Optical Imaging:
Technology and Applications for Radiology

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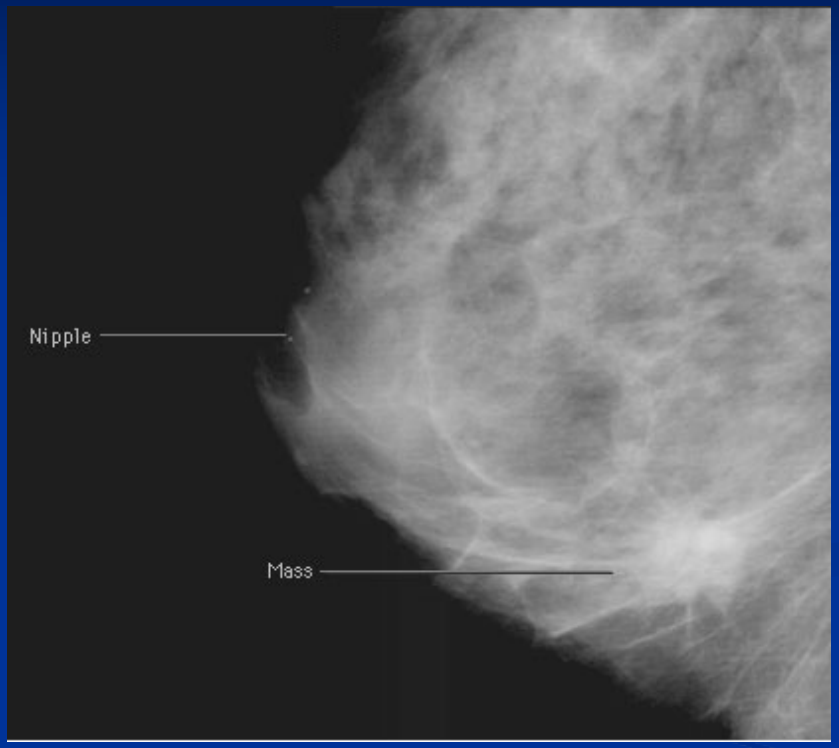
Our Patient: 61 yo female, yearly mammogram



- Suspicious right breast mass: spiculated, poorly defined margins, destruction of normal tissue architecture. no microcalcifications.
- Workup: US, biopsy yielded DCIS. Patient went on to surgery. Waiting to see if surgeons got all of the cancer.

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Patient Experience and Outcome

- How early could radiologists have found that cancer?
  - Mammography findings often equivocal:
    - Further workup
    - Masquerade as normal variants
  - One cancer raises suspicion for occult metastases

Patient Experience and Outcome

- What does the patient go through?
  - Radiation risk limits screening
  - Current mammography requires painful compressions

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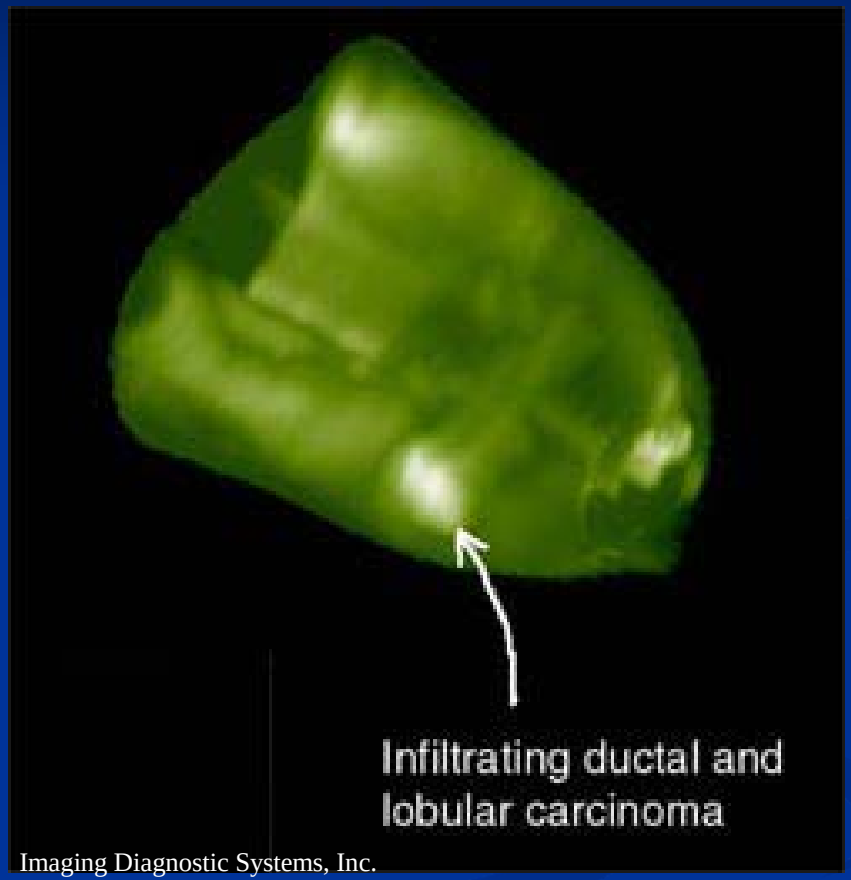
What if there were mammography …

