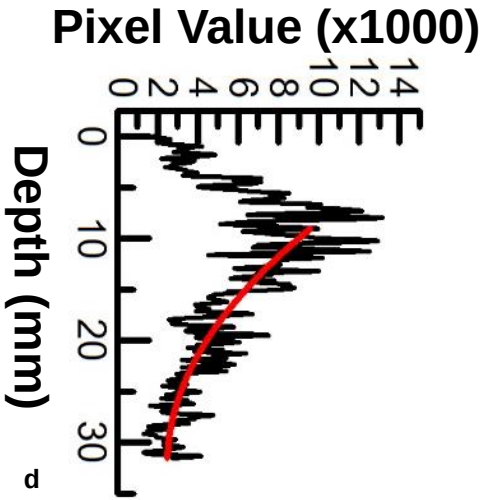


H&E

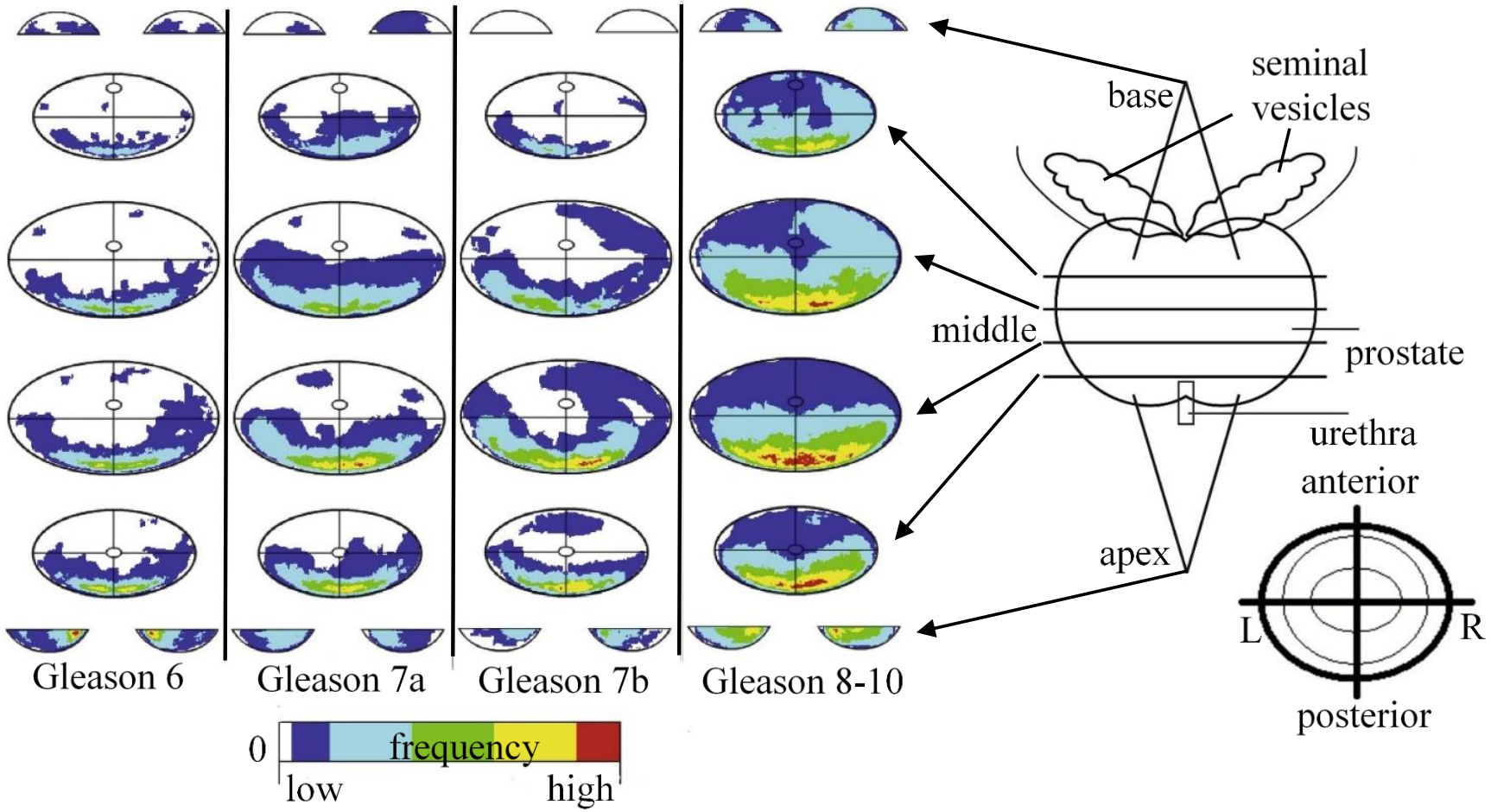


1064 nm PAT





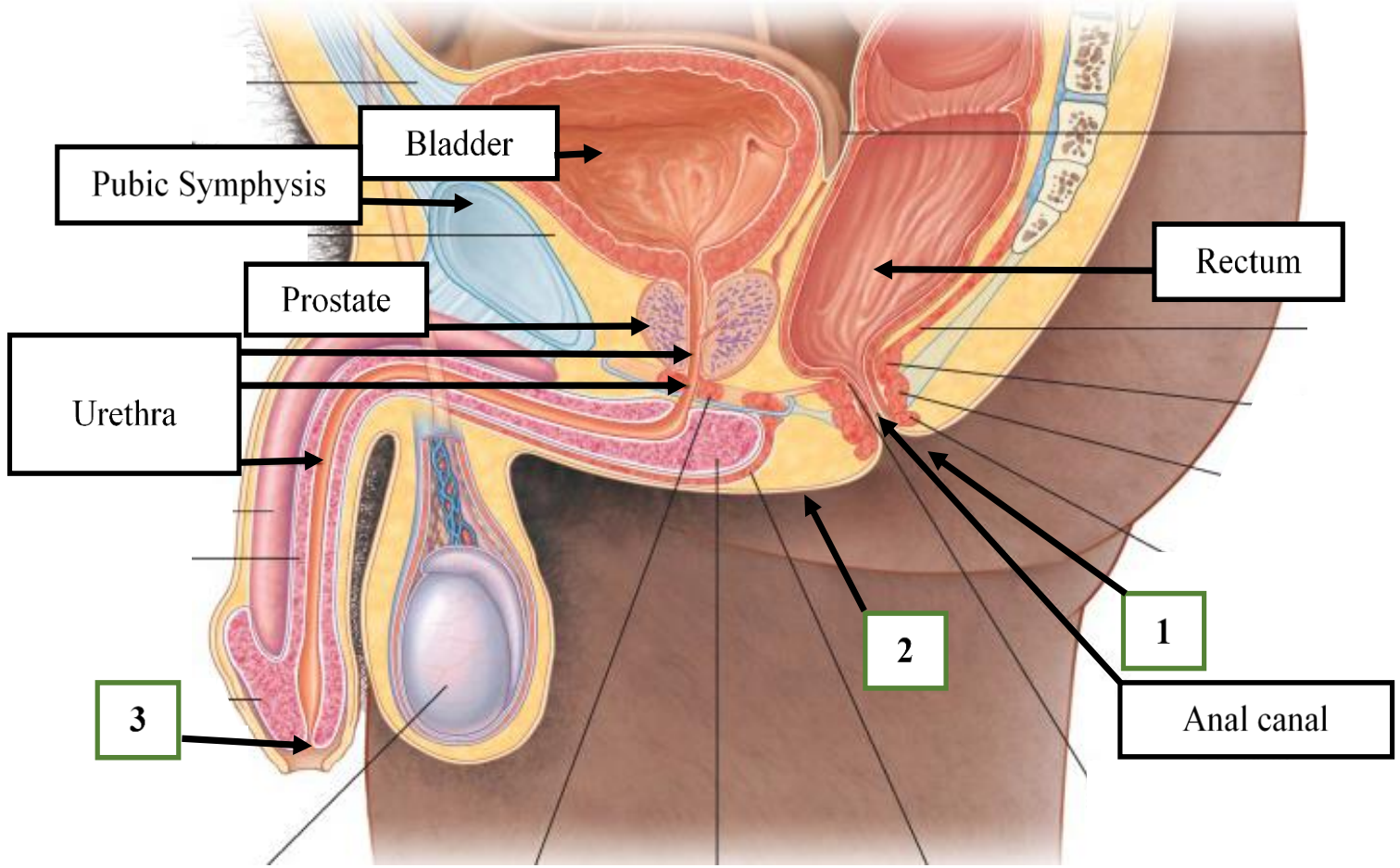
Need Improved Light Fluence to Anterior Prostate



