# Molecular Image-guided Targeted Biopsy for Prostate and other Cancer

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# Disclosures

- Dr. Schuster: No direct COI
  - Participate in Emory University grants including fluciclovine, and $^{99m}$Tc-MIP-1404
  - Research funding: Blue Earth Diagnostics Ltd., Nihon Medi-Physics Co. Ltd; SNMMI-CTN, Progenics
- Emory University and Dr. Mark Goodman
  - Eligible for royalties for Fluciclovine
  - BED provides Fluciclovine cassettes for research

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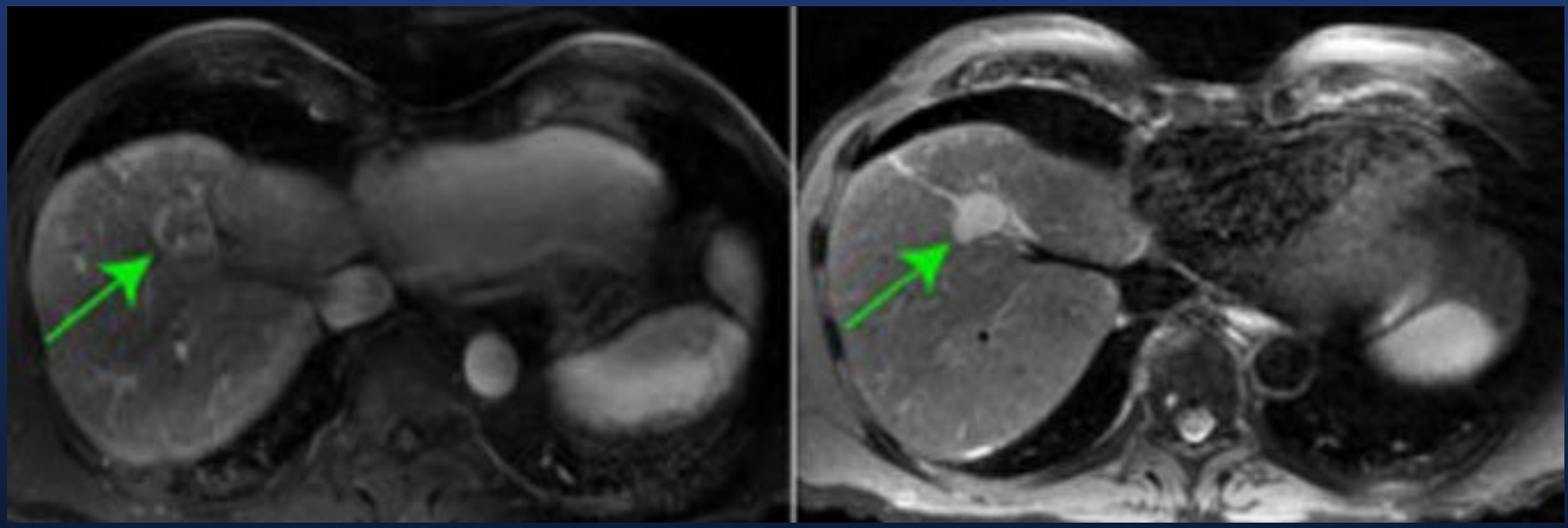
# Interesting research or greater potential?

Let’s look at some patients…

# Suspected Hepatocellular Carcinoma in Cirrhosis



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*Courtesy Umar Mahmood, MGH*

Sheth RA, et al. Radiology 2015;274:917-26.