- Without radiation?
- Without pain?
- In 2-D and 3-D?
- Sensitive enough to pick up tiny lesions?
- Able to characterize a lesion not just by what it looks like, but by the genes it expresses?
- Able to help surgeons resect a tumor and lymph nodes with greater confidence?

Optical Imaging: Laser Mammography

Traditional mammogram of left breast, MLO



3-D laser mammogram of left breast, MLO orientation

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Optical Imaging

We will cover …

- How the technology works
- Benefits and limitations
- Some Applications

… in the context of existing radiologic modalities

Technology

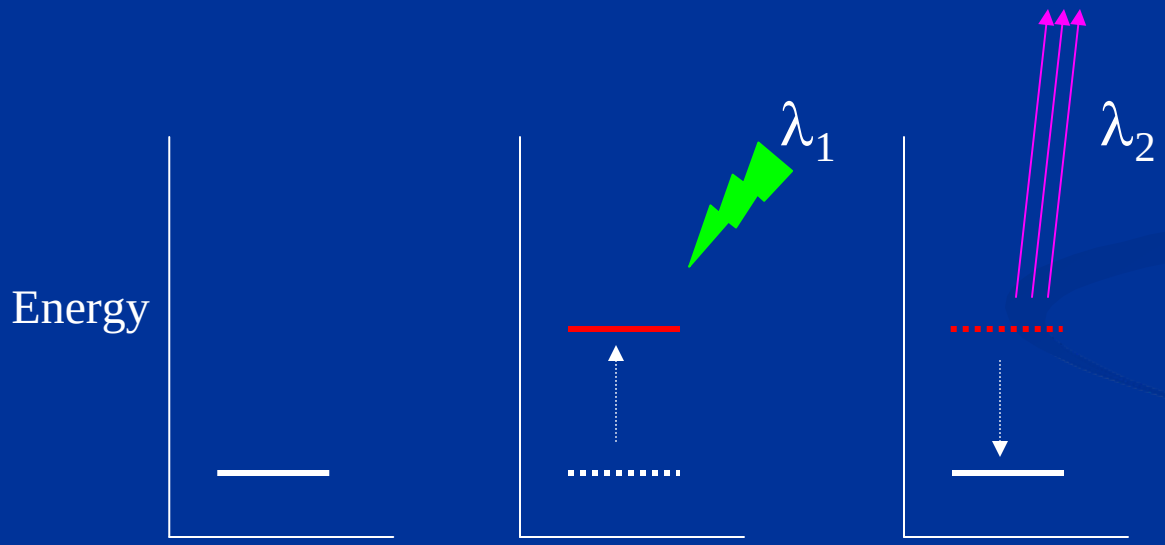
- X-ray :: radiograph

  sound waves :: ultrasound

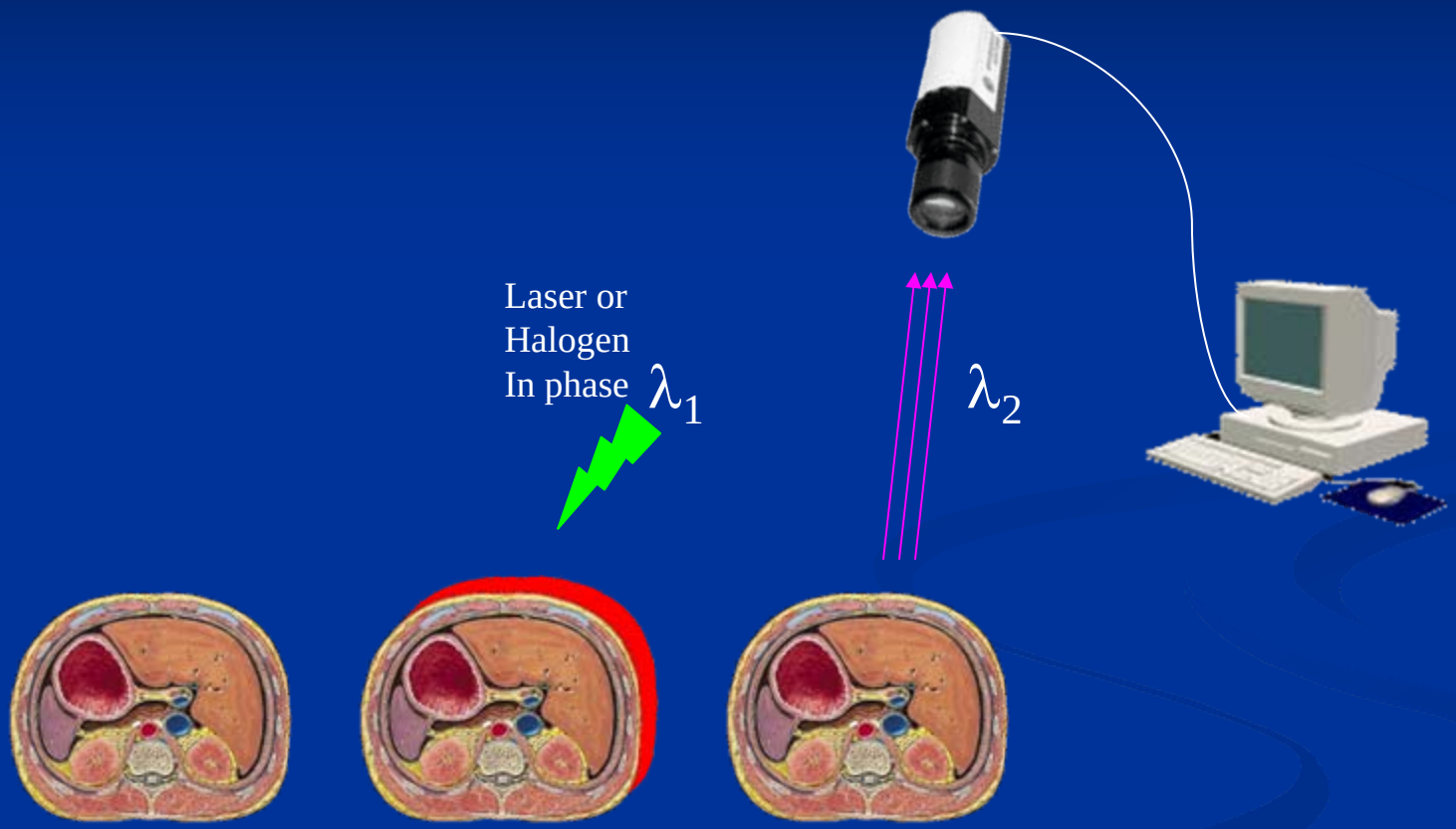
  fluorescent light :: optical imaging
- Bounce light off fluorescent tissue.

  Record light that bounces back as points in 3-D space.

Fluorescence



Setup



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About tissue optics

- An active field of research.
- Think of mammalian tissue as a semi-transparent medium.
- Different cells and proteins in the tissue have different optical characteristics.

About tissue optics

- Absorption: attenuated signal. Hemoglobin, lipids, and water absorb, especially blue/green light.
- Scatter: diffused signal.

  The thicker the tissue, the more cells and proteins available to reflect and scatter the light.
- Both excitation light and emitted light are affected by absorption and scatter.

About tissue optics

- Autofluorescence: loss of signal resolution. Gallbladder, bladder, and intestine can fluoresce green when excited with blue light.

About tissue optics

- Like other modalities, the physics can hinder our vision into the body, but it can also give information about the composition of the tissues we see.
- We can choose wavelengths of light that minimize those factors so the differences we do see are significant.
- The wavelength of choice: near-infrared (700-1000 nm). Hemoglobin is ‘transparent’ here, and autofluorescence is virtually eliminated.

