

# Volumetric Optical Imaging for Image Guided Therapy

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# Image Guided Therapy means . . .

- Adjustment of treatment course to ensure:
  - Complete treatment of target
  - Minimal damage to non-target } Balance between these goals based on clinical site
- Monitoring & Adaptation performed at appropriate
  - Time resolution (i.e. Surgery in real-time; Radiation per fraction)
  - Spatial resolution (smaller than required Treatment resolution)



# Presentation Overview

Introduce/Review REAL-TIME Image Guided Therapies using visible/Near-IR light for:

- Therapy
- Treatment monitoring

- **Phototherapies**

- Photodynamic & Photothermal
- Dosimetry & Monitoring using Photonics
- Prostate Cancer as a Model System

- **Fluorescence Guided Surgery**

- Image Guided tissue resection at margins
- How Quantitative Does it Need to Be?



## Why Optics?

- High Tissue Contrast across tissues
- Very Sensitive Detection
- High Dynamic Range
- Microscopic to Macroscopic
- Generally safe



## Why Optics?

- High Contrast
- Very Sensitive
- High Dynamic Range
- Microscopic to Macroscopic
- Generally safe

## Why not Optics?

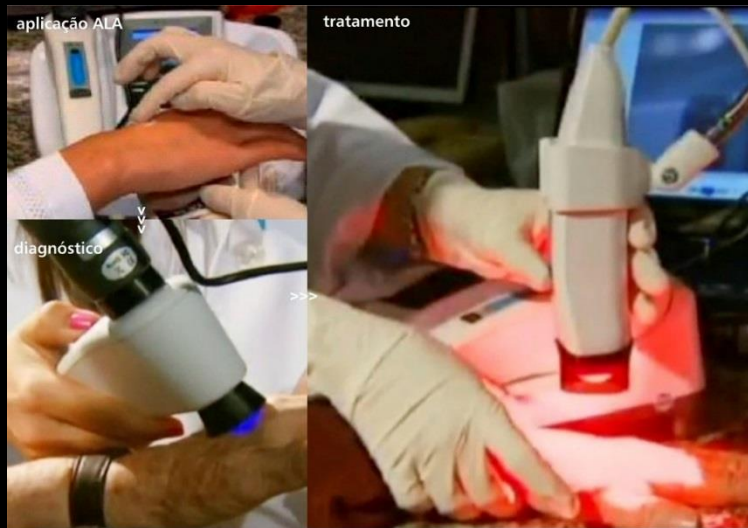
- Optical Scattering dominates limiting depth measurements
- Difficult to accurately measure optical properties
- Large variation in tissue optical properties
  - Between organs
  - Between people
  - But this is what gives us the useful info



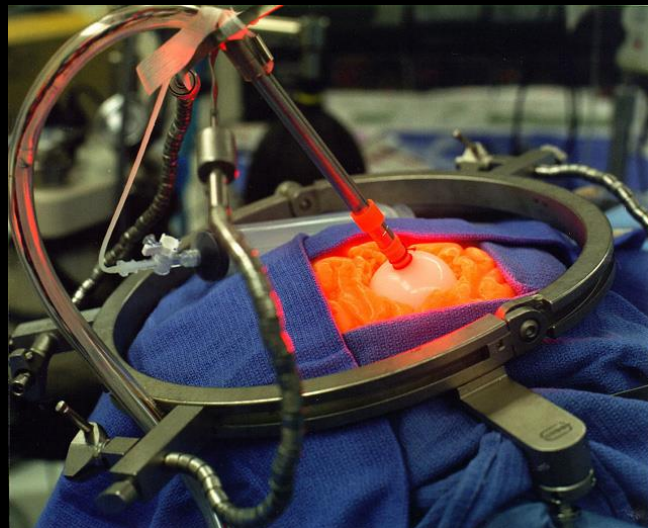
# Photodynamic Therapy Overview

- Based on Light Activated Agents: systemic or topical
  - Light or Drug alone has no therapeutic/toxic effect

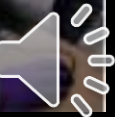
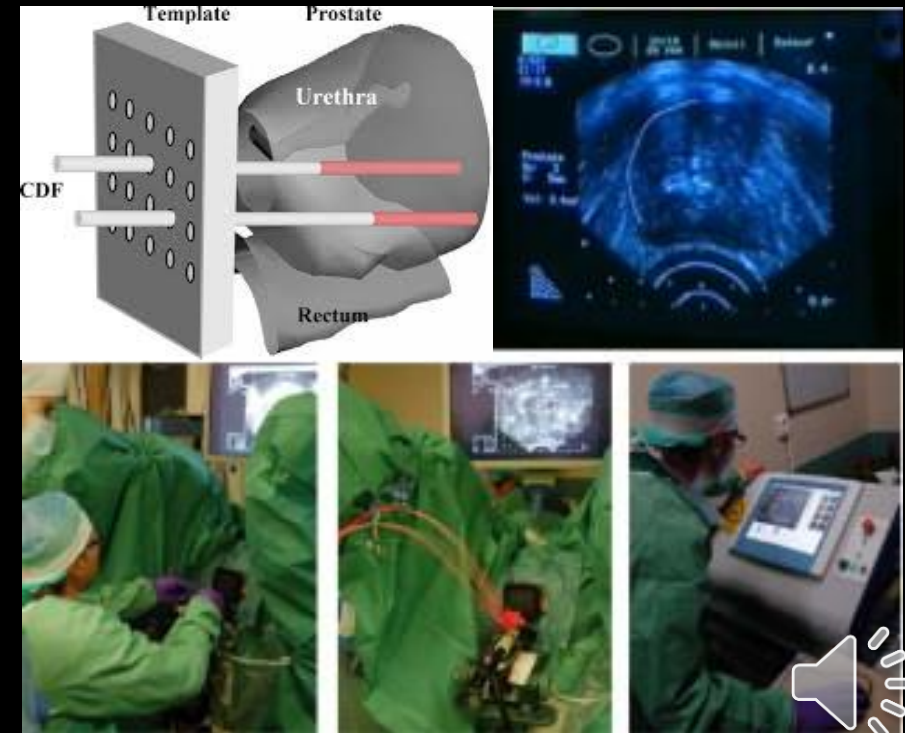
## Superficial: Skin



## Intraluminal: Neuro Resection

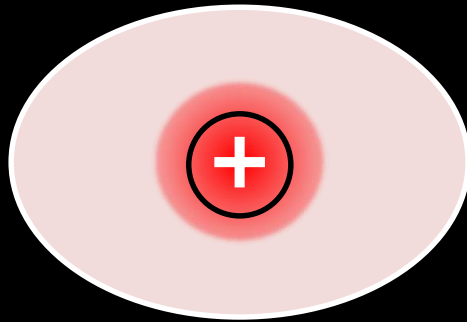


## Interstitial: Prostate

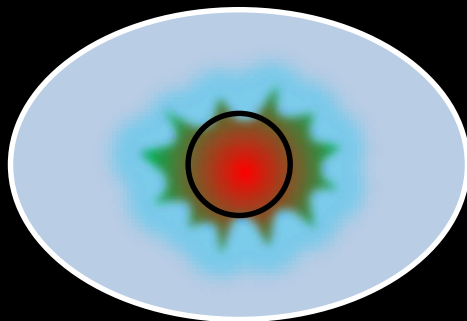


# Photodynamic Therapy Mechanism

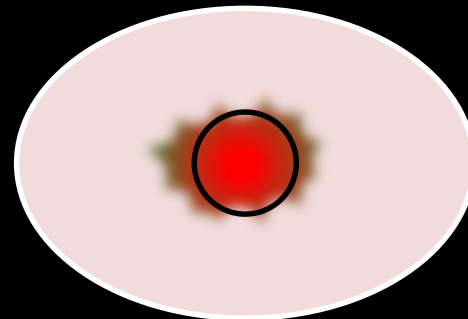
Light Distribution



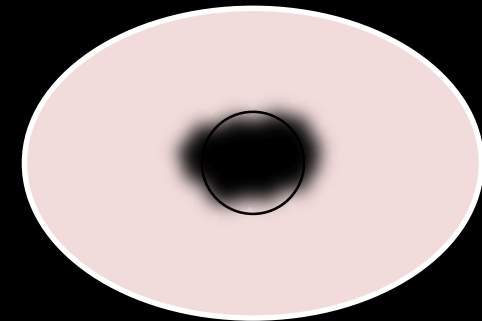
[PS]



Singlet Oxygen



$SOD_{threshold}$

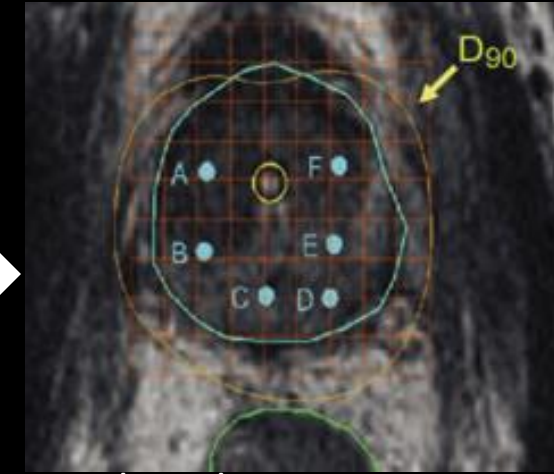
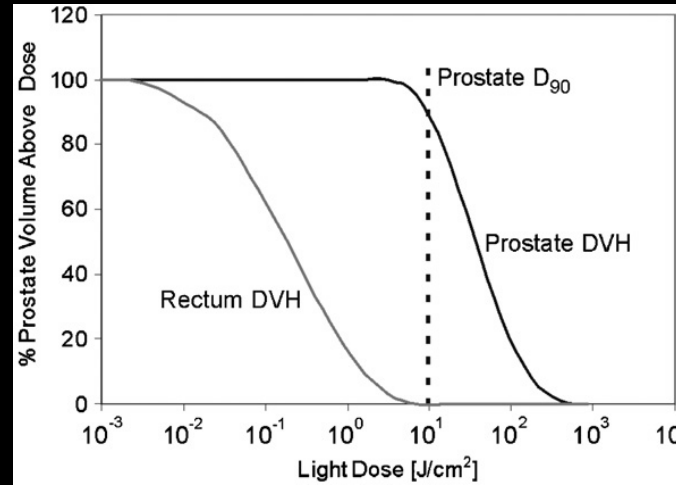
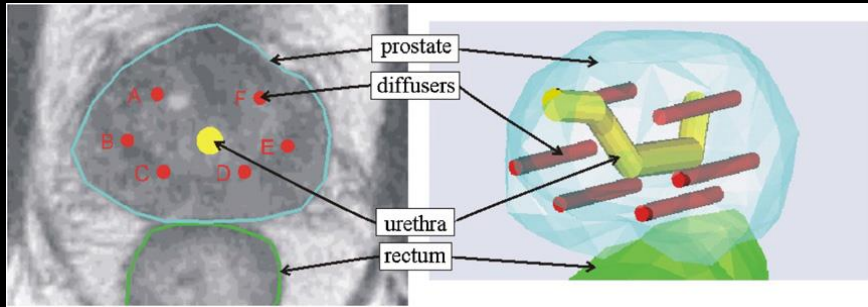