# Indocyanine Green (ICG)

- Clinically approved OMI agent
- Fluoresces in the near-infrared spectrum
- Localizes with high sensitivity and target-to-background ratios (TBRs) to:
  - hepatocellular carcinomas (HCCs)
  - intrahepatic colorectal cancer (CRC)

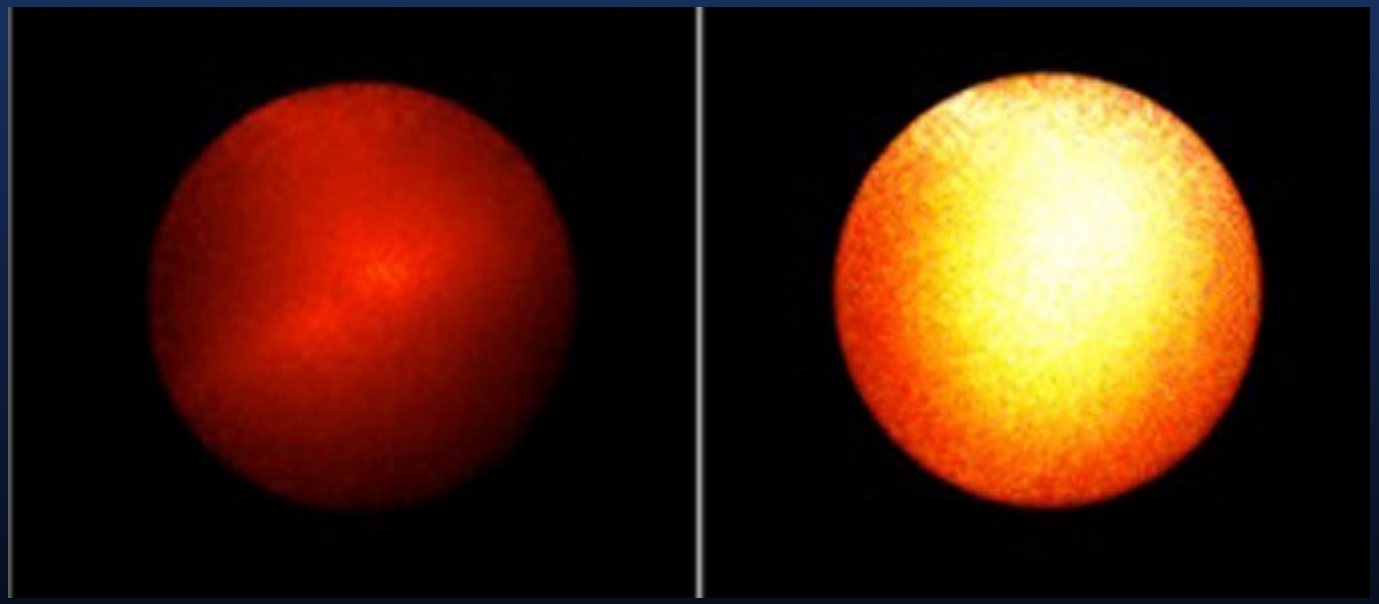


Sheth RA, et al. Radiology 2015;274:917-26.

# Patient given IV ICG 1 day prior. Needle introduced via image guidance toward the lesion. Intraprocedural optical molecular images demonstrate increased ICG.

Target to background liver

Within target



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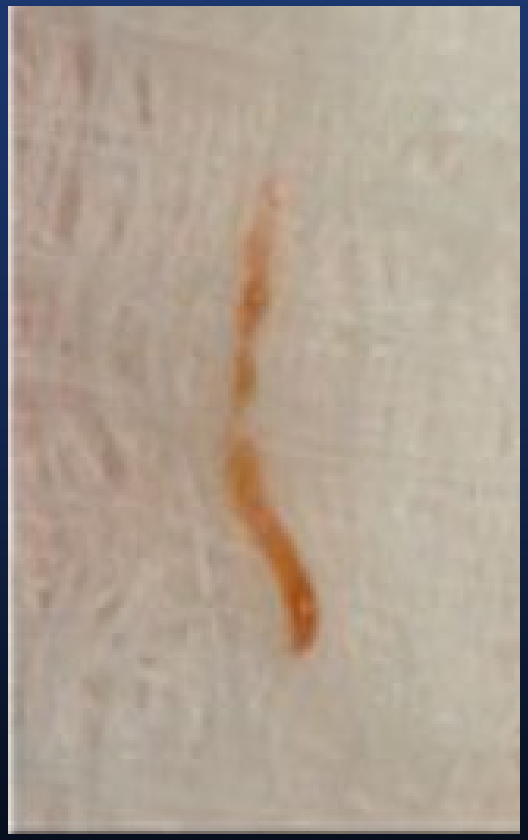
*Courtesy Umar Mahmood, MGH*

Sheth RA, et al. Radiology 2015;274:917-26.