Optical contrast agents

- Organic and inorganic molecules that fluoresce at different wavelengths.
- Can be conjugated to molecules that bind to any number of cell receptors or enzymes, creating designer probes.
- A favorite optical contrast agent is the NIR fluorophore indocyanine green (ICG), non-toxic and in use for decades.

Sounds like PET/CT …

- However, each FDG can only be hit once. With fluorescence, you can excite the same contrast molecule again and again for amplified signal.
- Still, PET signal (gamma rays) are less subject to absorption and scatter than IR light rays…
- So which technology is better? Will depend on what you're using it for, and on optimizing a number of parameters in the fluorescent imaging technology.

Other considerations

- Reduce attenuation:
  - Intensity, concentration of optical contrast
  - Intensity of excitation light source
  - Light wavelengths used
  - Sensitivity of CCD camera
- Software that can use knowledge about tissue optics to extrapolate accurate data from scattered light.
- All of these parameters combined affect whether one can get an image with high sensitivity and resolution.

Depth: achieving a fluorescent tomogram

- Making optical imaging a workhorse for human use means conquering thick tissues.
- Resolution and sensitivity falter at depths greater than a few centimeters. Tomogram: emit and collect light from many angles.
- Modulated intensity technique: delivering excitation light in pulses gives more information about the depth at which a fluorescent signal is coming from.