Death

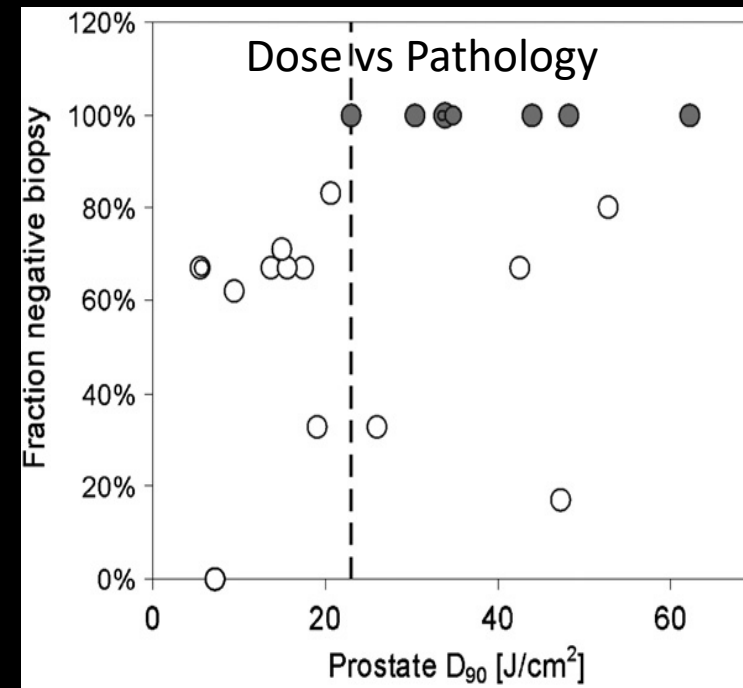
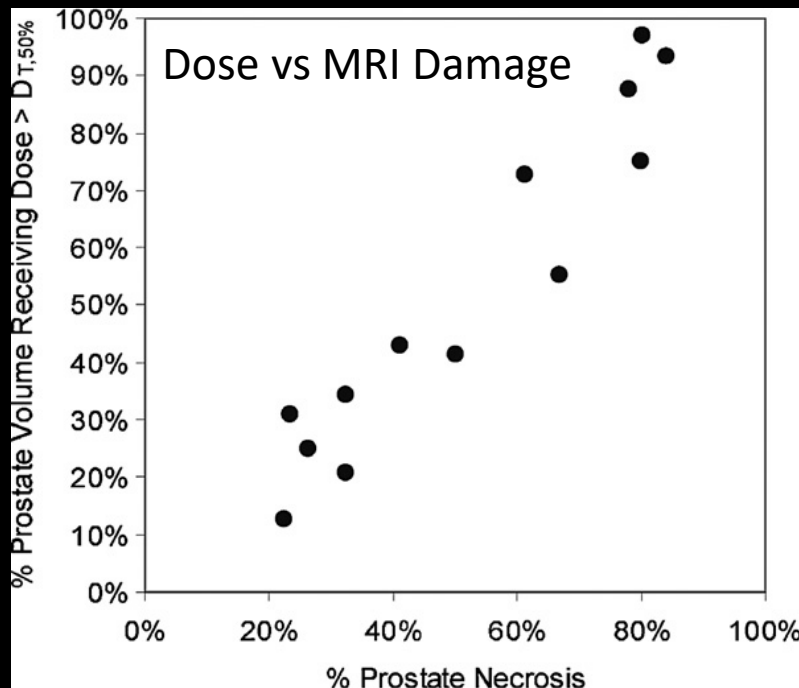


# Photodynamic Therapy Monitoring

## Comparing Explicit Dose to Response

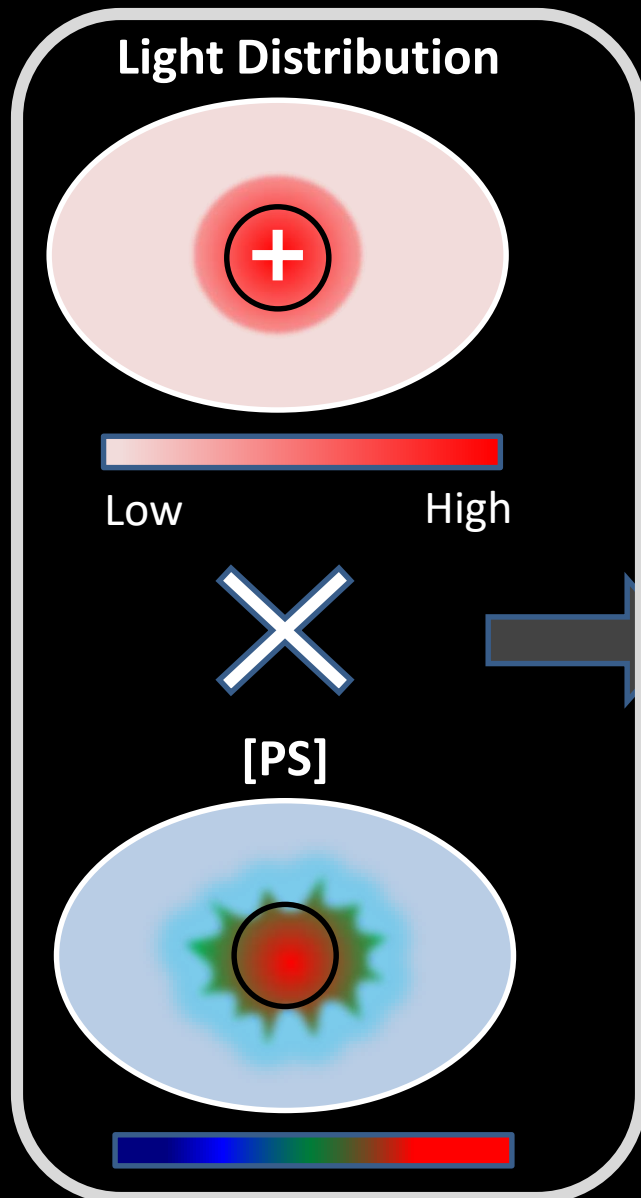


48hr Gd Contrast MRI



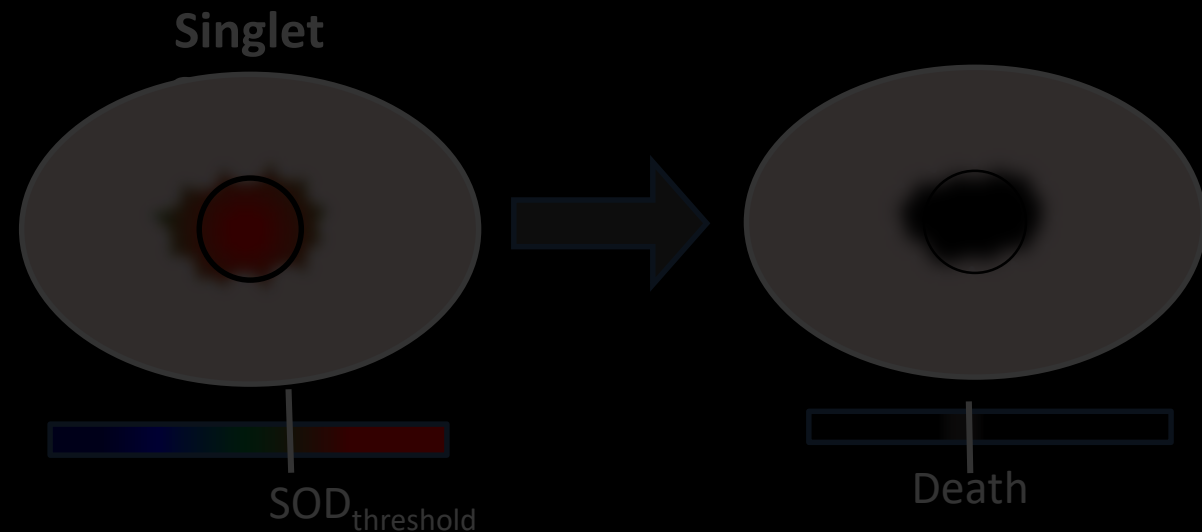


# Photodynamic Therapy Mechanism



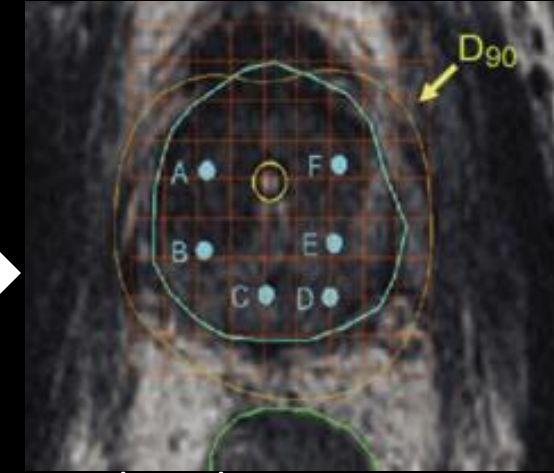
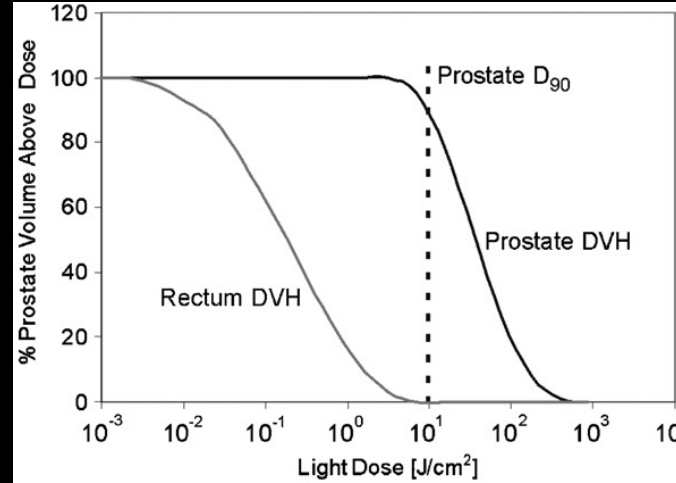
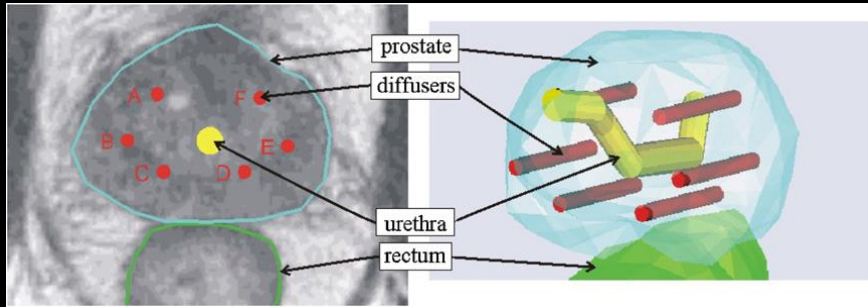
Explicit in situ Measurements of "Inputs"

- Photosensitizer, light fluence, pO<sub>2</sub>
- Vary during treatment

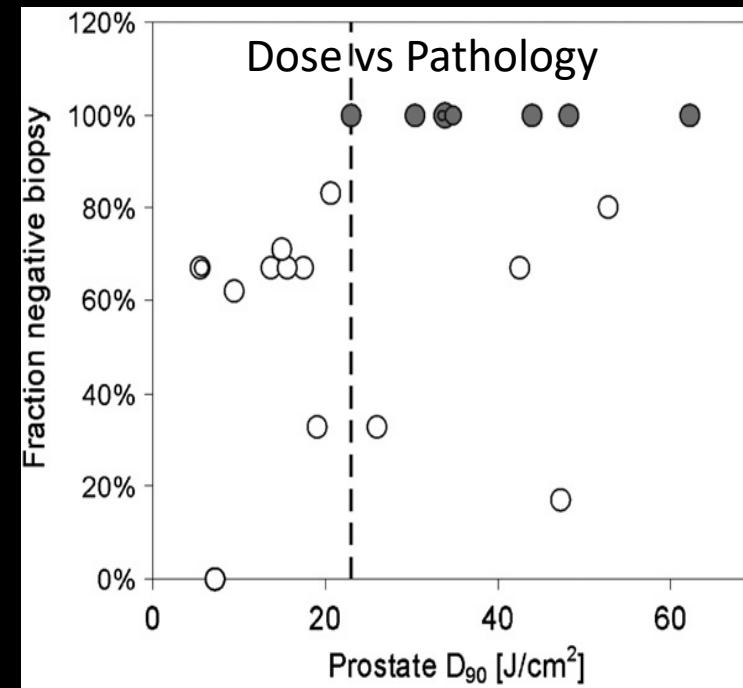
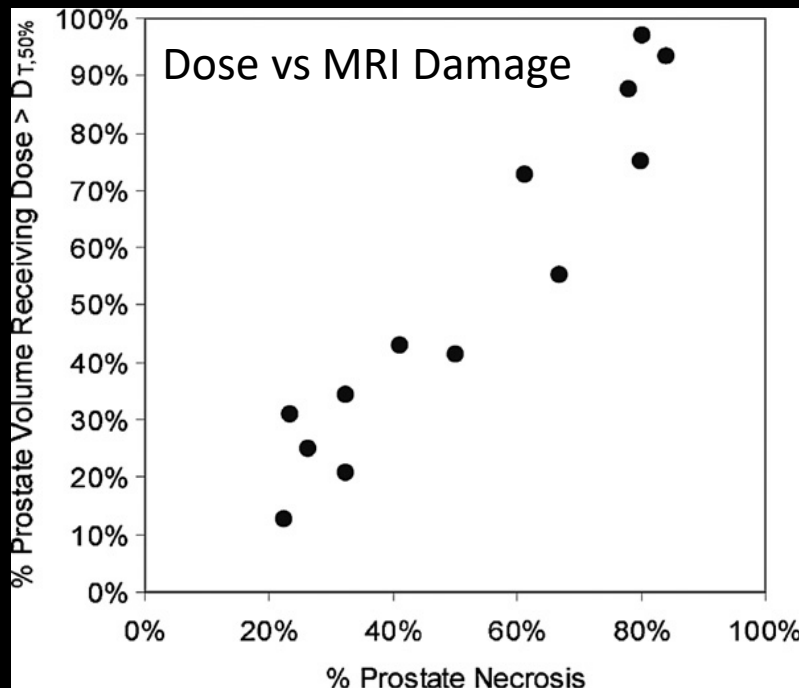