# Immediate confirmation of target



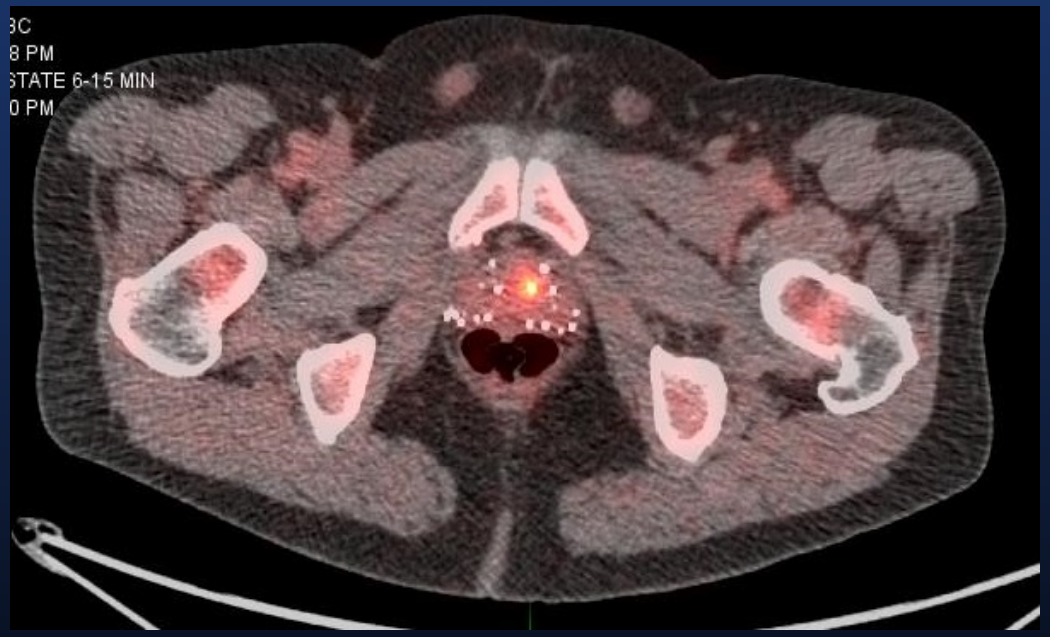
*Courtesy Umar Mahmood, MGH*

Sheth RA, et al. Radiology 2015;274:917-26.