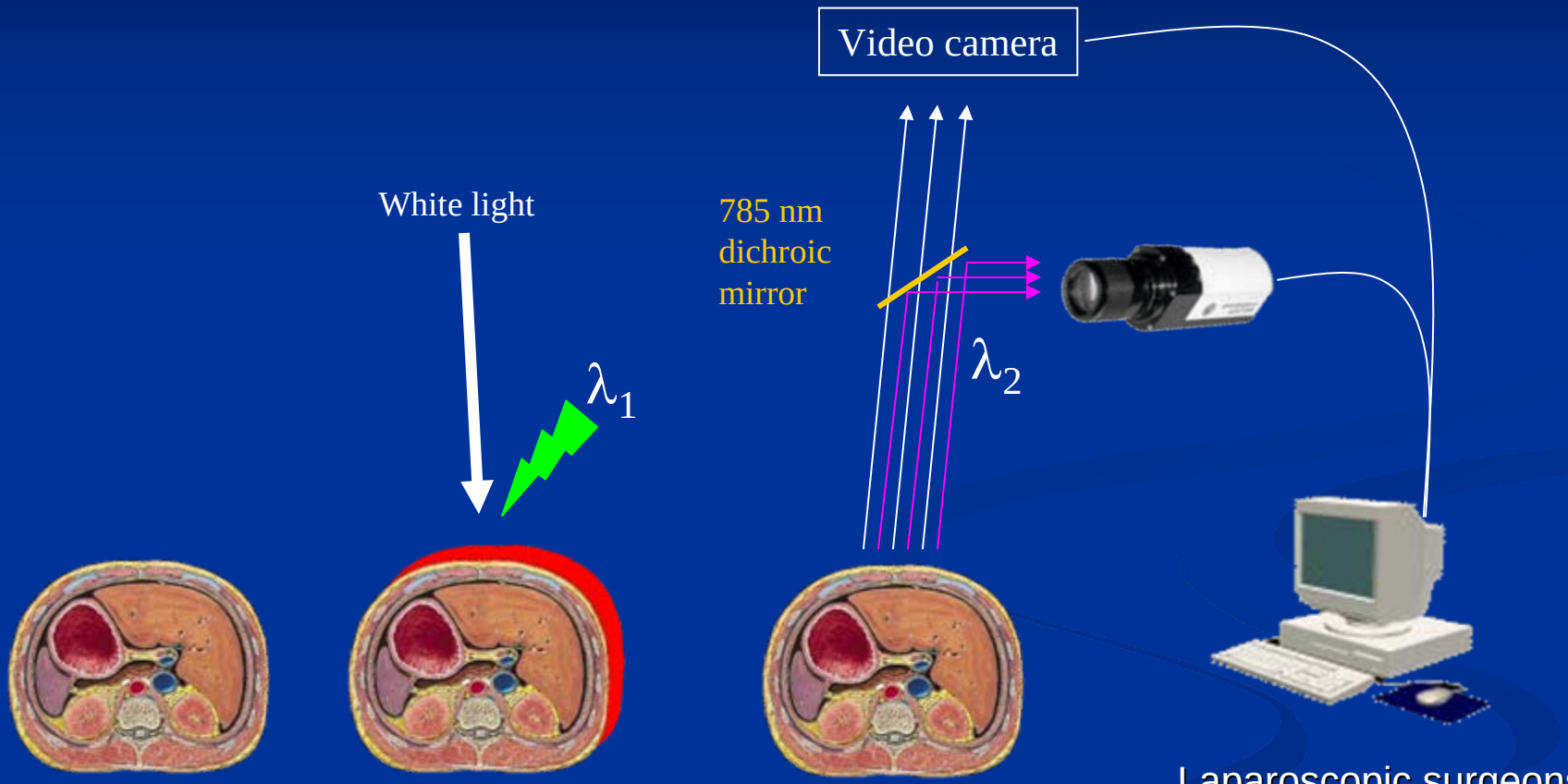
Current Reach of the Technology

- In different mouse studies, researchers have found micrometer-sized tumors, and/or tumors 50-1000 cells in size.
- 10-15cm penetration is possible, bringing us to the earlier mammogram. But optical imaging isn't just for mammograms …

Application: intraoperative fluorescent imaging

- Multimodality: fluorescence/visual imaging combine sensitivity and anatomy. “Intraoperative PET/CT.”
- Fifty percent of cancers are still cured by surgery; surgical visualization of tumor is therefore essential for staging and treatment
- Currently, this application uses planar fluorescence only.
- Successful on large animals; FDA approval for human trials pending.

Add video to setup



Laparoscopic surgeons comfortable with setup.

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Add optical contrast

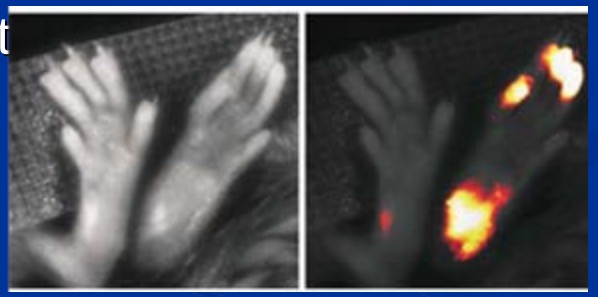
- With optical contrast, this intraoperative imaging machine can have as many uses as there are cellular targets for pathology … or normal anatomy.

  Find:

  - occult cancer: cathepsins, prot
    ligands (Weissleder *et al*)
  - cell death: annexin
  - ectopic tissue
  - inflammation: cathepsin B

  (Ntziachristos & Weissleder)

  - blood clots: fibrinogen (Frangioni *et al*)



Add Fluorescent Tomography

- Intraoperative angiography, sentinel node localization, cytoscopy, etc.

Summary

- Optical imaging: based on molecular composition of tissue.

  Morphology-based radiology =>

  function-based radiology
- Bounce light off surface and deeper structures; gather data for 3-D image.
- Limited penetration: won't replace other modalities
- However: sensitive, fast, cost-effective, versatile.

Summary

- Many applications:
  - Combine modalities: planar fluorescent/ visual imaging, planar/tomographic fluorescent imaging
  - “Small parts” imaging: mammography, solitary pulmonary nodules, etc.
  - Intraoperative imaging: tag tissue to find cancer, necrosis; intraoperative lymph node localization, angiography

References

- Choy G, Choyke P, Libutti SK. Current advances in molecular imaging: noninvasive in vivo bioluminescent and fluorescent optical imaging in cancer research. *Molecular Imaging* 2003; 2: 303-312.
- De Grand AM, Frangioni JV. An operational near-infrared fluorescence imaging system prototype for large animal surgery. *Technology in Cancer Research and Treatment* 2003; 2: 1-10.
- Frangioni JV. In vivo near-infrared fluorescence imaging. *Current Opinion in Chemical Biology* 2003; 7: 626-634.
- Ntziachristos V, Weissleder R. Shedding light onto live molecular targets. *Nature Medicine* 2003; 9: 123-128.
- Sevick-Muraca EM, Houston JP, Gurfinkel M. Fluorescence-enhanced, near-infrared diagnostic imaging with contrast agents. *Current Opinion in Chemical Biology* 2002; 6: 642-650.

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