# Photodynamic Therapy Monitoring

## Comparing Explicit Dose to Response

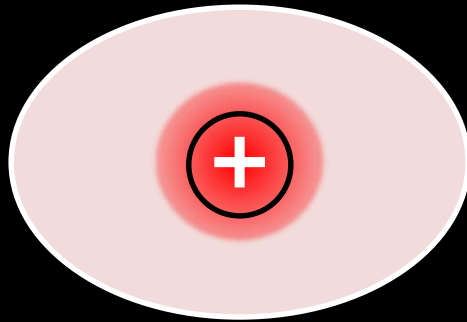


48hr Gd Contrast MRI

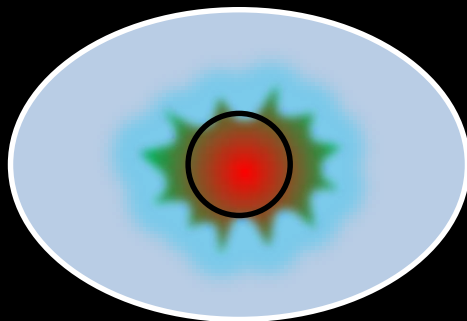


# Photodynamic Therapy Mechanism

Light Distribution



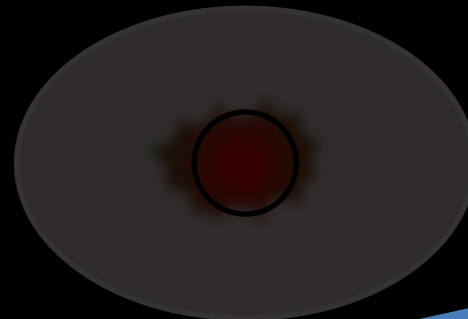
[PS]



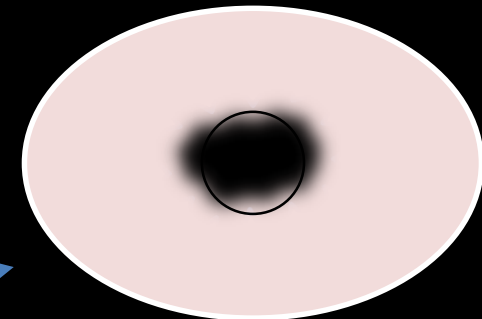
Surrogate of Tissue Damage

“Photobleaching” correlates with Tissue Damage

Singlet Oxygen



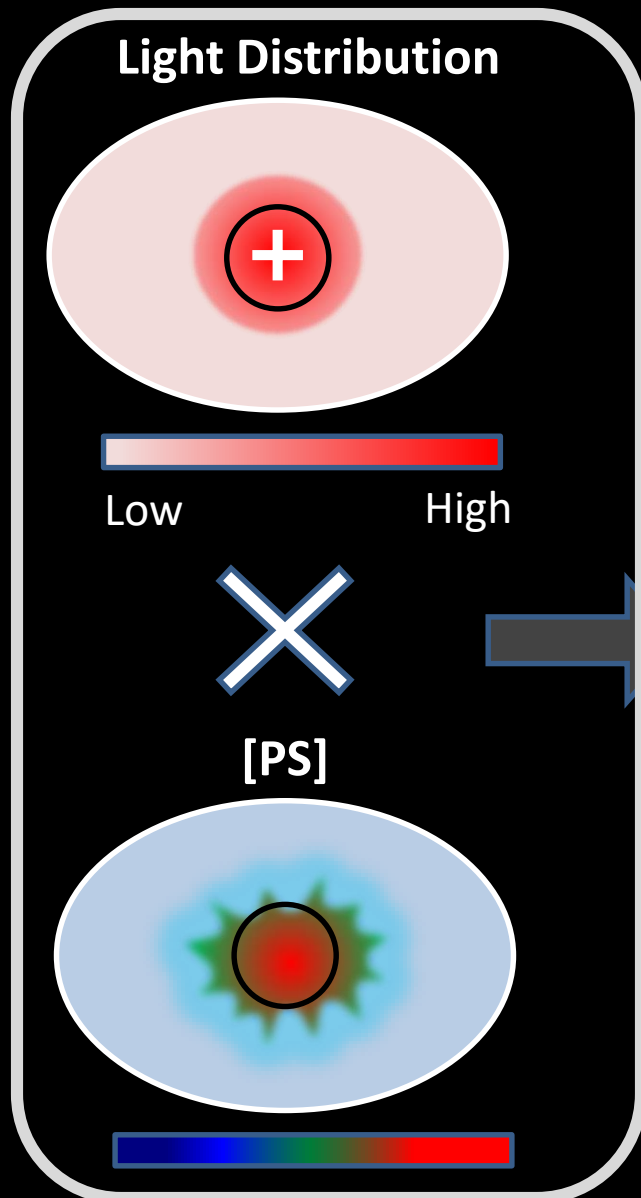
$SOD_{threshold}$



Death



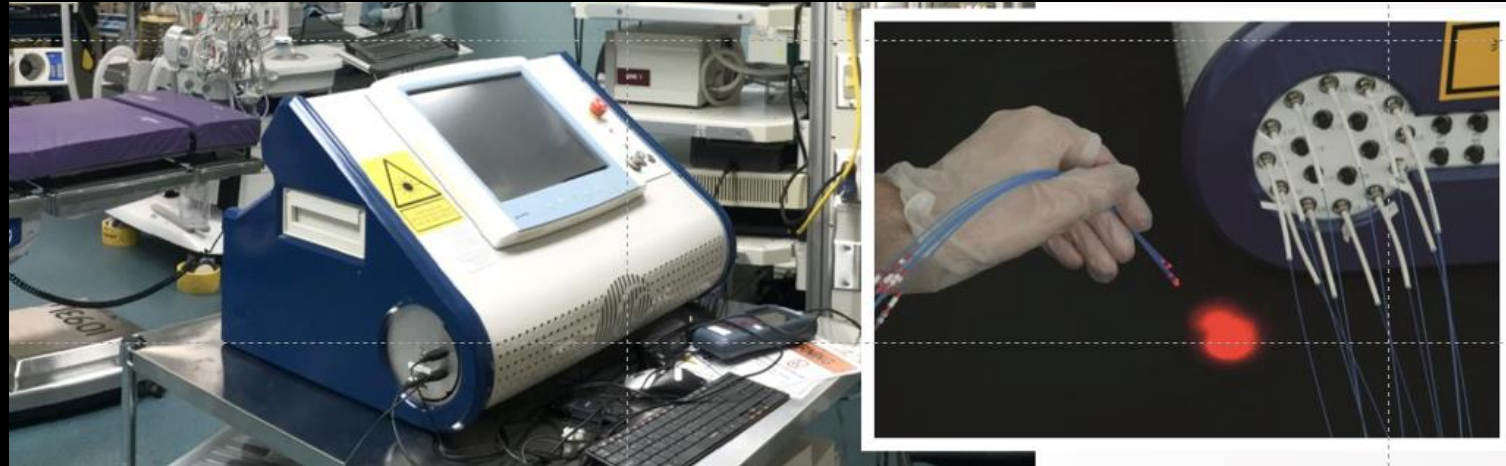
# Photodynamic Therapy Monitoring



## Measurements of "Inputs"

- Photosensitizer, light fluence, pO<sub>2</sub>
- Vary during treatment

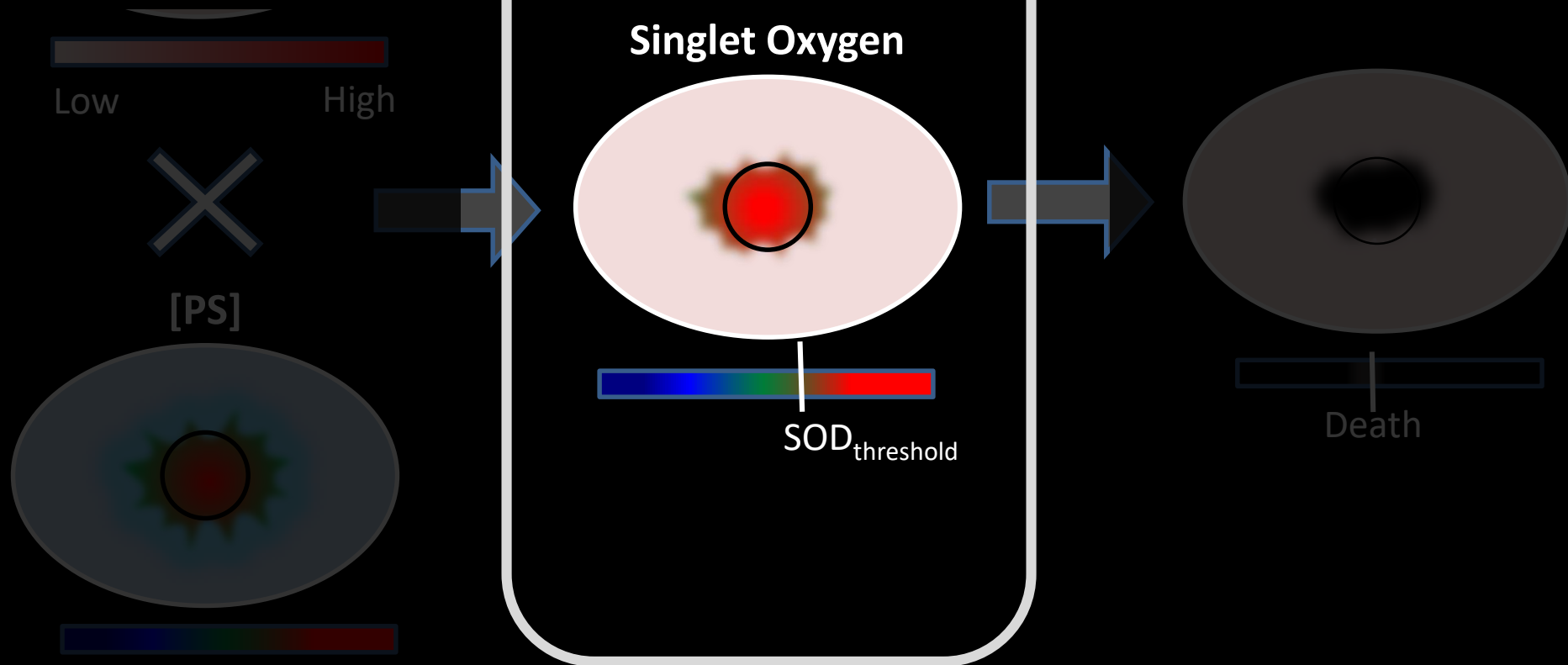
SpectraCure: Each Fiber used to deliver treatment light, and take measurements (fluorescence, light dose)