# Another patient with suspected recurrent prostate cancer…

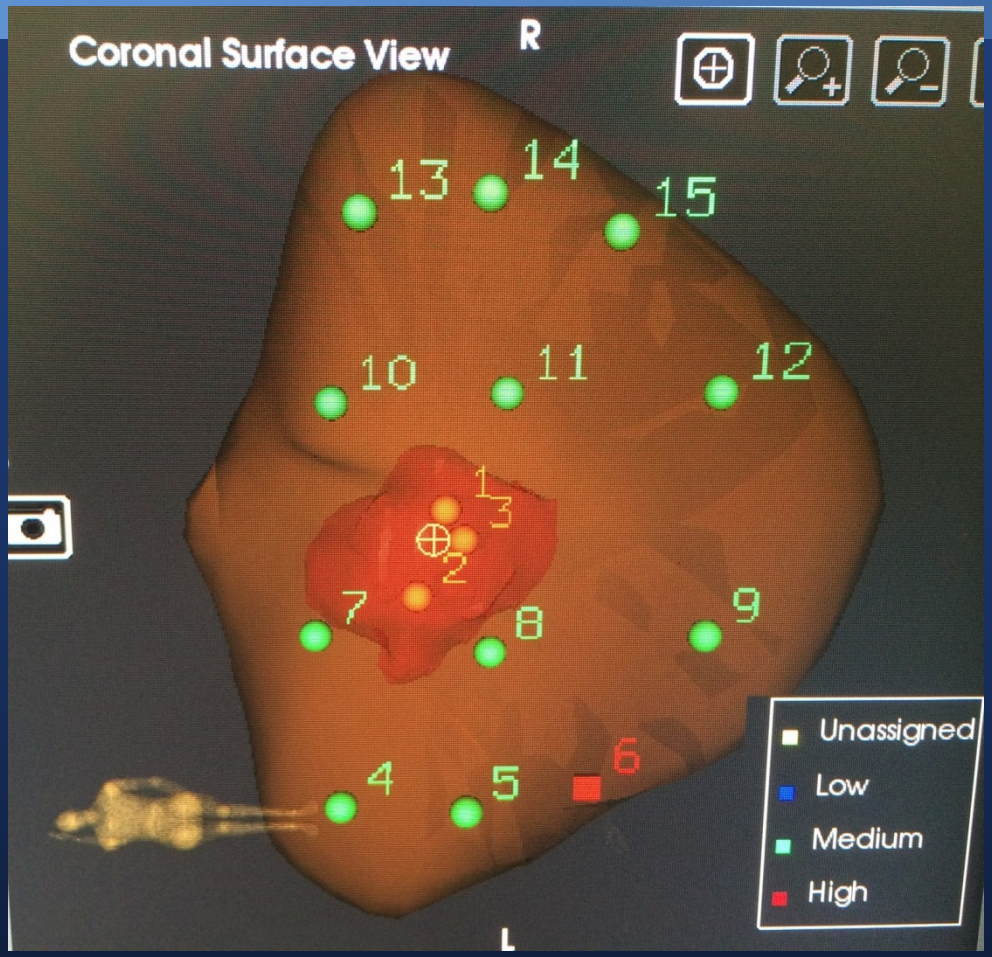
# Post-Brachytherapy. Nadir 0.74 ng/ml. Rising PSA to 3.55

Underwent fluciclovine PET in a clinical trial in which patient gets standard TRUS/Bx then targeted biopsy based on PET




Uptake only in left base.

No extraprostatic uptake.




**Standard 12-Core (4-15):**

**Negative for malignancy with radiation changes.**

**Targeted Cores (1-3):**

**Gleason 4+3=7**

Standard template 12 core biopsies missed the tumor.

The fluciclovine targeted cores detected the cancer Gleason 7 (4+3) in the left base lesion.

Underwent salvage cryotherapy. PSA 0.53 (less than nadir).

# From the visible to the invisible to the visible…

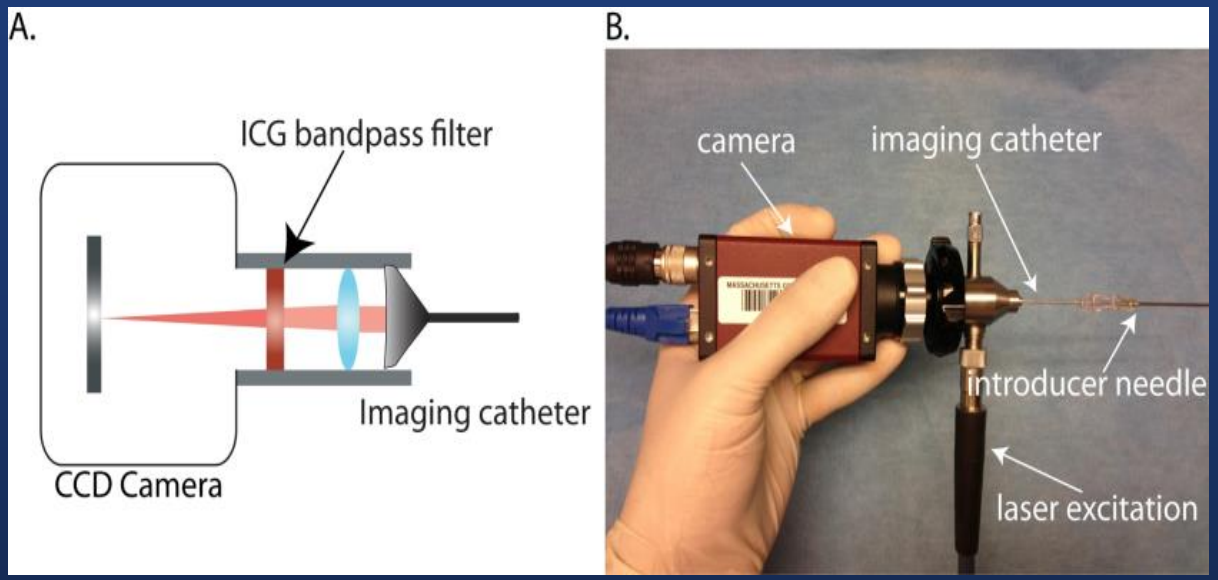
- Examples of molecular guided biopsy include:
  - PET/SPECT/Optical/mMRI to *eyeball guide* CT or MR directed biopsy
  - Dedicated equipment to biopsy via real-time molecular techniques
    - interventional PET or mMRI suite
  - Fold molecular information into multimodality techniques including advanced EM tracking