J. Biomed. Inform. 59, 240–247 (2016).

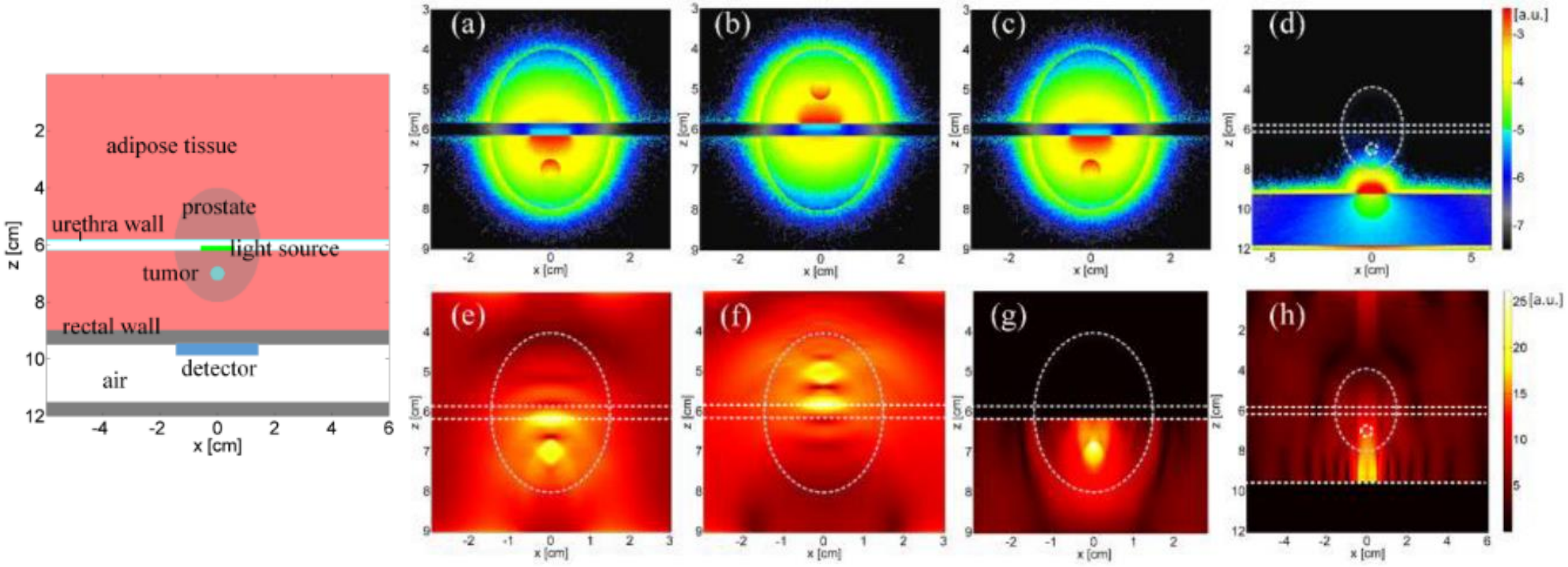
Light Delivery Approaches for Prostate

1. Transrectal
2. Transperineal
3. Transurethral



"Pelvis and Perineum," in *Gray's Atlas of Anatomy*, Second (Churchill Livingston, Elsevier Inc., 2015), pp. 212–284.

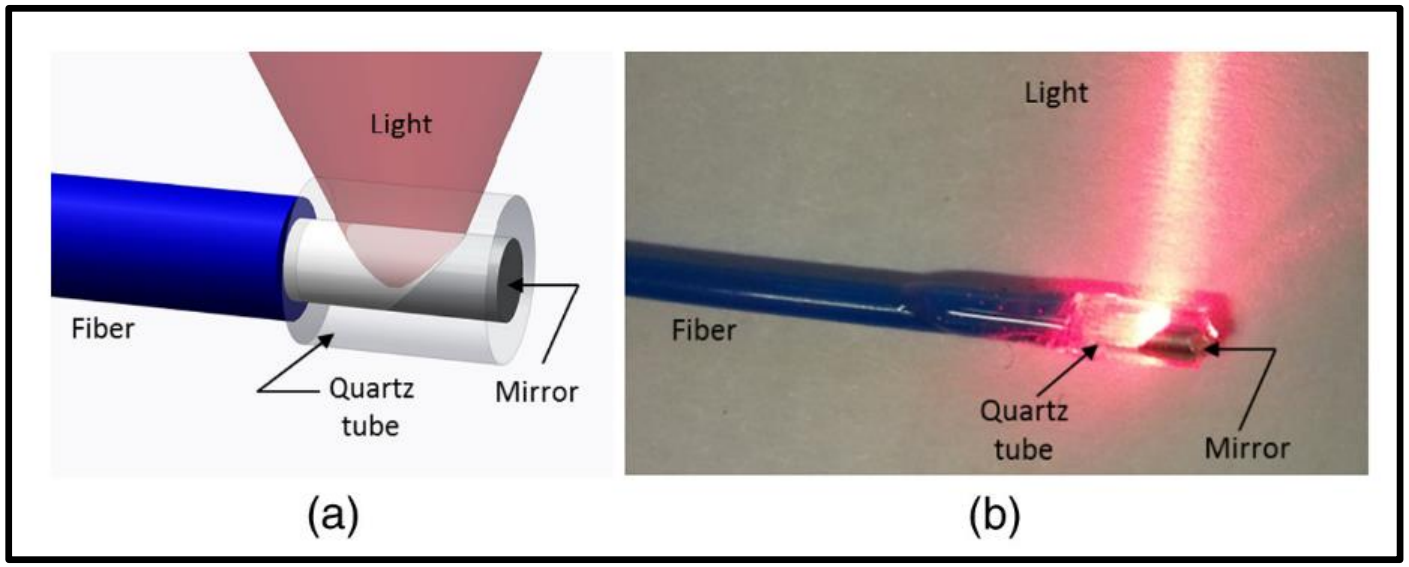
Simulation Study on Light Delivery

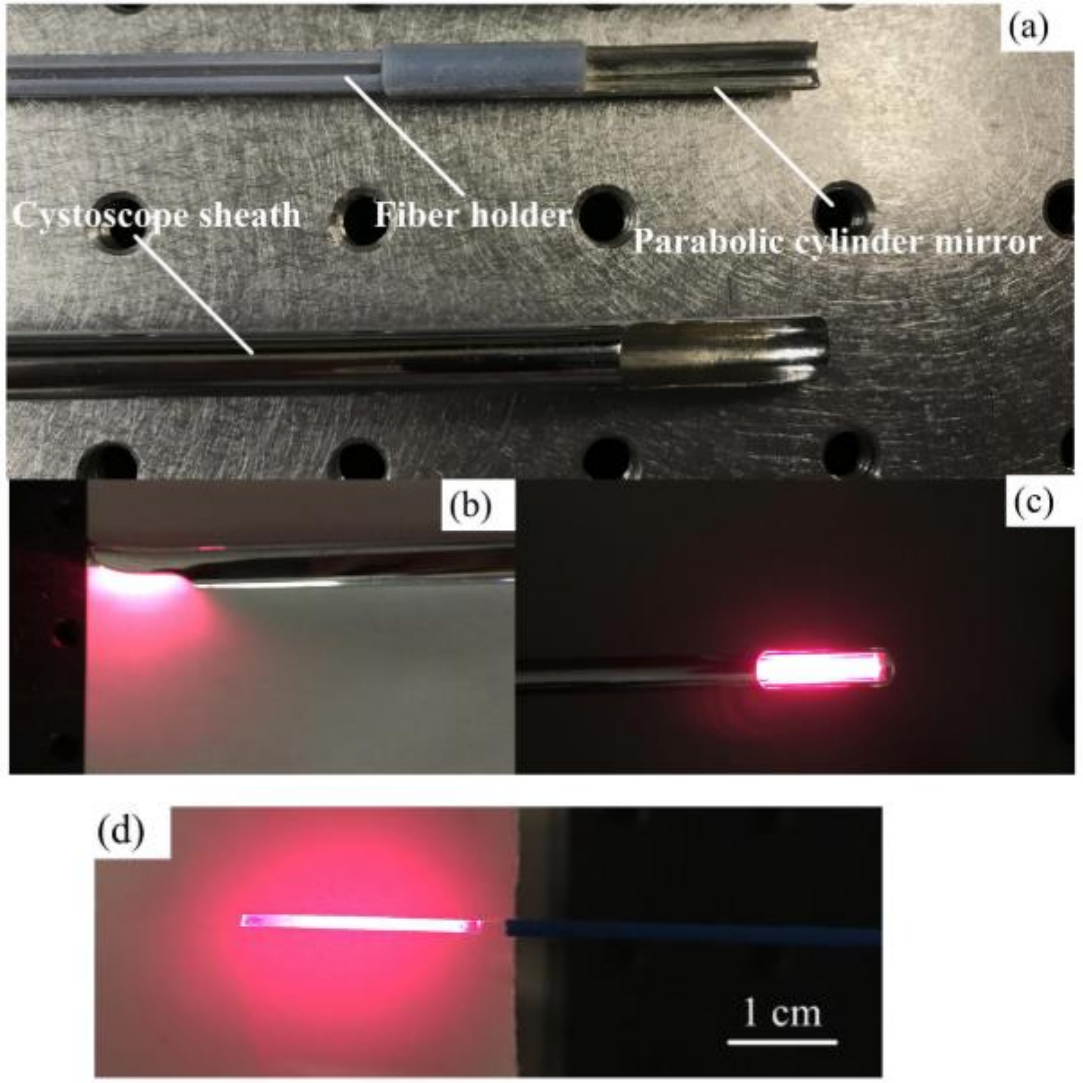


Use transurethral illumination with transrectal US.

IEEE Trans. Med. Imaging 35, 1780–1787 (2016).