# Photodynamic Therapy Monitoring

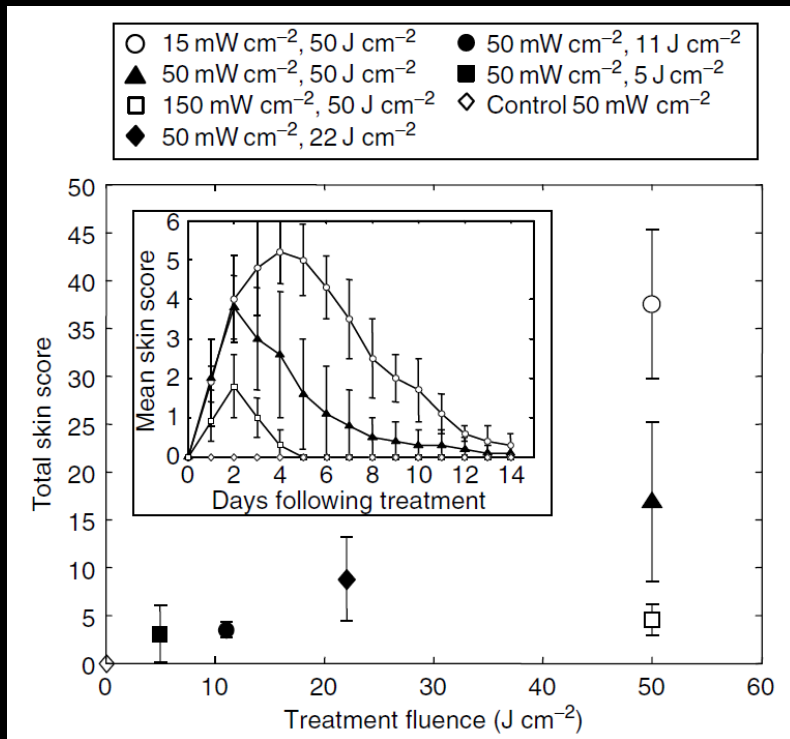
## Measurements of Singlet Oxygen

- **Reactive agent**

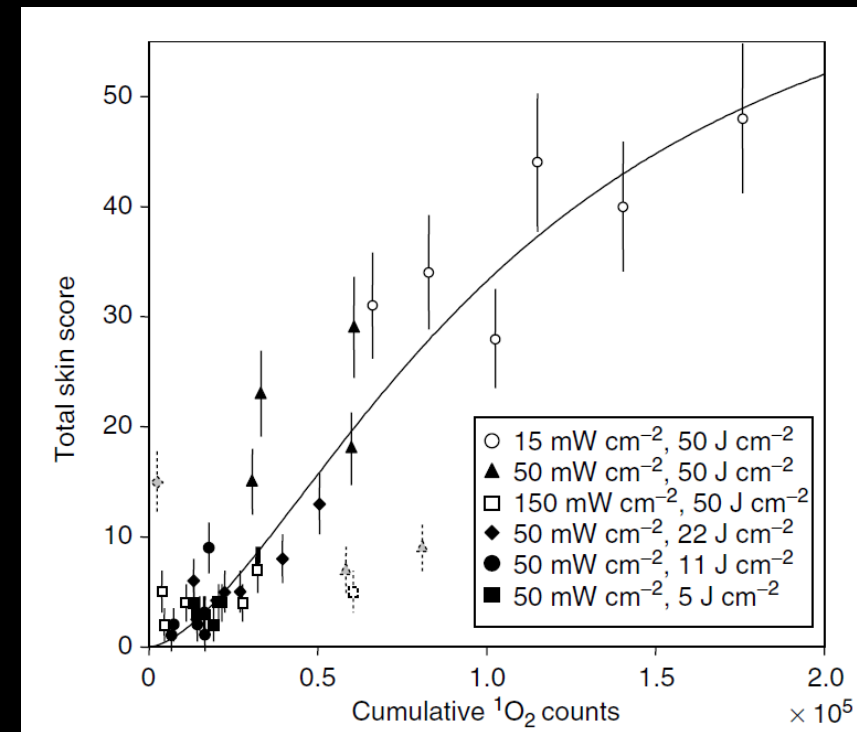


# Photodynamic Therapy Mechanism

## Variable Treatment Delivery Parameters



## Variation collapses when using Singlet O<sub>2</sub>



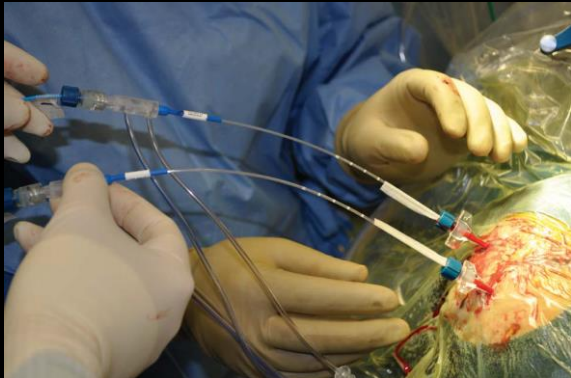
- Singlet O<sub>2</sub> measurements using luminescence are very difficult
  - Weak signal, poor detectors



# Photothermal Therapy Overview

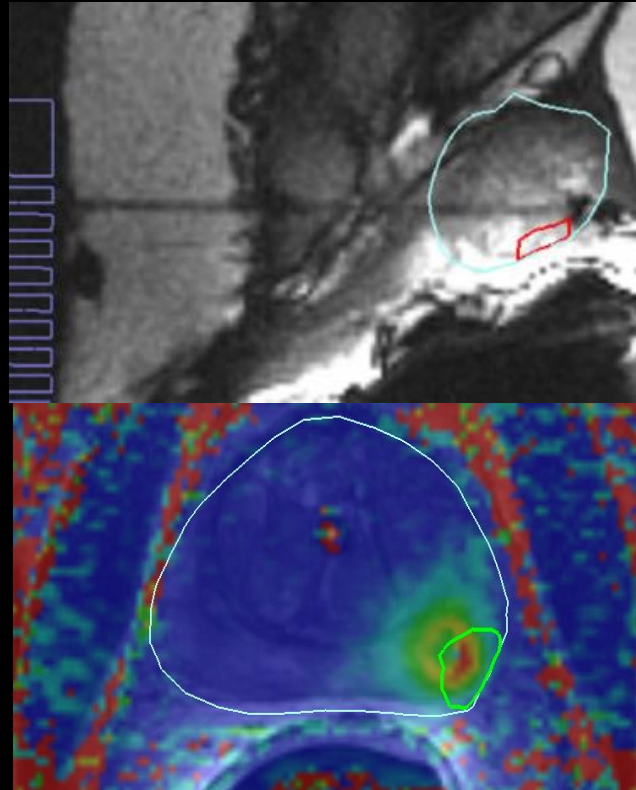
- Thermally-induced coagulation of tissue (like RFA, HIFU)
  - Just different methods of putting energy into the tissue
- Interstitial Irradiation at powers that lead to increased tissue temperature

## Neurology

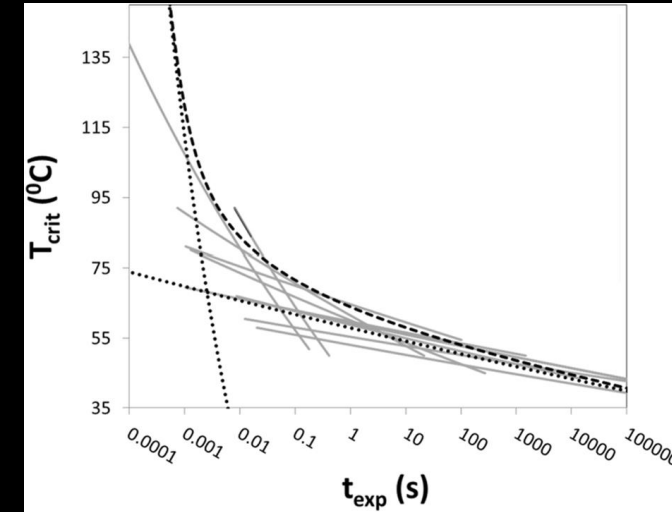
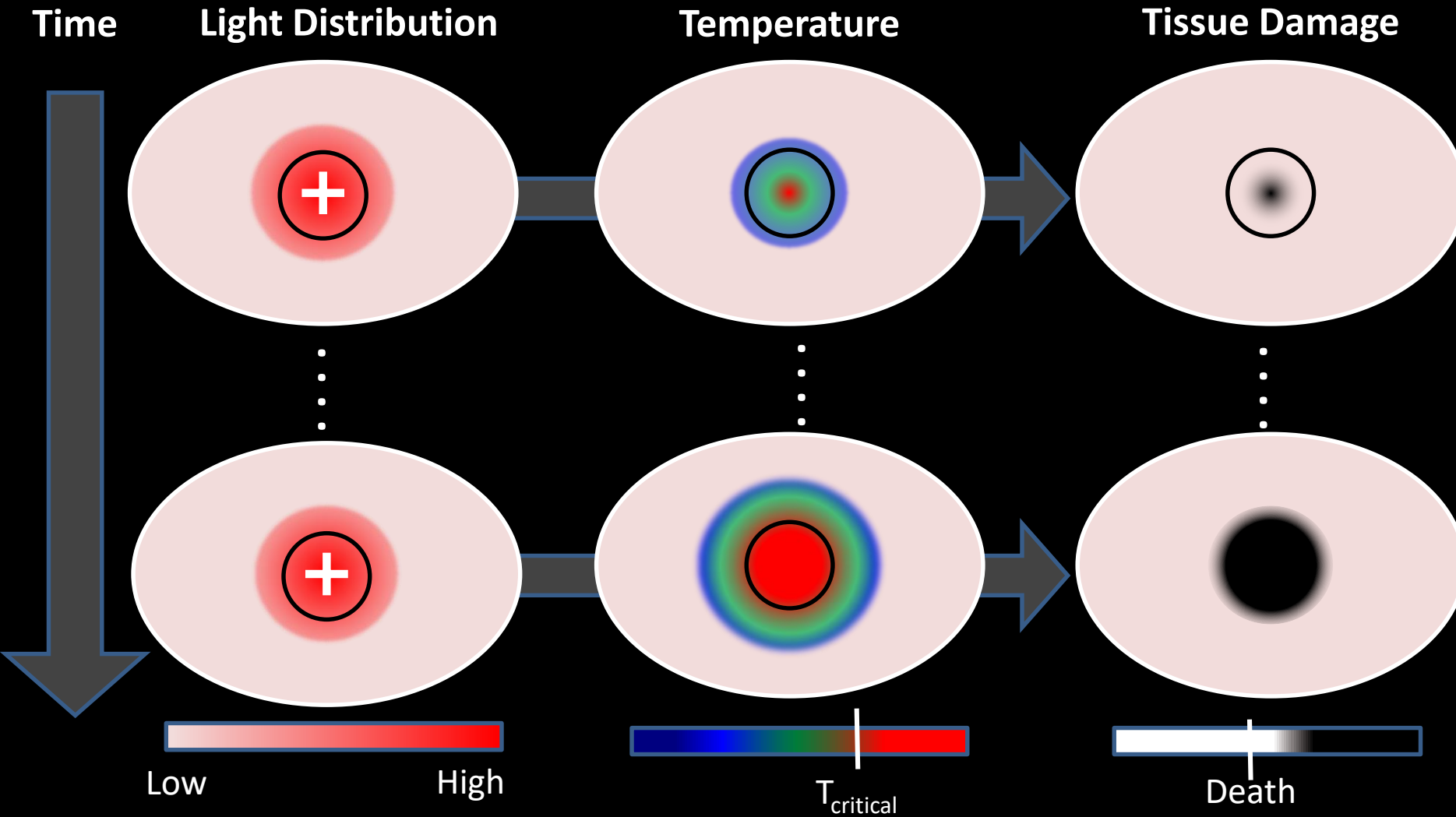


Medtronic/Visualase

## Prostate



# Photothermal Therapy Mechanism



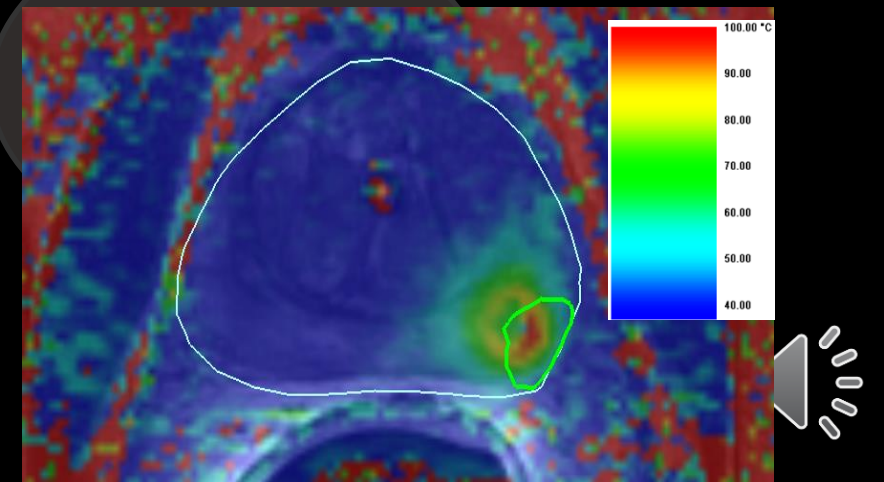
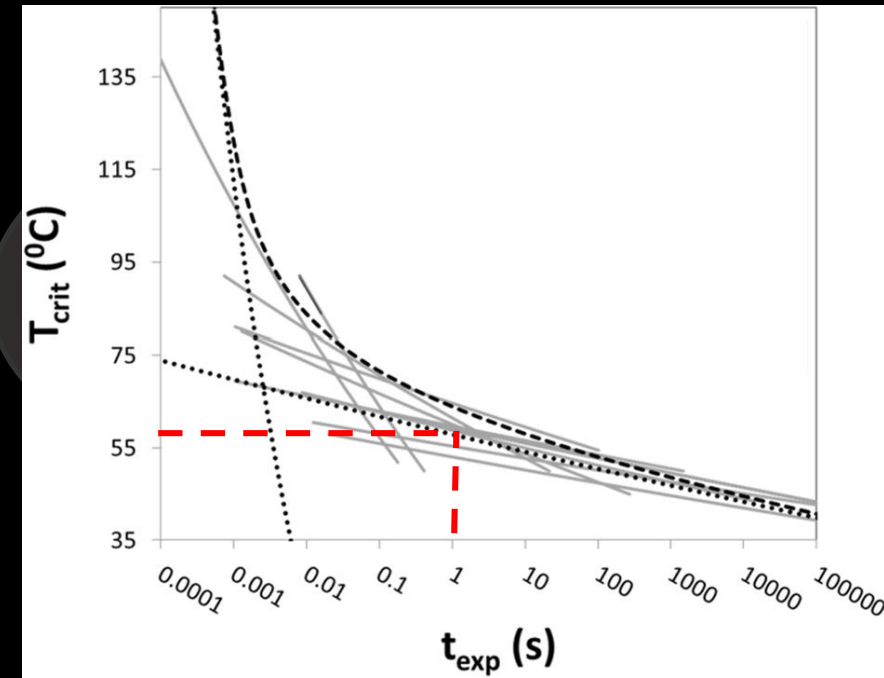
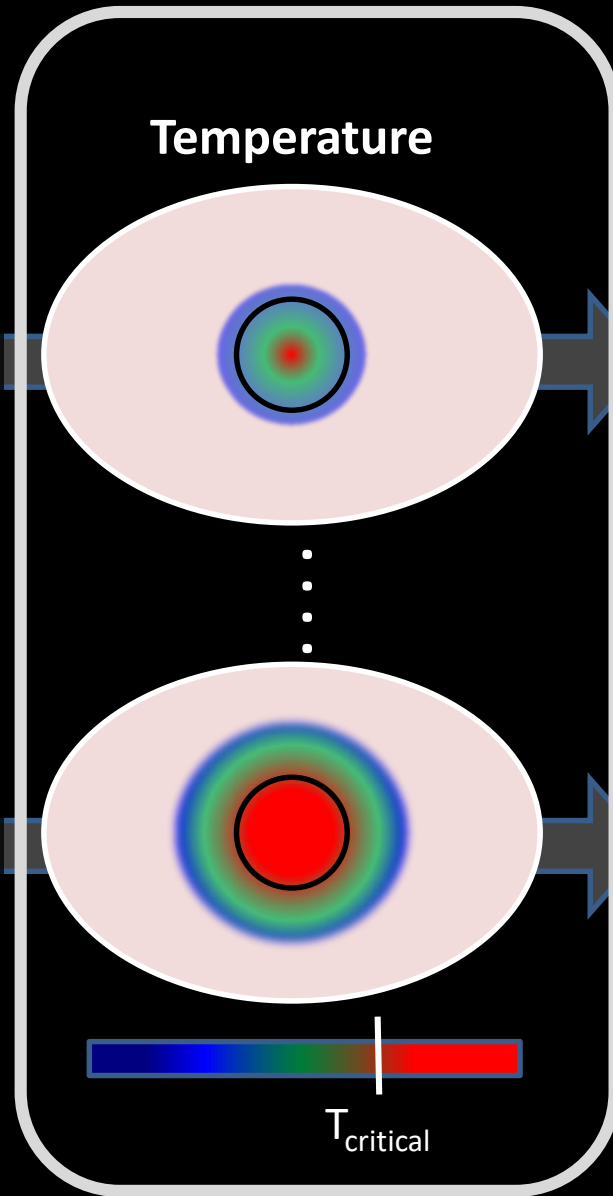
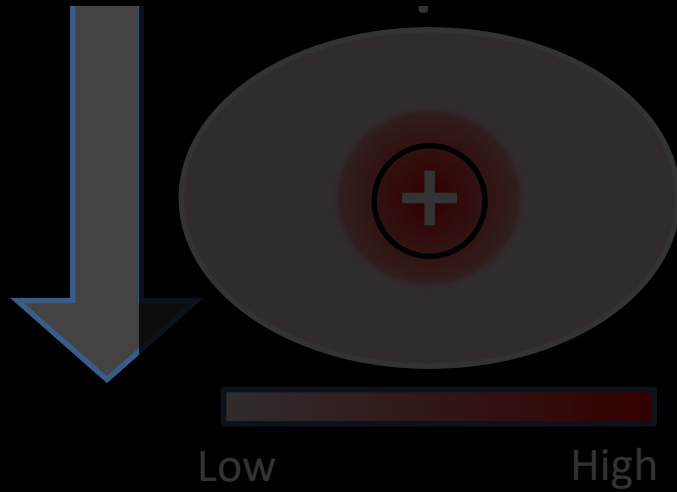