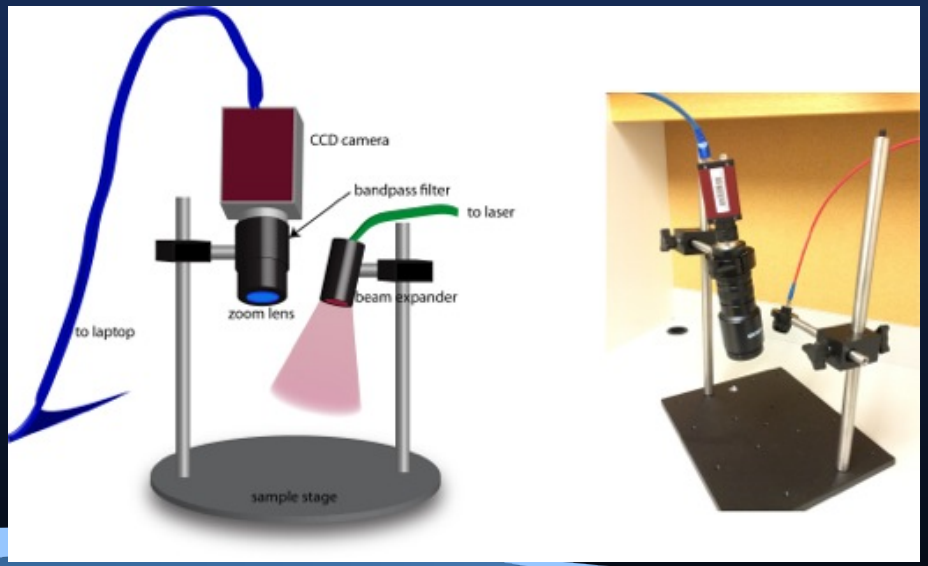
# Why do it?

- Anatomic biopsy blind to metabolism
- Molecular guidance to most avid lesion
- Avoid necrosis
- Improve true positivity
- Some lesions only visible with molecular imaging
- Steer biopsy to unique metabolic profile
- Research to validate new tracers/agents