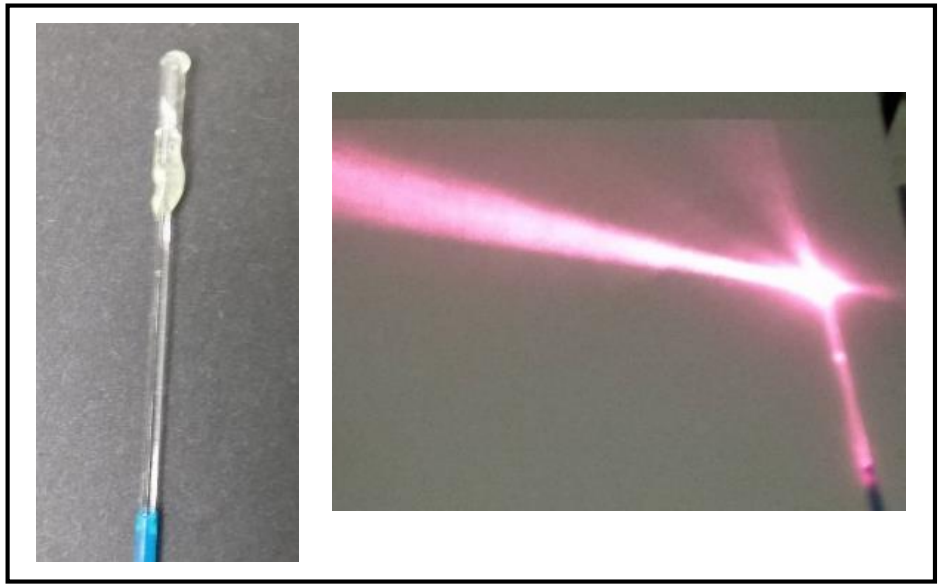
Prior Advancements for Transurethral Light Delivery



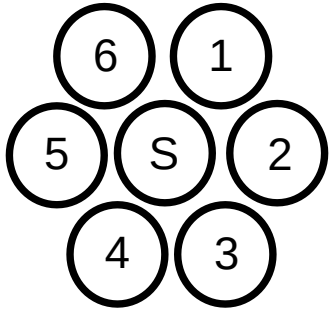


J. Biomed. Opt. 20, 036002 (2015).; *Proceedings of SPIE* (SPIE, 2018), Vol. 10494, p. 104940C.

Transurethral Light Delivery Device V1

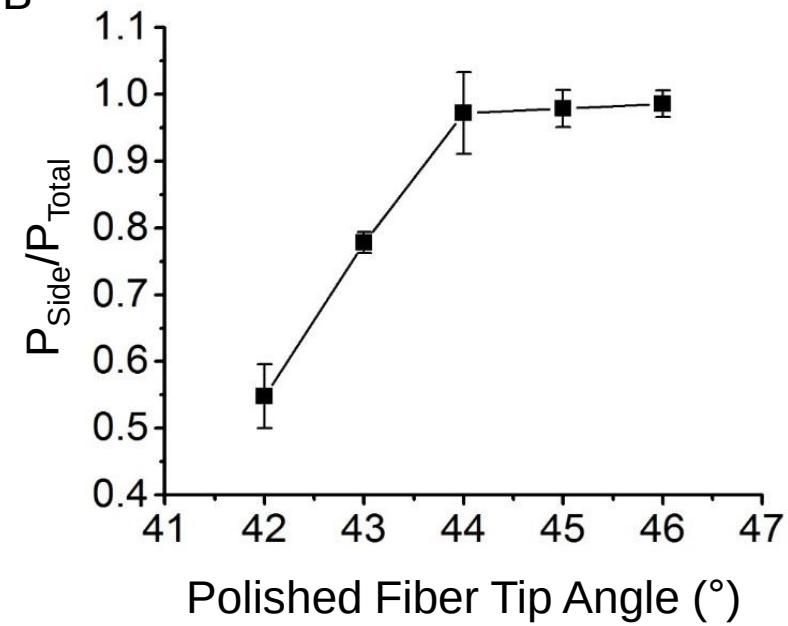


Fiber Bundle Layout with Side-firing Fibers



A

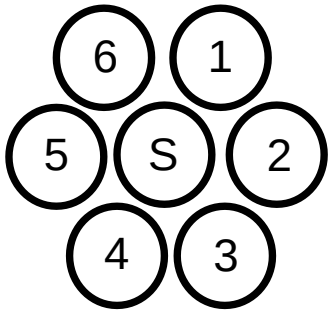
B



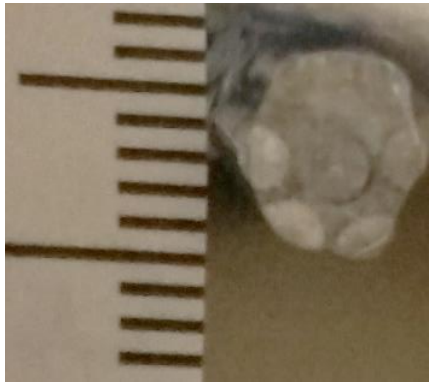
Use 44° for bevel tip.

Transurethral Bevel-tipped Fiber Bundle

A



B



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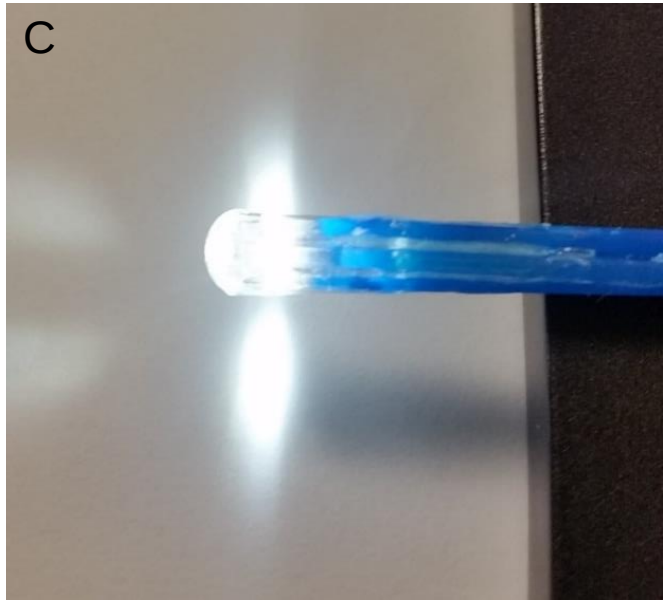
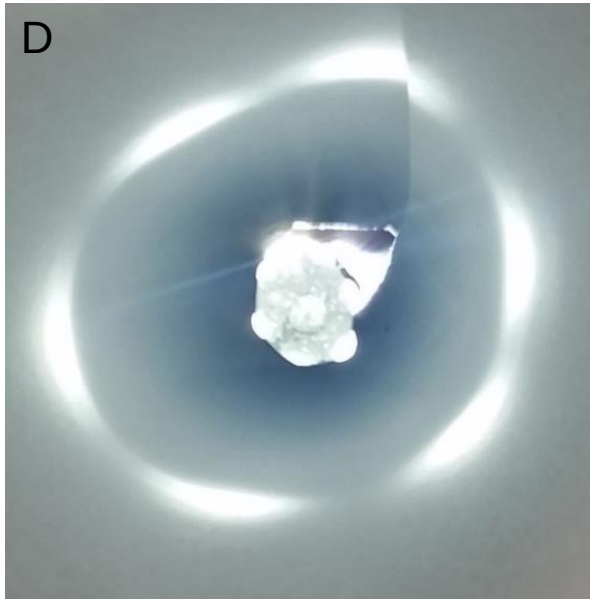
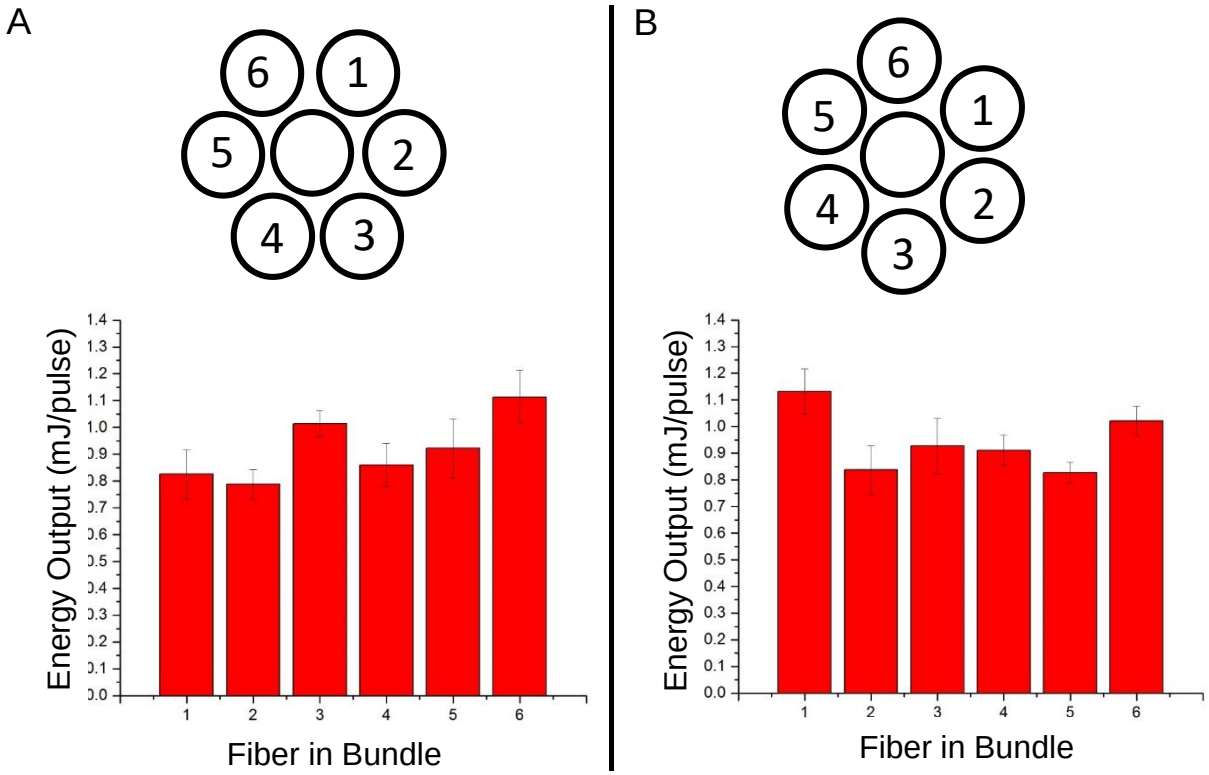
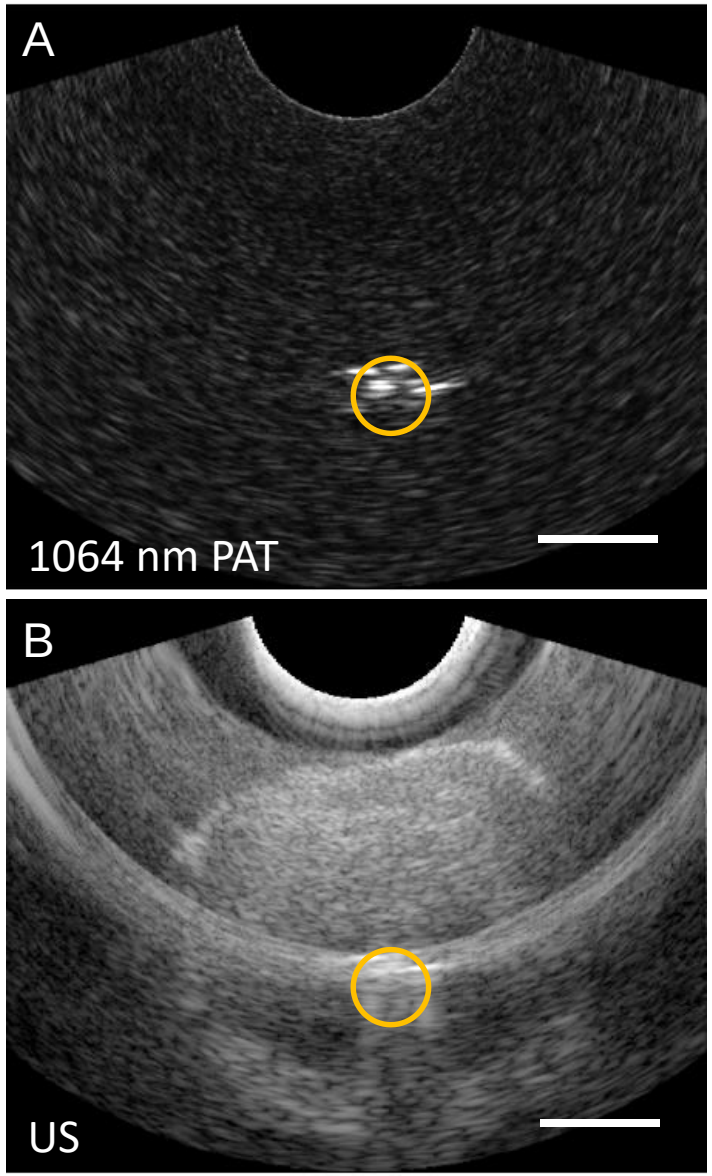