# Photothermal Therapy Monitoring

## Surrogate

Temperature used as surrogate of tissue response ( $\sim 55^{\circ}\text{C}$ )

Point thermocouples  
Fiber optic Probes  
MR Thermometry

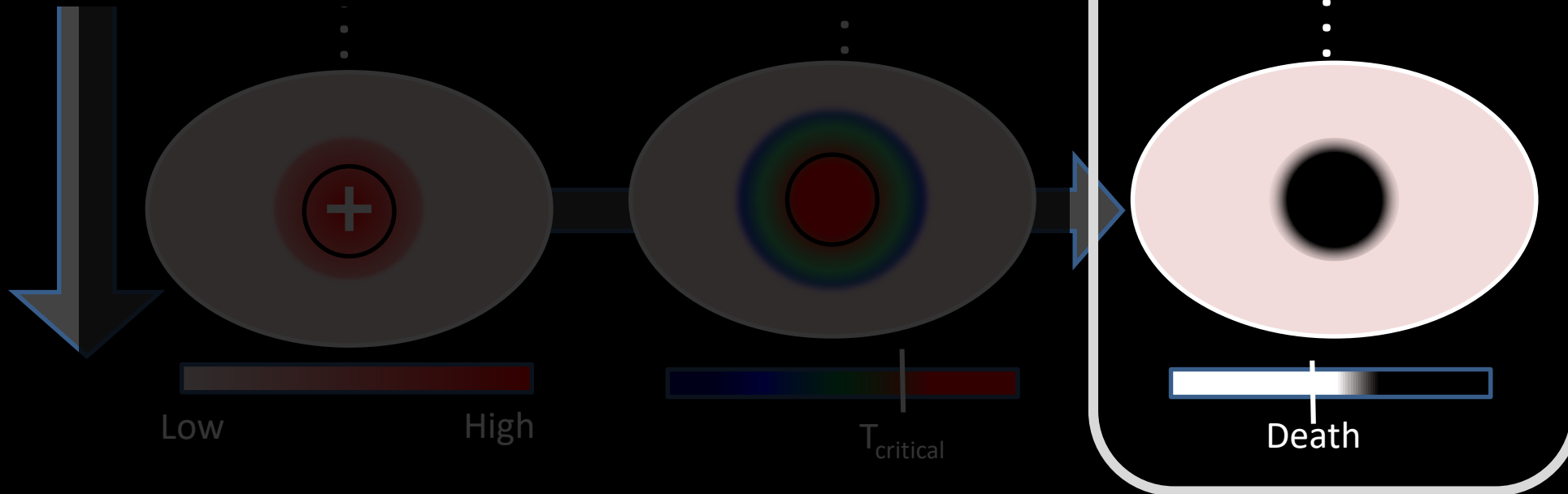


# Photothermal Therapy Dosimetry

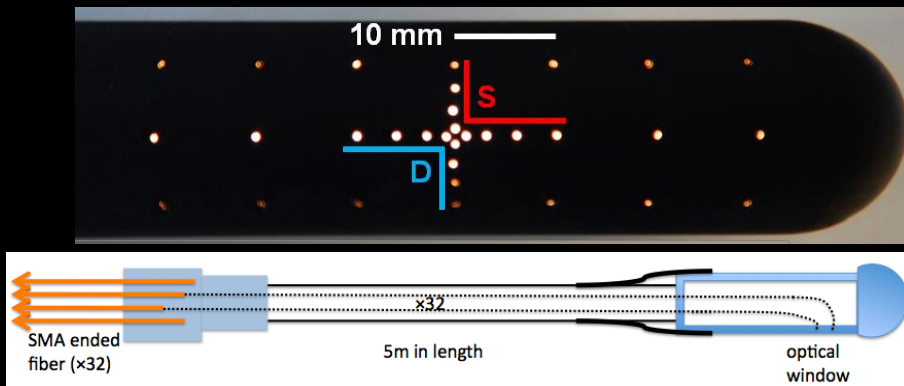
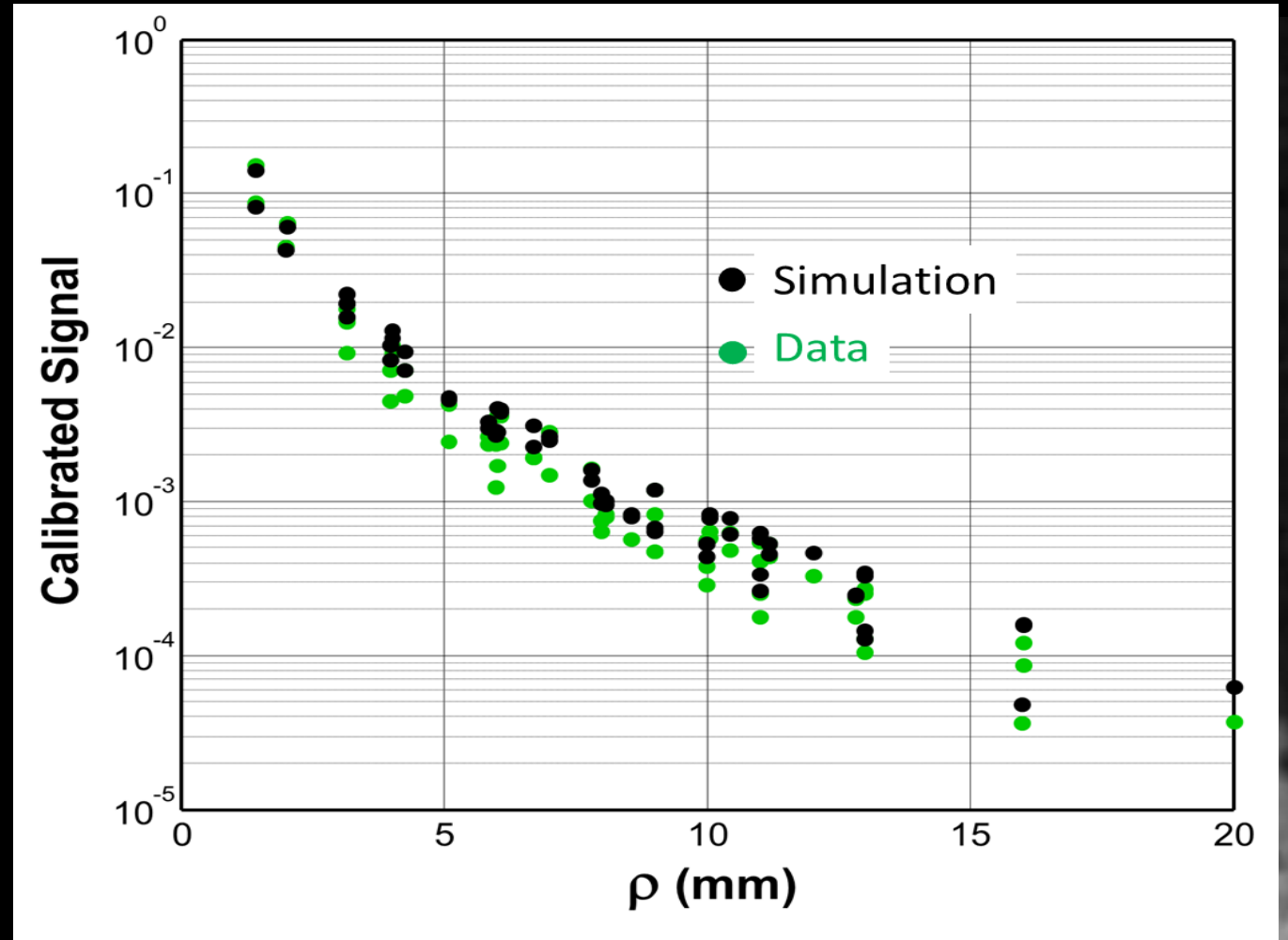
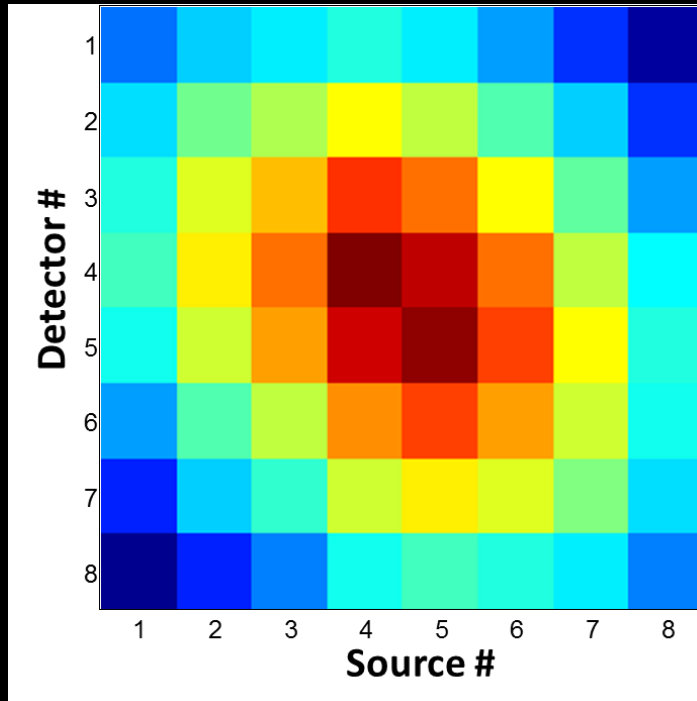
## Direct Monitoring

Real-time measurement of tissue changes

Diffuse Optical Tomography  
(Photoacoustic)  
(Ultrasound)