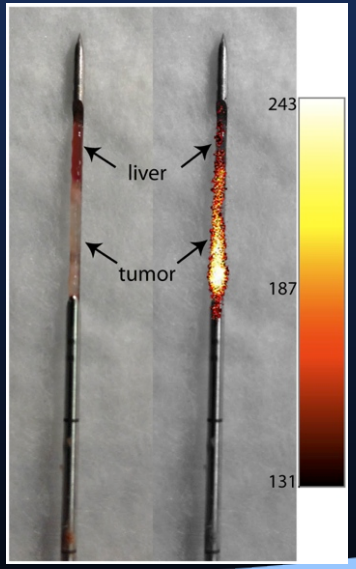
# Optical

# Handheld Imaging Device



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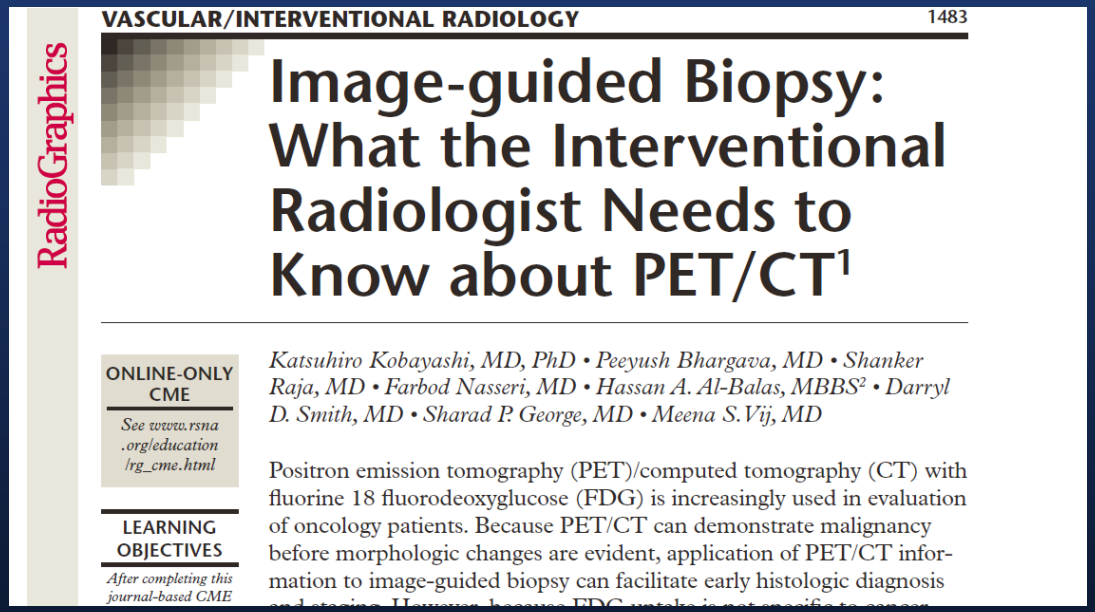
*Courtesy Umar Mahmood, MGH*

Sheth RA, et al. Radiology 2014;271:770-7.

# Eyeball

# Eyeball to Most Avid Site and Avoid Necrosis



RadioGraphics

VASCULAR/INTERVENTIONAL RADIOLOGY 1483

## Image-guided Biopsy: What the Interventional Radiologist Needs to Know about PET/CT[1]

*Katsuhiro Kobayashi, MD, PhD • Peeyush Bhargava, MD • Shanker Raja, MD • Farbod Nasseri, MD • Hassan A. Al-Balas, MBBS[2] • Darryl D. Smith, MD • Sharad P. George, MD • Meena S. Vij, MD*

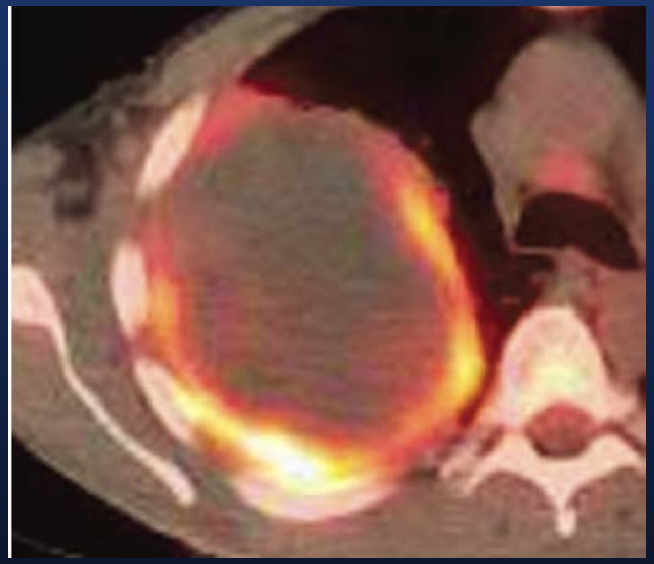
ONLINE-ONLY CME

*See www.rsna.org/education/rg_cme.html*

LEARNING OBJECTIVES

*After completing this journal-based CME*

Positron emission tomography (PET)/computed tomography (CT) with fluorine 18 fluorodeoxyglucose (FDG) is increasingly used in evaluation of oncology patients. Because PET/CT can demonstrate malignancy before morphologic changes are evident, application of PET/CT information to image-guided biopsy can facilitate early histologic diagnosis