D



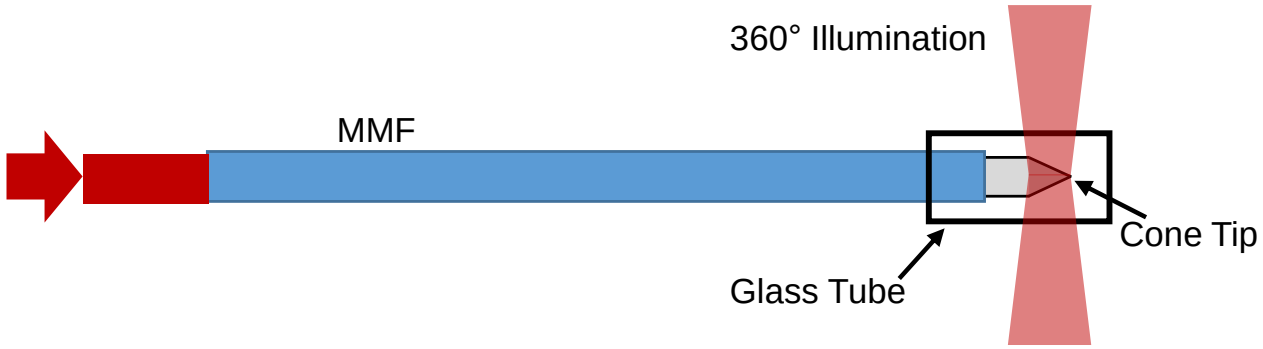
Bevel-tipped Fiber Bundle Performance



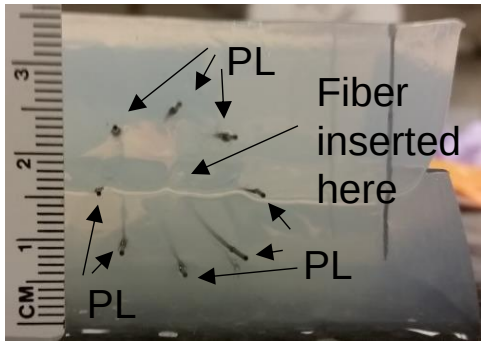


Transurethral Light Delivery Device V2

A



B



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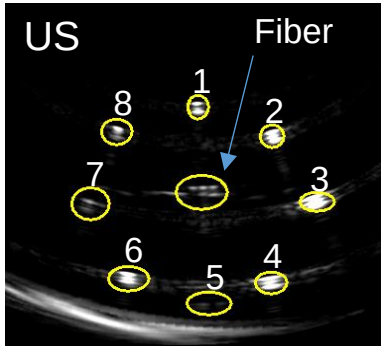
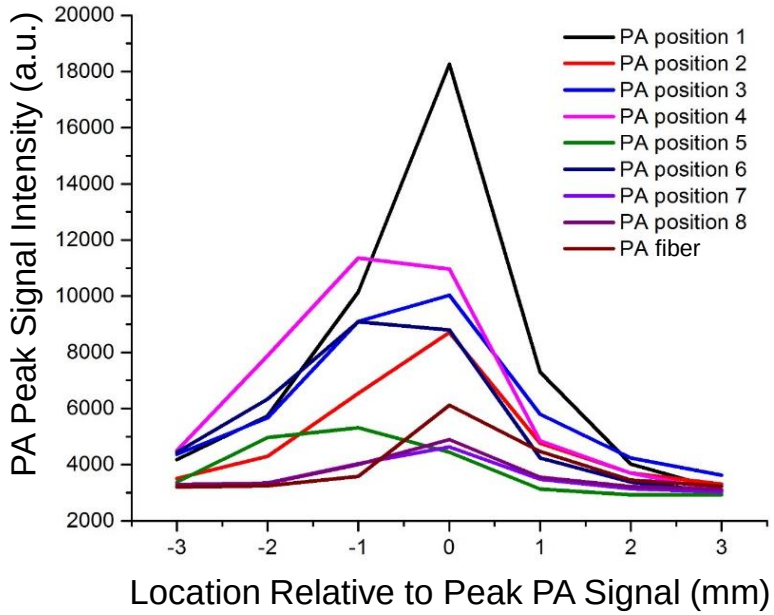
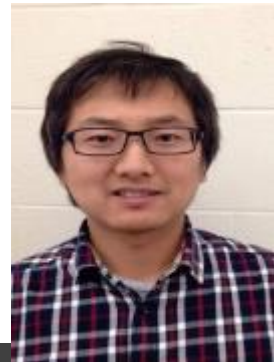


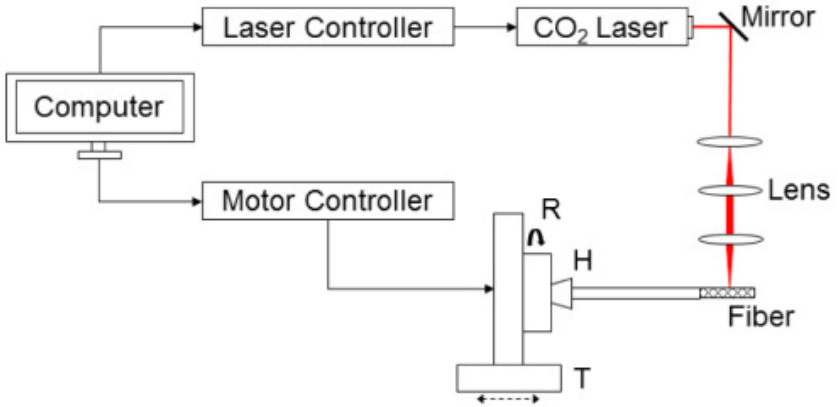
D

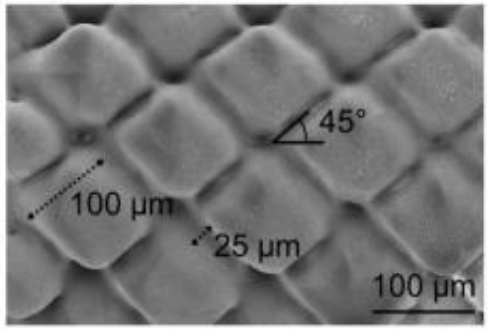


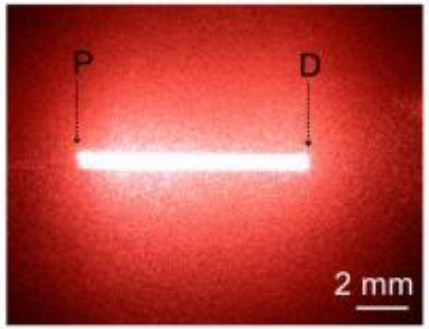
Need cylindrical illumination.