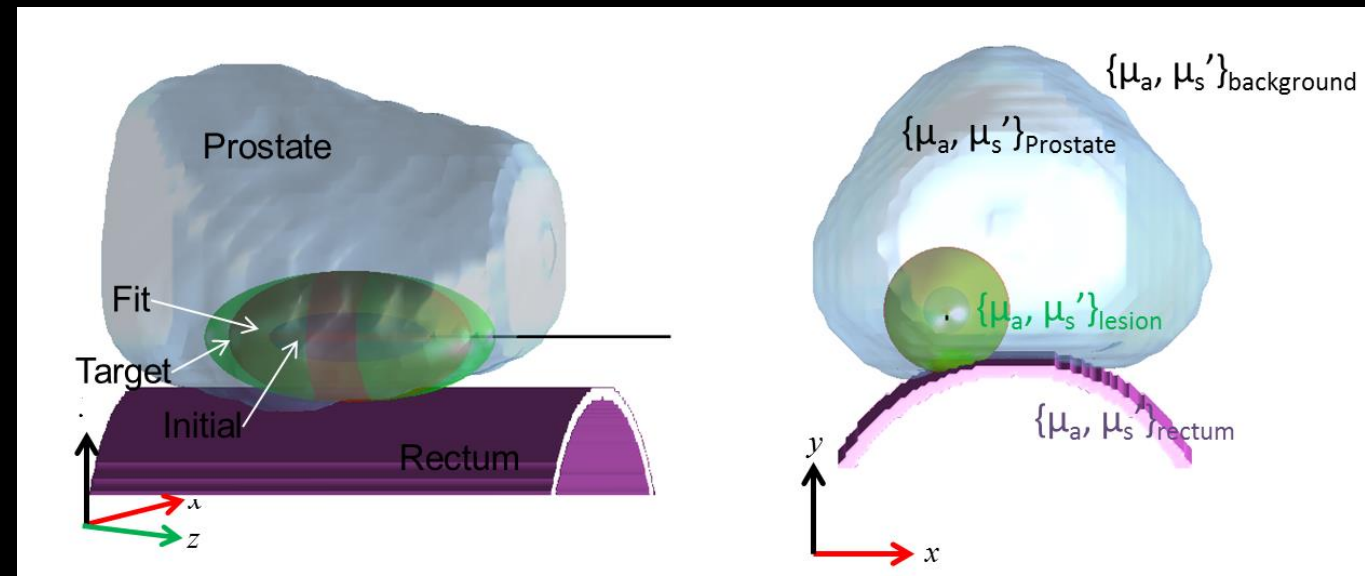
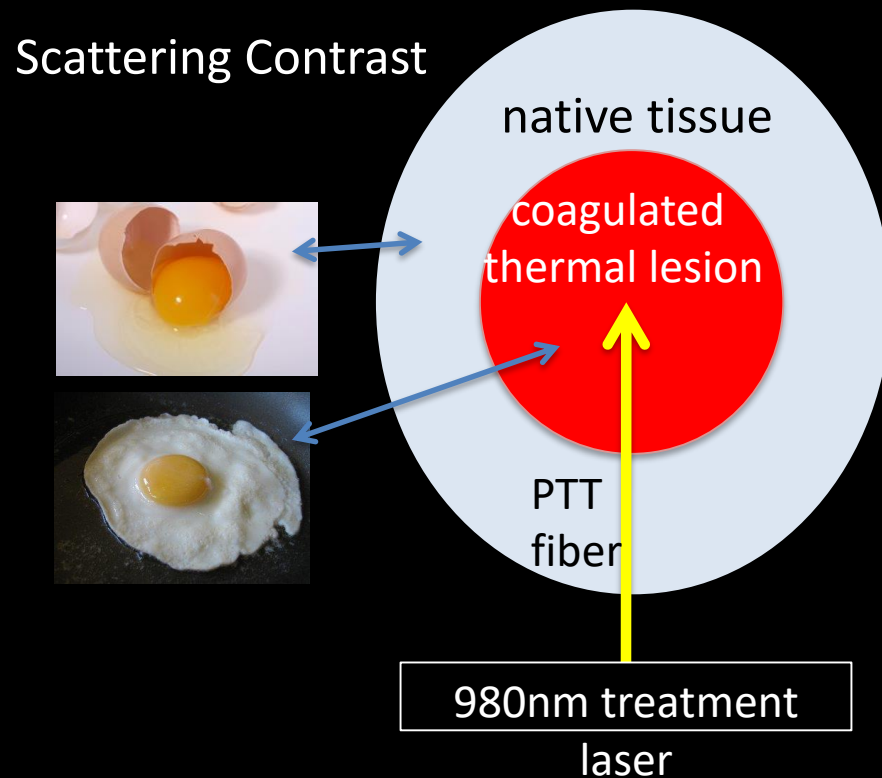


# Prostate TR-DOT System



# DOT Reconstruction of Lesion

- FEM Model of Light Transport through Tissue (NIRFAST)
- For PTT, lesions are generally ellipsoid
- **Constrain** inverse problem by using **shape parameters** rather than nodal optical properties
- Only max of 4 fitting parameters: **Ellipsoid size and lesion optical properties**

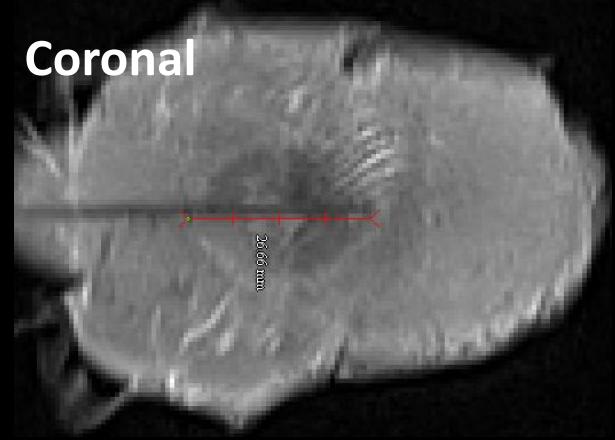
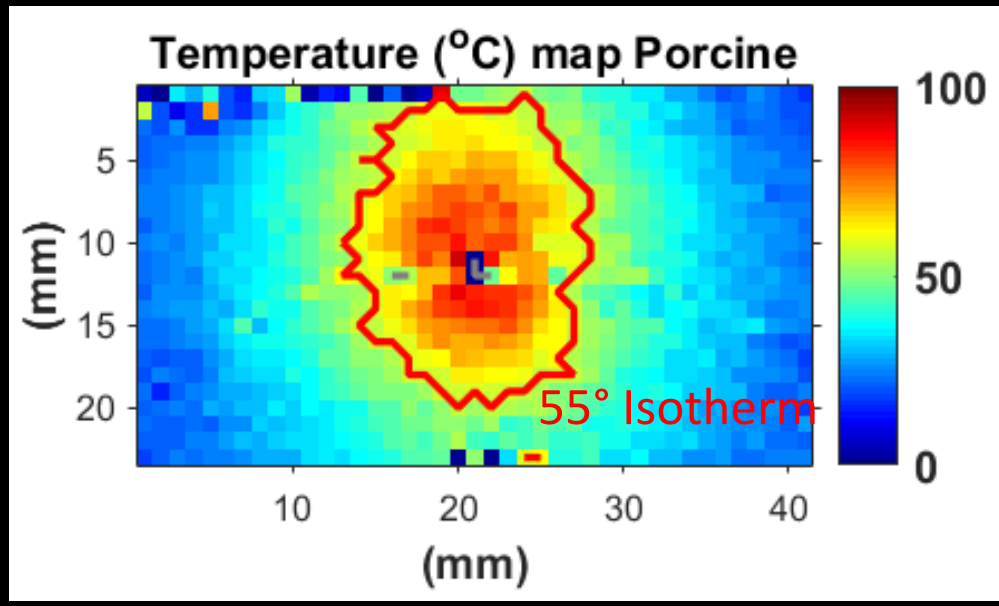
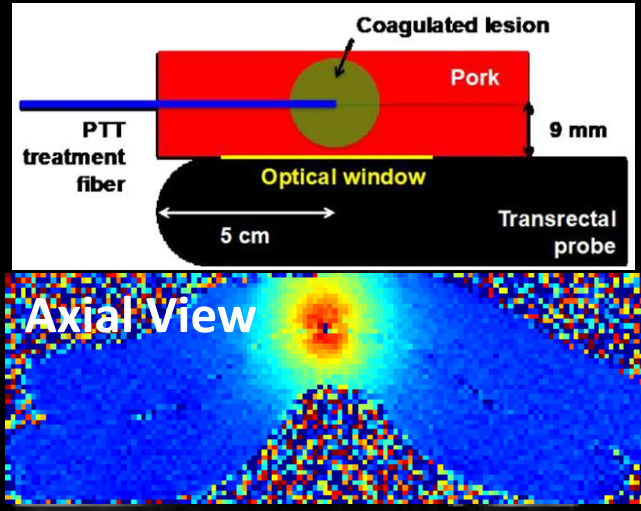


RA Weersink, Journal of Biomedical Optics, 2017. 22(4): p. 45004



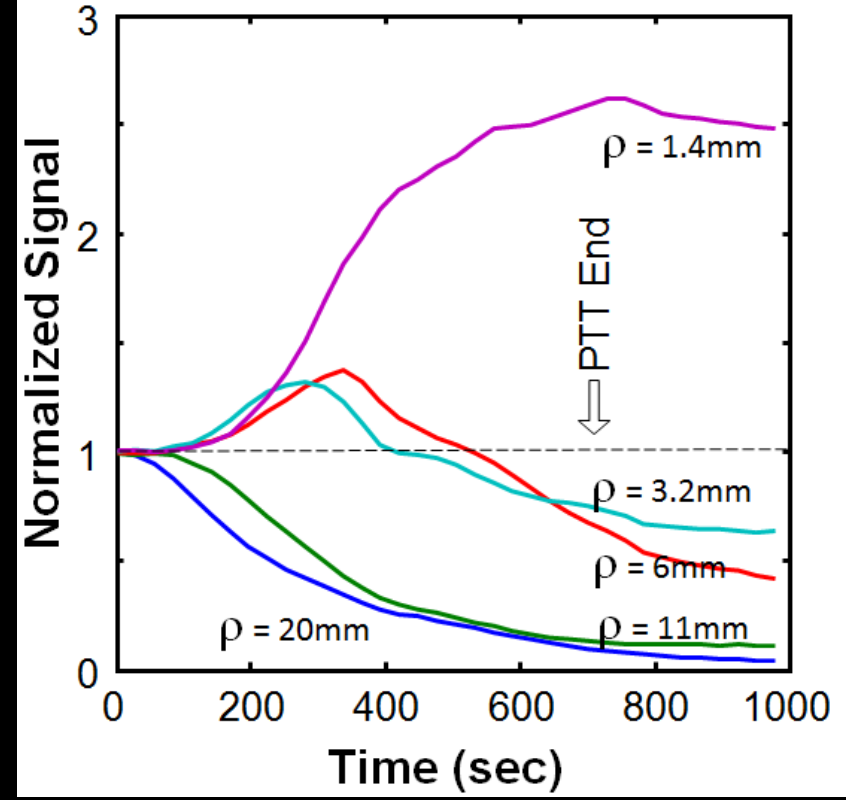
# Ex Vivo Validation of Treatment Monitoring

## MRI Validation



- PTT at 5W for 12min.
- DOT Monitoring at 750nm.
- MRI 1\*1\*3mm.

## DOT Measurements

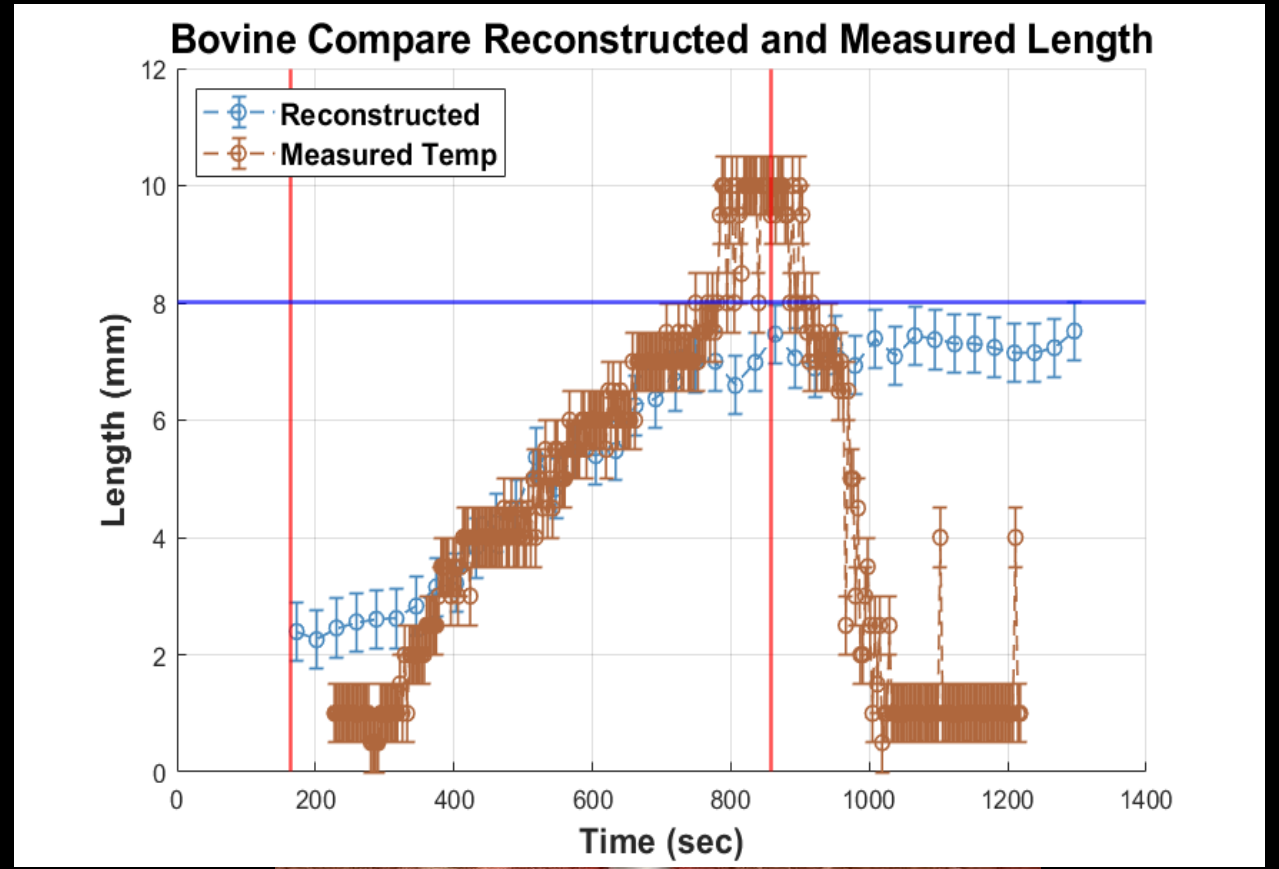
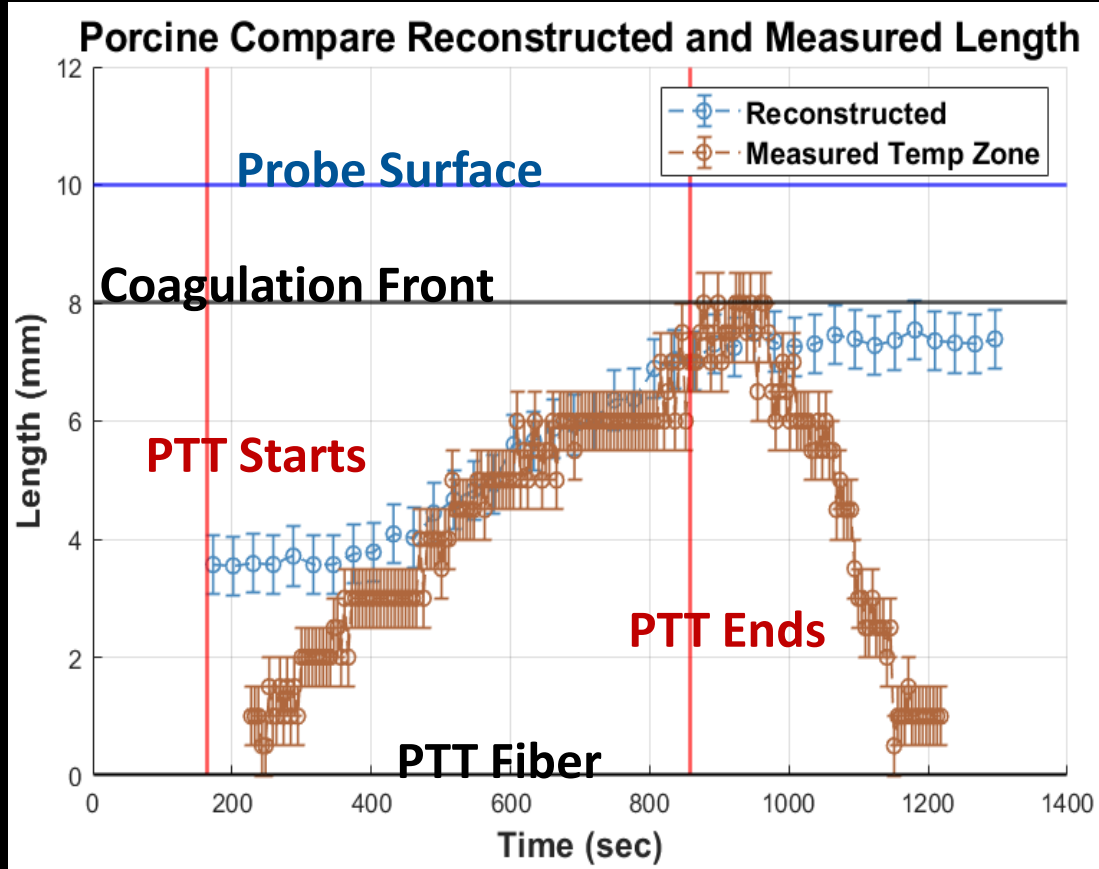


C. Li, Masters Thesis

Does the DOT-predicted Lesion Match  $55^{\circ}$  Isotherm line

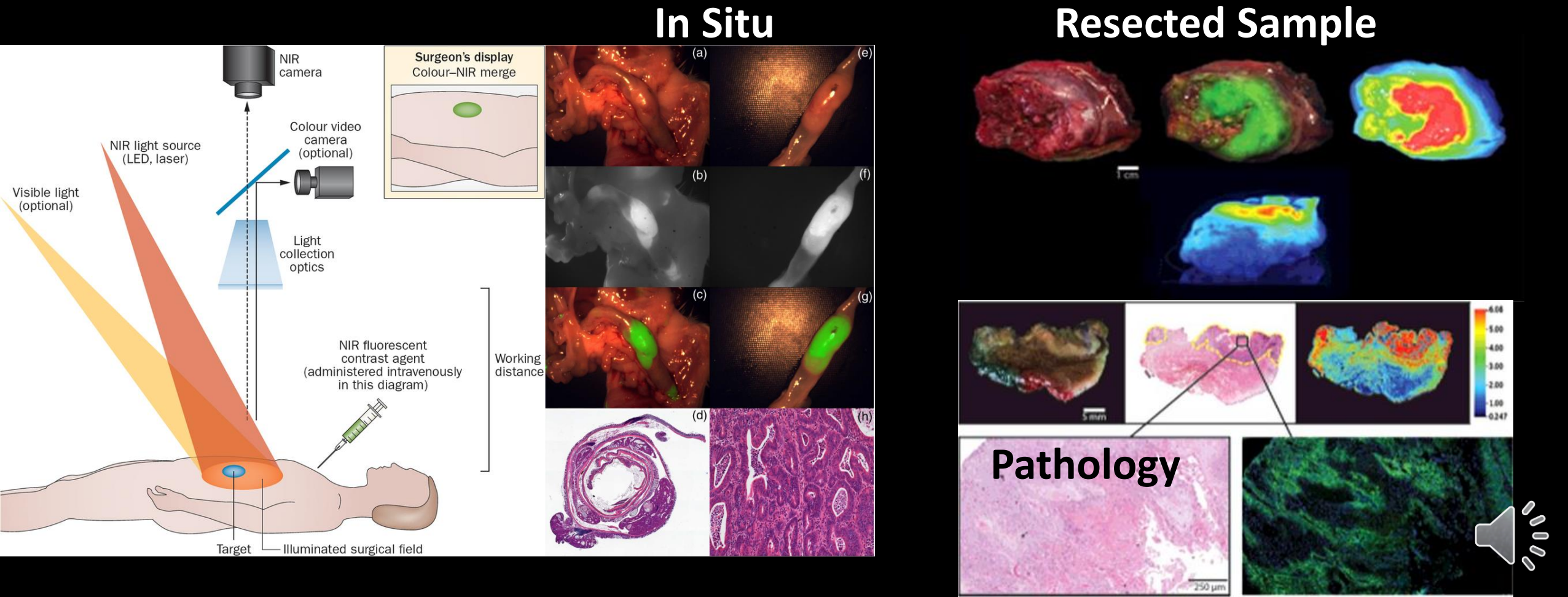


# DOT Reconstruction vs MR-Thermometry

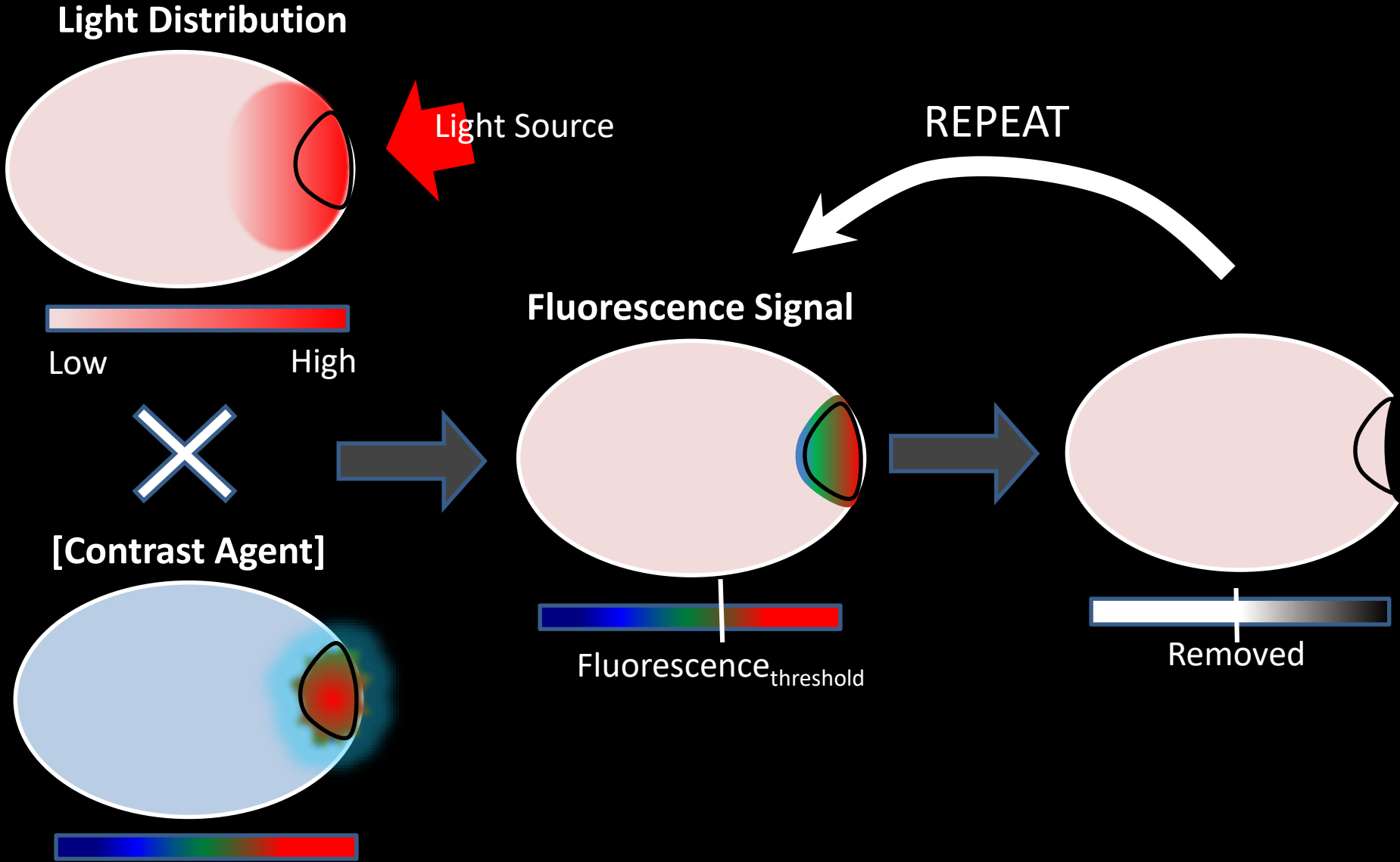


# Fluorescence Guided Surgery Overview

- Tumor Targeted Fluorescence Contrast Agents guide surgical resection
- Goal is reducing positive margins