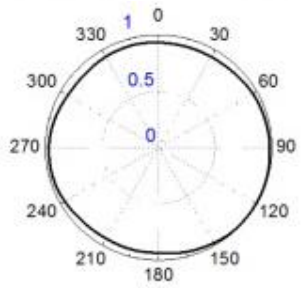


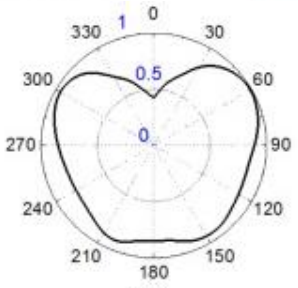
Prior literature on High Energy Cylindrical Emitters

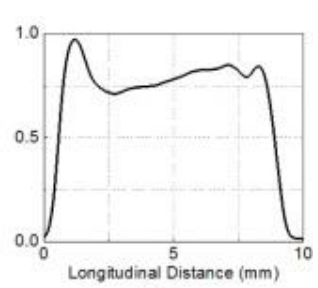


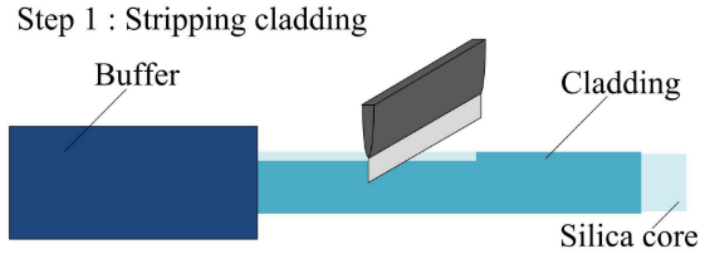


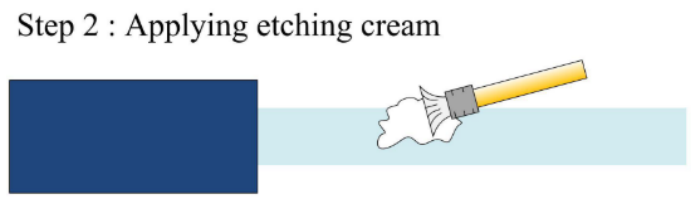


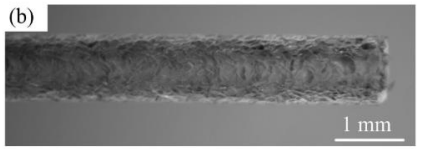


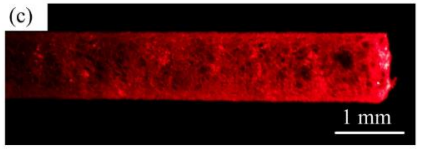


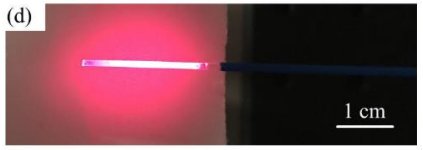


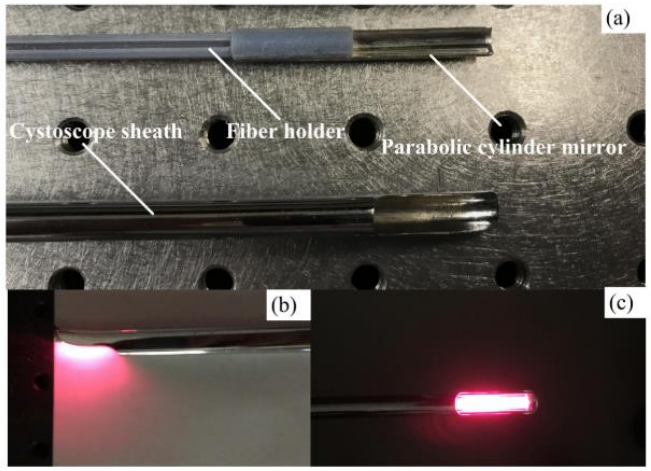






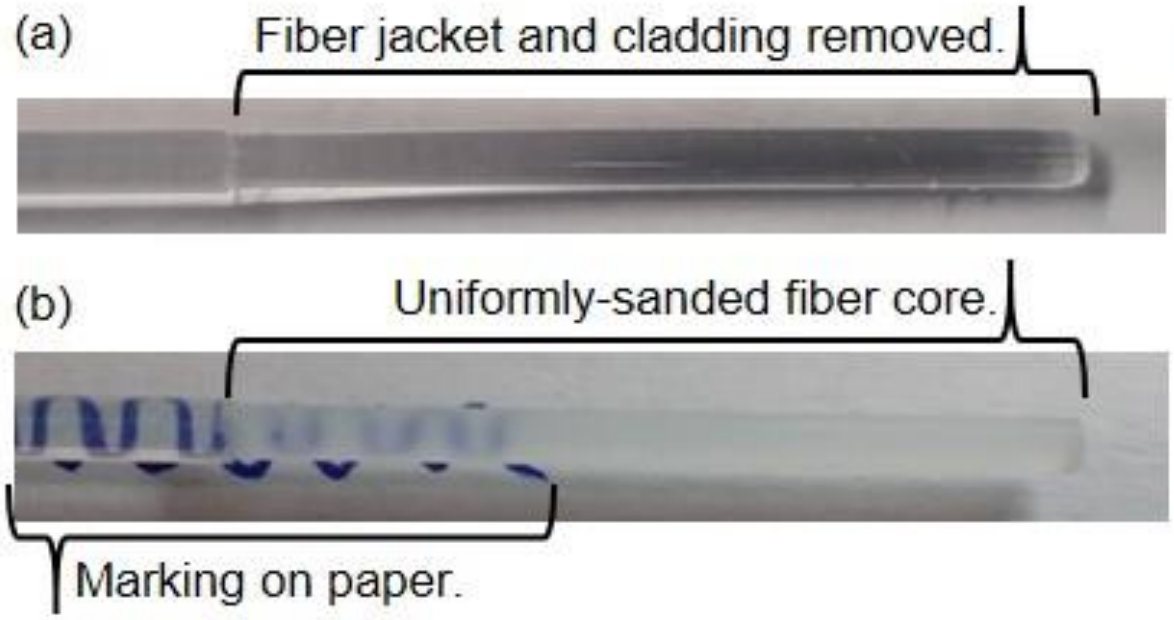


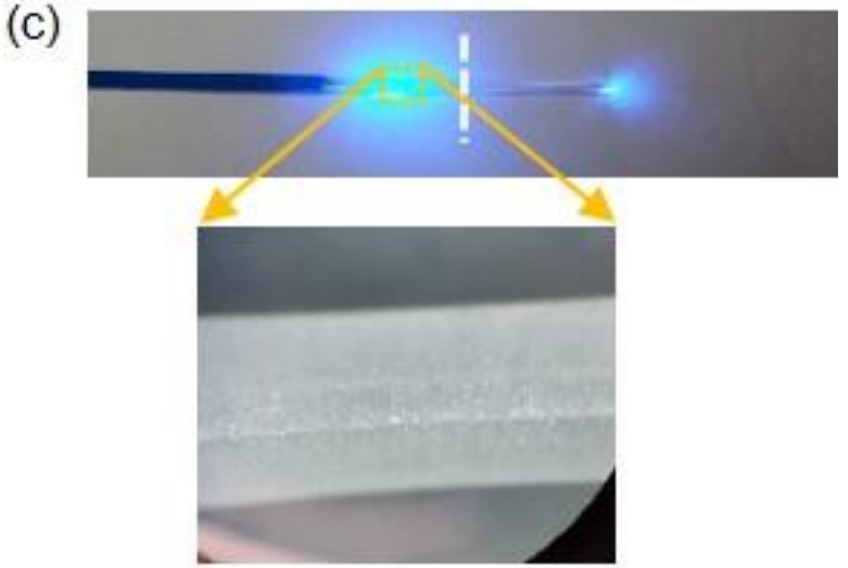




Opt. Express **23**, 20829–20840 (2015).; *Proceedings of SPIE* (SPIE, 2018), Vol. 10494, p. 104940C.

Fiber with Sandpaper-abraded Diffuser End

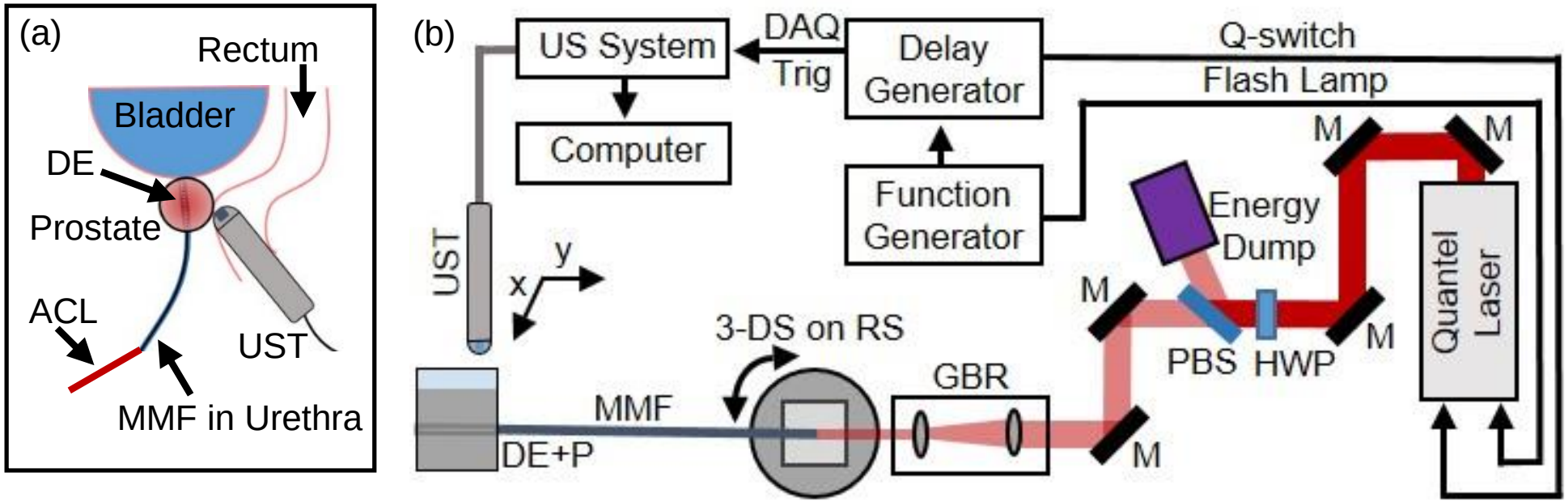




PAT/US System with Transurethral Illumination

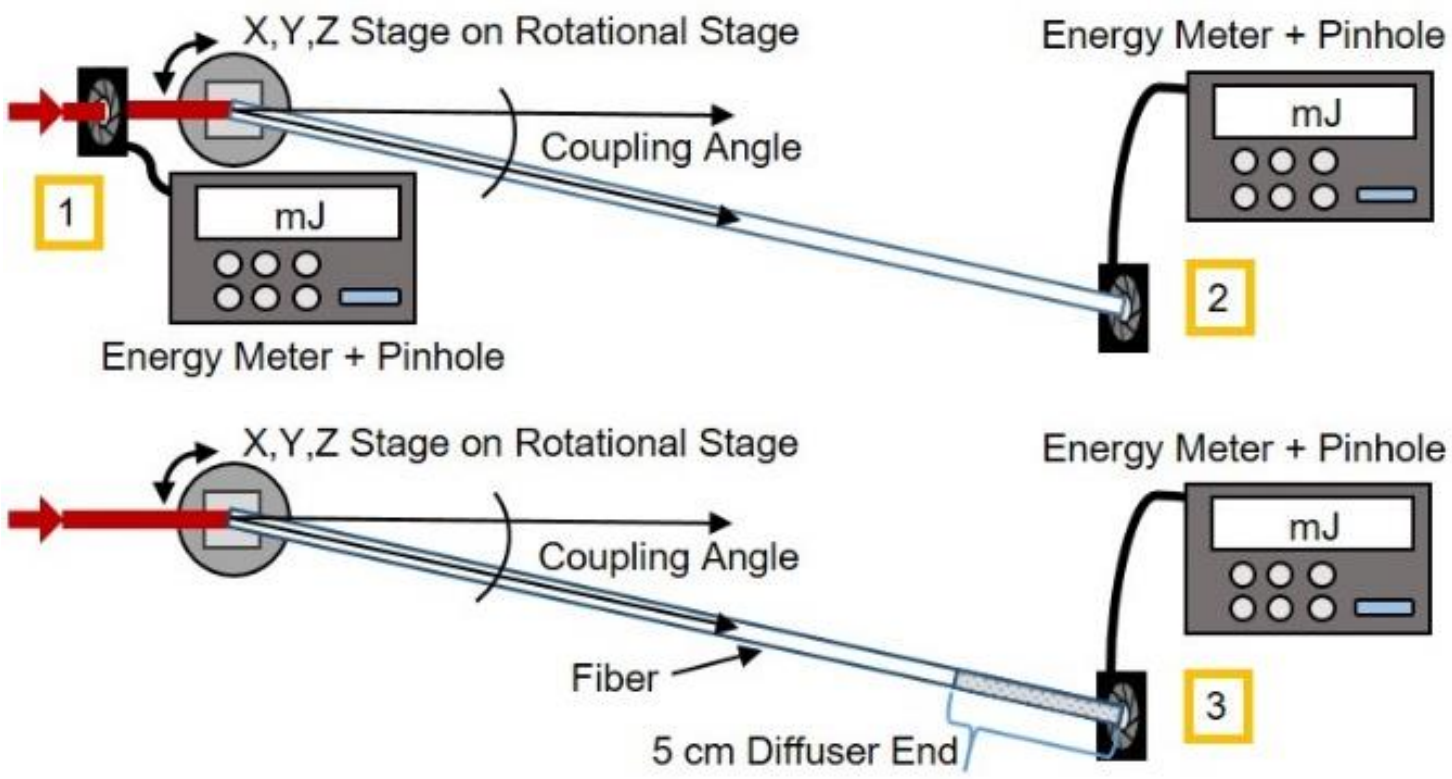
Changes to PAT/US System:

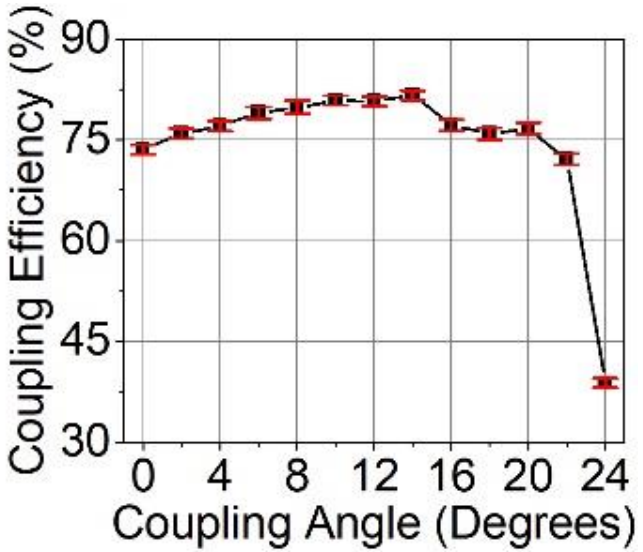
1. Uncoupled illumination source and detector
2. 6W Nd:YAG laser with 8 ns pulse width
3. Galilean beam reducer

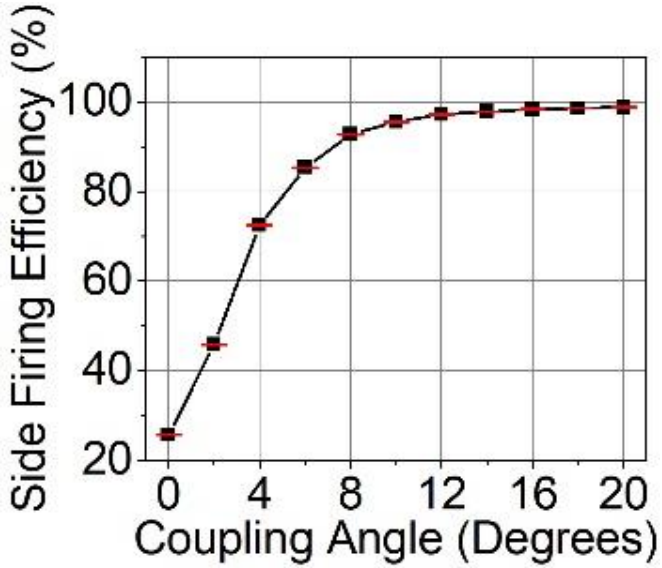


DE: diffuser end; ACL: angularly-coupled light; MMF: multimode fiber; UST: ultrasound transducer; DAQ Trig: data acquisition system trigger; M: Nd:YAG laser line 45° mirror; HWP: half wave plate; PBS: polarized beam splitter; GBR: Galilean beam reducer; 3-DS on RS: 3-dimensional stage on rotational stage; DE+P: diffuser end + phantom.