# Fluorescence Guided Surgery Mechanism





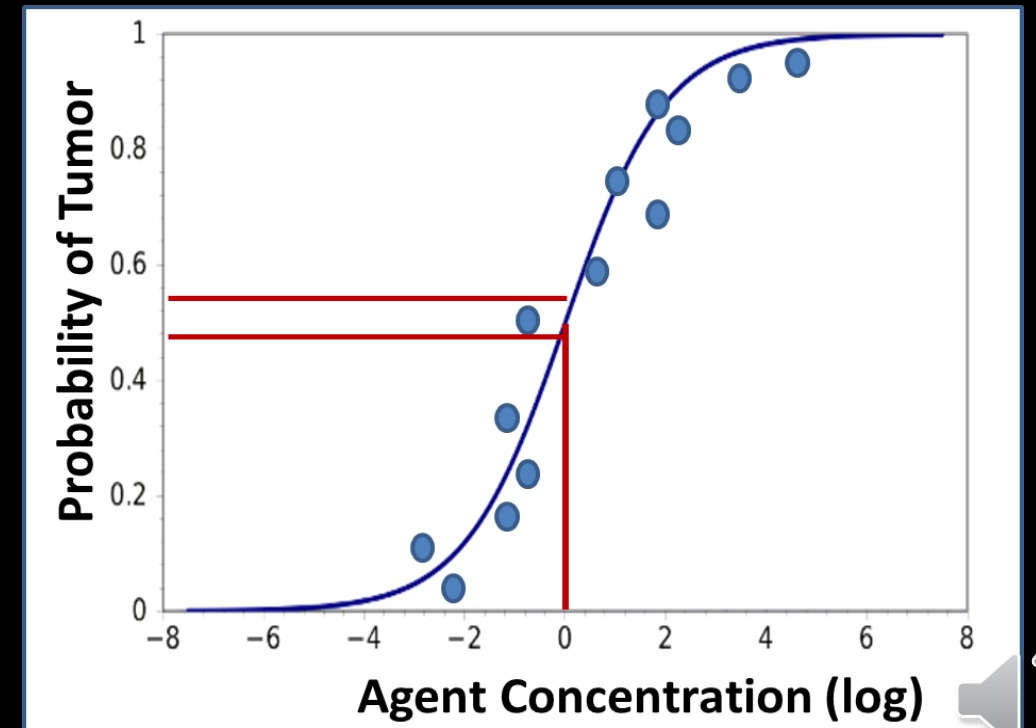
# Limitations of Current FGR Technique

- Image interpretation is Qualitative, Subjective
- Removal of only “Strongly Fluorescing” Tissue
- Sub-surface tumor is not localized, even if fluorescence is visible



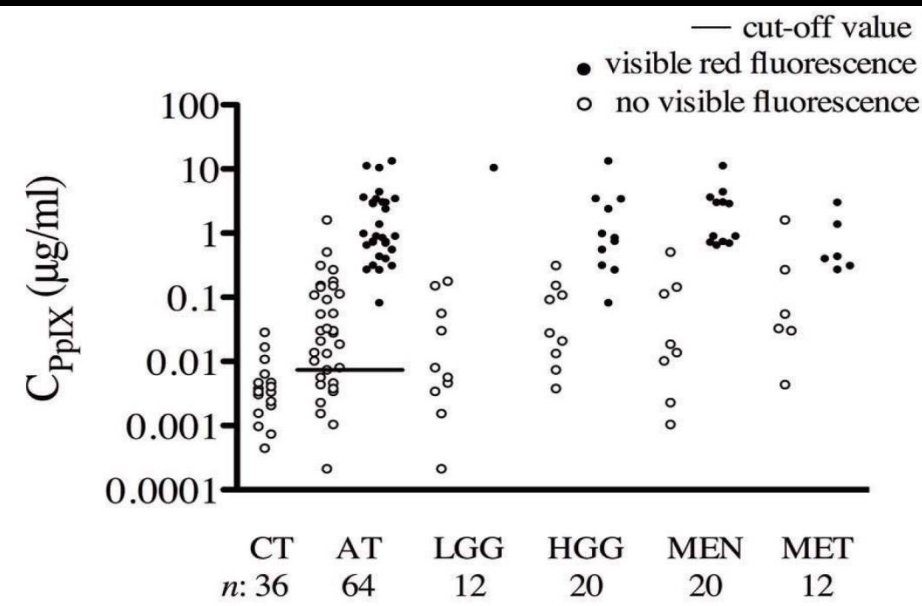
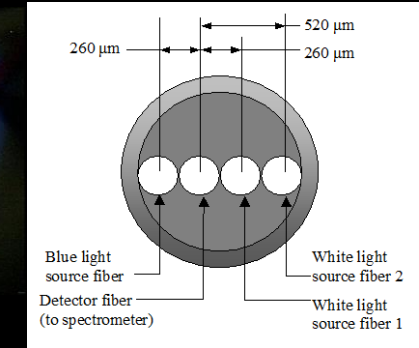
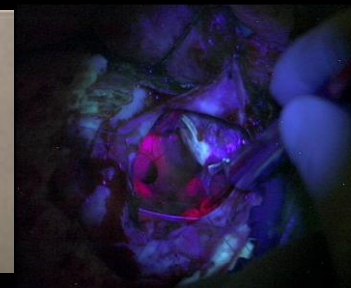
## GOAL: MAKE FGR QUANTITATIVE

- Superficial or Volumetric Reconstruction of Agent Concentration
- Correlate to Probability of Tumor



# Point Fluorescence Measurements

- Combination of **white light reflectance** and **fluorescence** to extract tissue concentration
- Reflectance measurement “corrects” for varying optical properties in each patient



## High-grade glioma patients

	Sensitivity (%)	Specificity (%)
Zeiss OPMI Pentero	63	83
<b>[PpIX] from the qF probe (?g/mL)</b>	<b>88</b>	<b>93</b>
<b>Linear discriminant analysis from probe data</b>	<b>93</b>	<b>96</b>

P.A. Valdes et al. *J. Neurosurgery*, 2011

Orders of magnitude variability from point to point and patient to patient even for the same pathology

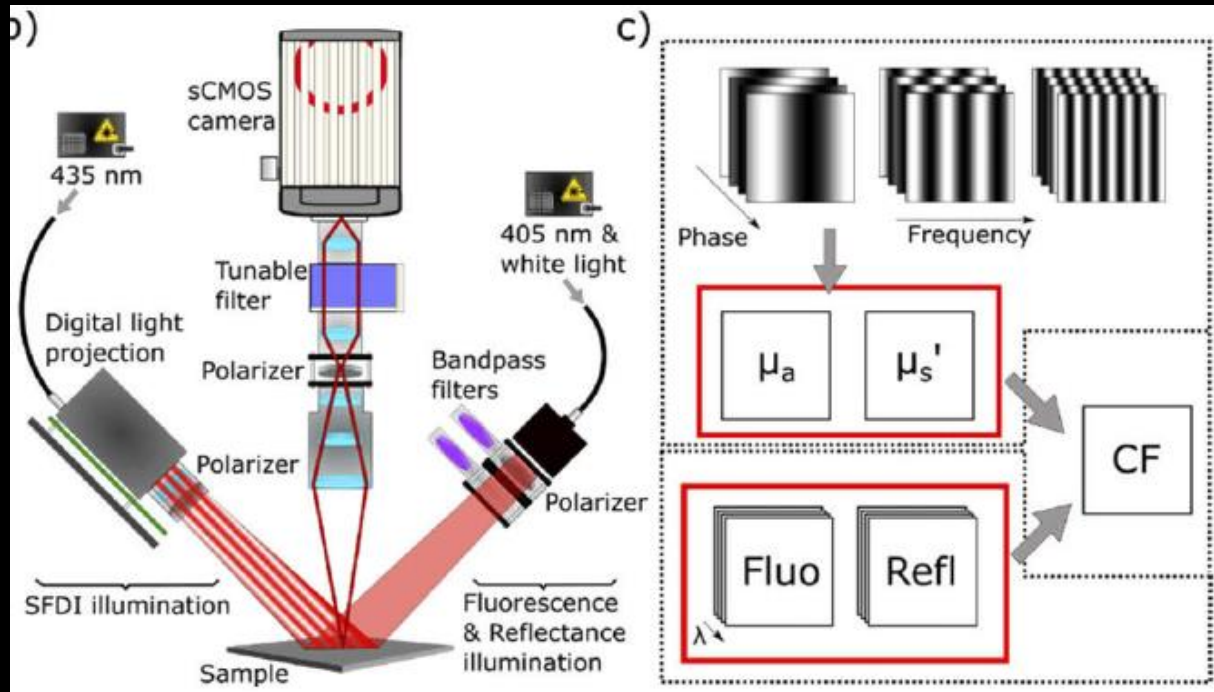
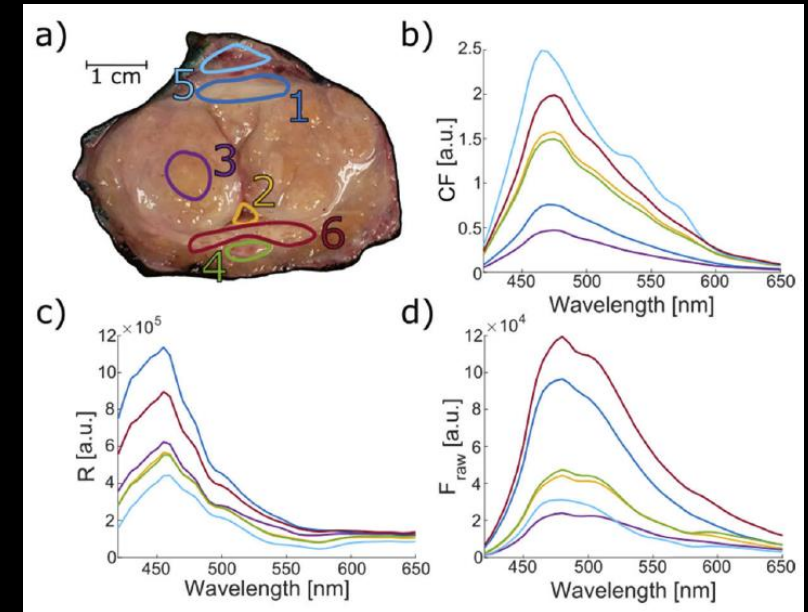
qFS detects residual tumor even if not visible in standard FGR (10 ng/g vs. 500 ng/g)

# Spatially Modulated Imaging

Recovers tissue optical properties  
Corrects fluorescence image

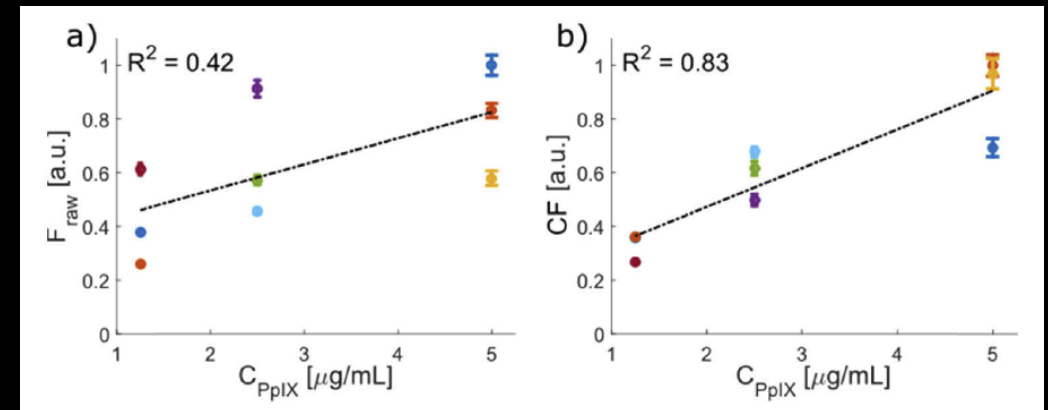


Agent Concentration  
At Depth



Wide-field optical spectroscopy system integrating reflectance and spatial frequency domain imaging to measure attenuation-corrected intrinsic tissue fluorescence in **radical prostatectomy** specimens

Beaulieu E, et al Vol. 11, No. 4 / 1 April 2020 / Biomedical Optics Express 2052



Uncorrected FI

Corrected FI



# Comparison

	Photodynamic	Photothermal	FGS
Endo vs Exo	Photosensitizer	Endogenous	Targeted Fluorophore
Treatment & Monitoring Spatial Resolution	Cellular to millimeter	Millimeter	Micro- to Millimeter
Monitoring Temporal Resolution	Tens of Seconds	Seconds	Surgeon dependent
Future Needs	Direct Monitoring of Tissue Response	Use Targeting/Thermal Enhancement Agent, i.e. thermal sensitizer (some recent work on this: Au Nanoparicles)	Make Quantitative; Depth Sensitivity



# Summary

- Photonics Therapies and Monitoring Methods are:
  - Safe
  - Fast
  - Portable
  - Cheap(er)
- Photonics Therapies & Monitoring Techniques are improving:
  - Dosimetry Methods
  - Delivery Techniques
  - Monitoring/Guidance



# Funding Support



- Research Hospital Fund (CFI)
- Kevin & Sandra Sullivan Chair in Surgical Oncology
- Fidani Chair in Radiation Physics
- Hatch Engineering Fund
- Strobele Family GTx Fund
- RACH Fund
- Princess Margaret Cancer Foundation



**THANK YOU . . .**

Questions?