Coupling Angle Affects Side Emission Conversion

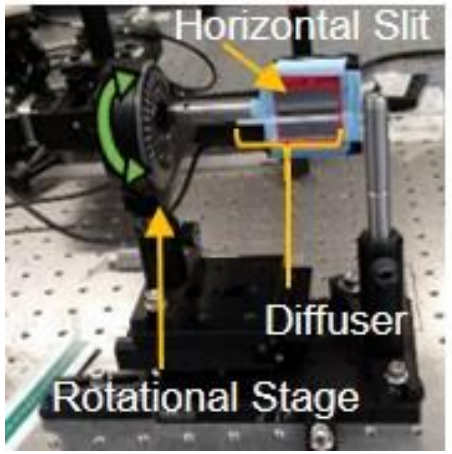




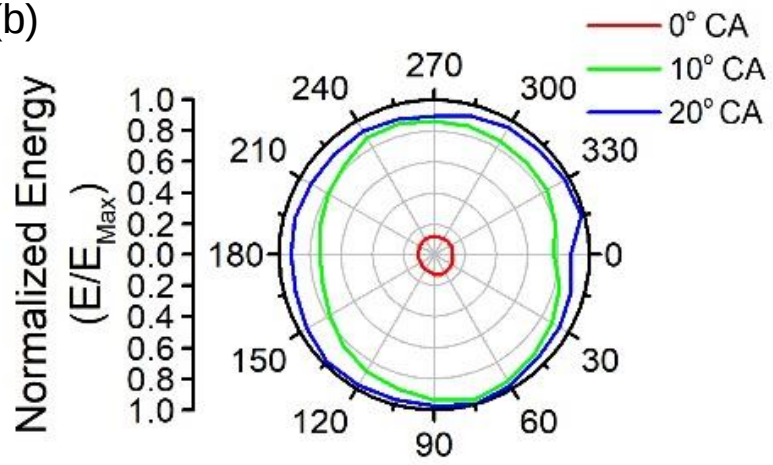


Coupling Angle Affects Longitudinal Emission Profile

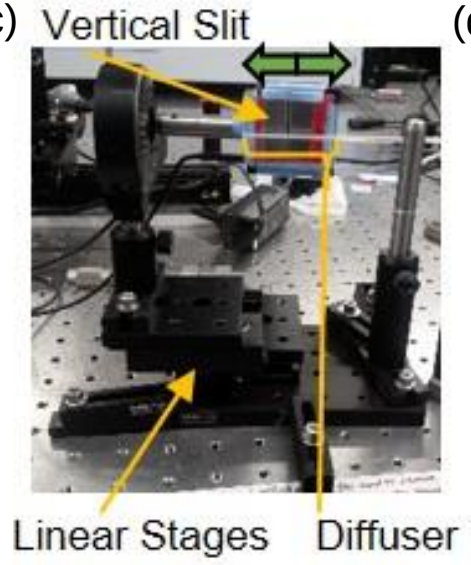
(a)



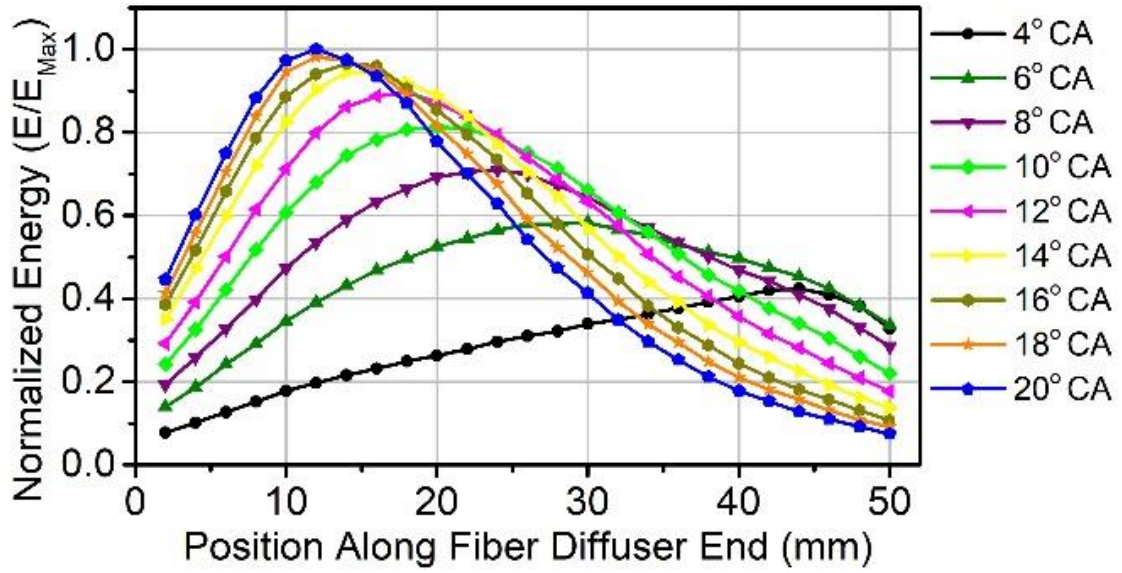
(b)



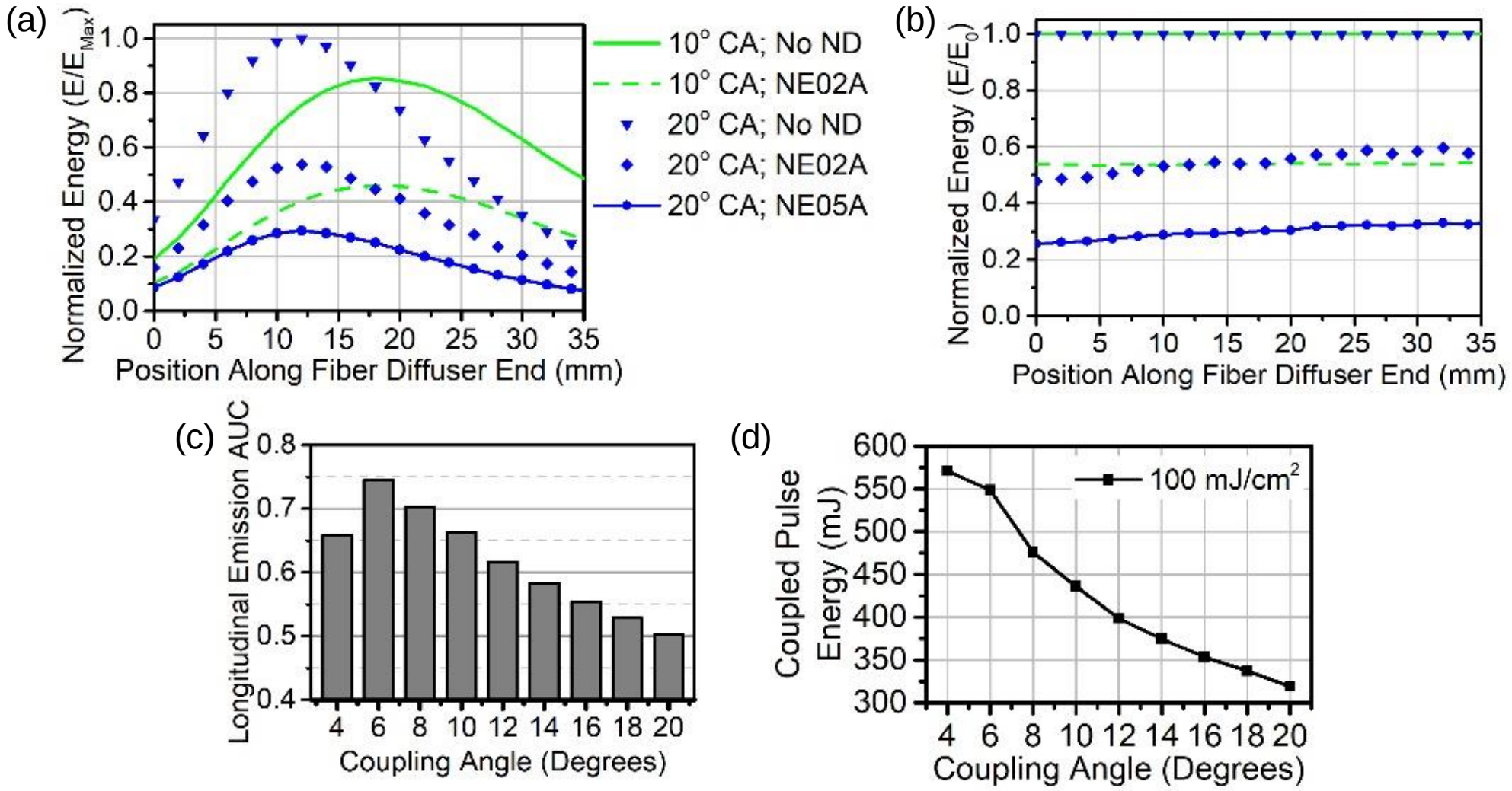
(c)



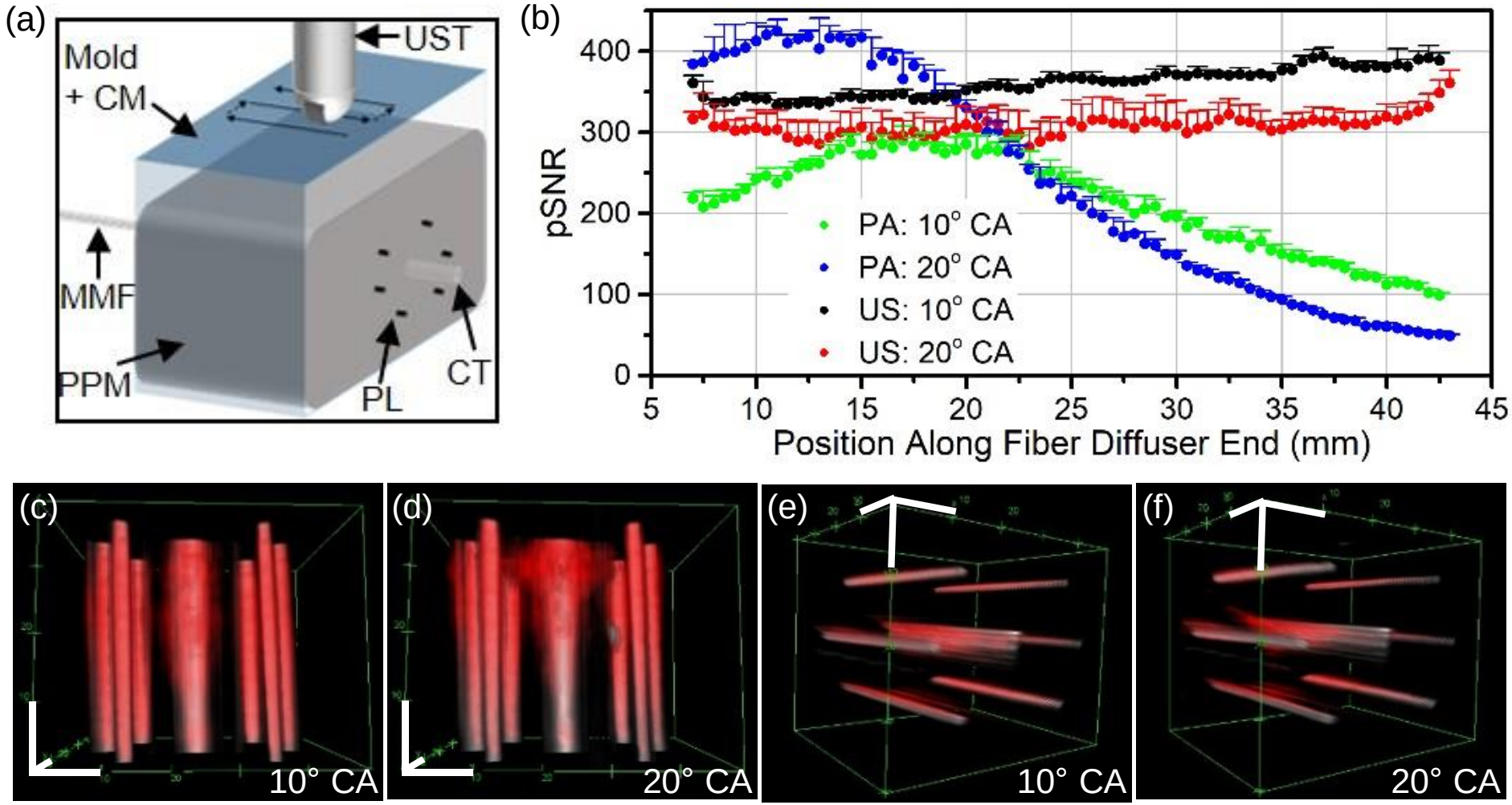
(d)



Energy Profiles Stable and Allow Calculation of Fluence



Angular Coupling Enables PA Signal from Whole Phantom

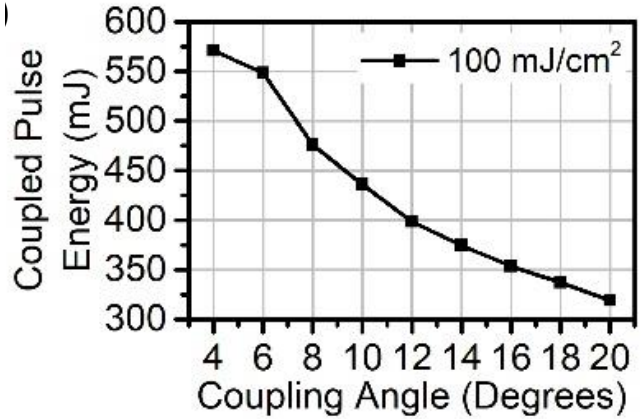


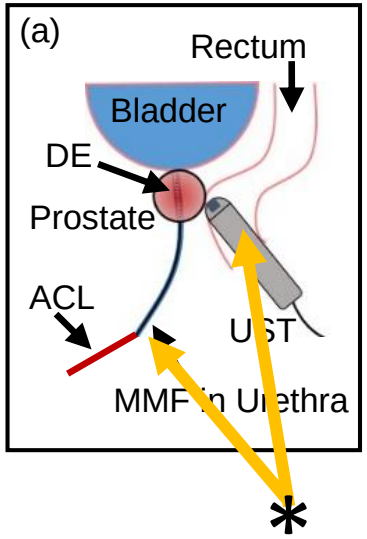
Conclusions

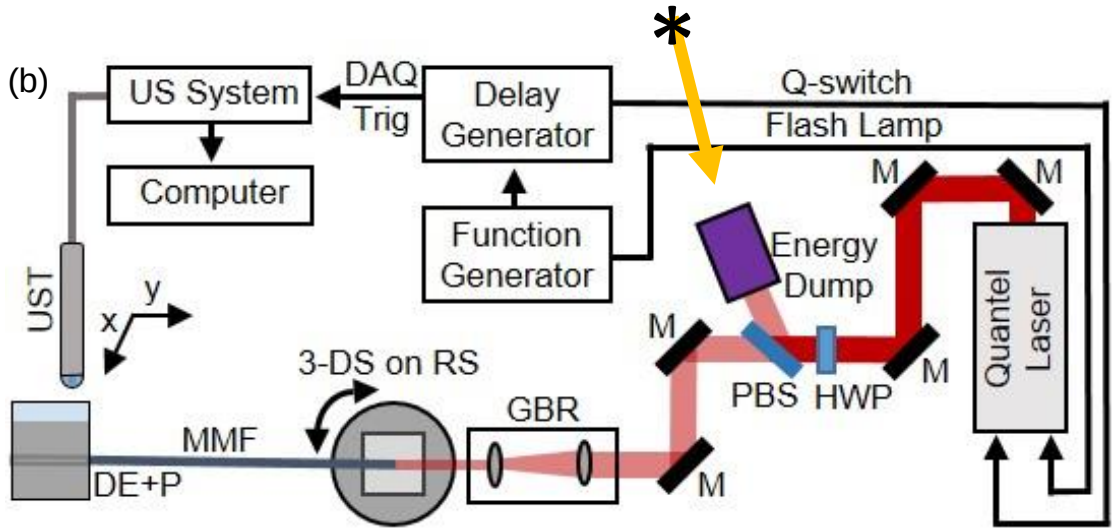
1. Bifurcated PAT/US imaging device with angled fiber bundles is the best design for *ex vivo* prostate imaging.
2. Texture-based image processing with K-means feature learning has the potential to identify biopsy targets using 1064 nm PAT and US imaging.
3. Sandpaper micro-machining method to fabricate fibers with diffuser ends is simple, safe, and resource efficient.
4. Angular coupling of light into cylindrical diffusing fiber improves forward propagating to side firing conversion to enable transurethral light deliver.

Future Directions

1. Improve transurethral fiber design by making more flexible and couple more energy
   - <OD core fiber; >pulse width
2. *Incorporate dual light illumination
3. *In vivo* imaging study
4. Exogenous contrast







Acknowledgments

CO-MENTORS

Ji-Xin Cheng, PhD
Young Kim, PhD

THESIS COMMITTEE

Craig Goergen, PhD
Timothy Masterson, MD

CHENG LAB MEMBERS

Pu Wang, PhD
Rui Li, PhD
Lu Lan
Yingchun Cao, PhD
Jie Hui, PhD
Jiayingzi Wu
Delong Zhang, PhD
Hyeon Jeon Lee, PhD
Yi Zhang
Tiffany Yang-Tran

COLLABORATORS

Michael Koch, MD
Liang Cheng, MD
Timothy Ratliff, PhD
Murat Dundar, PhD
Darren Roblyer, PhD
Sean Gorsky
Emil Atz

PURDUE ENGINEERING
WELDON SCHOOL OF BIOMEDICAL ENGINEERING

SCHOOL OF MEDICINE
INDIANA UNIVERSITY

FUNDING SOURCES

Walther Cancer Foundation
Indiana Clinical and Translational Science Institute
Bilsland Dissertation Fellowship

ADDITIONAL SUPPORT

IU MSTP
Raghu Mirmira, MD PhD
Maureen Harrington, PhD
Janice Receveur
Lauren Lynch
Weldon School of BME
Andrew Brightman, PhD
Sherry Harbin, PhD
Linda Doyle
Sandra May
Susan Hardy
Bill Schoenlein
BU Photonics Center and ECE Dept.