Kobayashi et al. RadioGraphics 2012; 32:1483–1501

# Fusion to biopsy CT

# In house software to register CT for FNA with PET/CT

## Metabolic PET/CT-Guided Lung Lesion Biopsies: Impact on Diagnostic Accuracy and Rate of Sampling Error

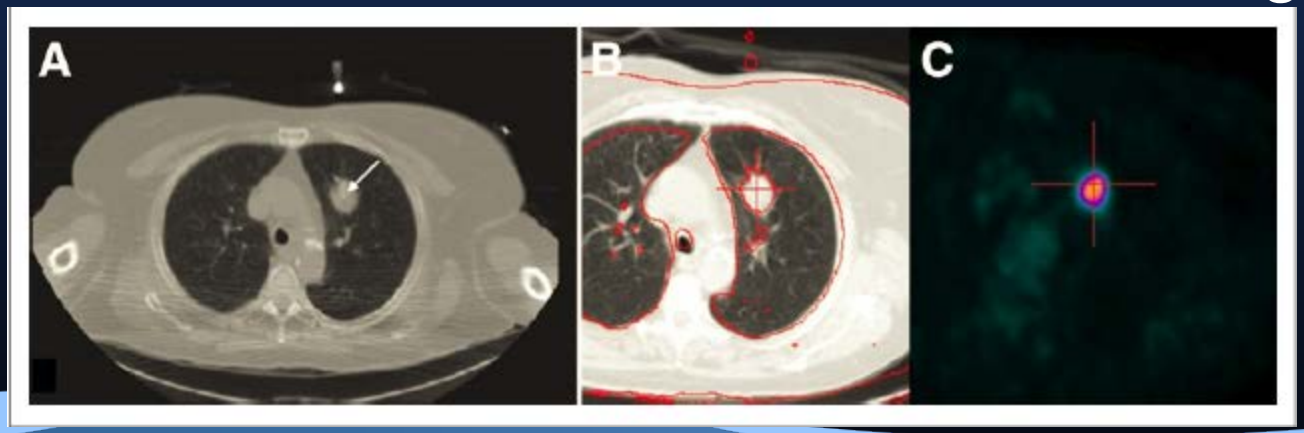
Ludmila Guralnik*[1], Radu Rozenberg*[1], Alex Frenkel[2], Ora Israel[2,3], and Zohar Keidar[2,3]

*[1]Department of Radiology, Rambam Health Care Campus, Haifa, Israel; [2]Department of Nuclear Medicine, Rambam Health Care Campus, Haifa, Israel; and [3]B & R Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel*

CT-guided fine-needle aspiration (FNA) of lung lesions is subject to sampling errors. The current study assessed whether information provided by $^{18}$F-FDG PET/CT will decrease the false-negative (FN) rate and thus improve the accuracy of CT-guided FNA. **Methods:** Data from 311 consecutive patients with lung nodules who underwent $^{18}$F-FDG PET/CT and CT-guided FNA within an interval of less than 30 d were retrospectively assessed. In-house–developed software was used to register CT images performed for the FNA procedure (CT FNA) with corresponding slices of the PET/CT study. The quality of registration was rated on a scale of 1 (excellent) to

Percutaneous CT-guided fine-needle aspiration (FNA) is routinely used for lung lesions and is a relatively safe method for diagnosis of benign and malignant processes (*1*). The diagnostic accuracy of CT-guided FNA for malignant lung tumors varies between 64% and 97% (*2*), depending on factors such as the size and depth of the lesion and the number of needle paths (*1,2*). $^{18}$F-FDG imaging provides information on the metabolic characteristics of lung lesions (*3*). Its inherent advantages include early detection of malignancy and differentiation from nonmalignant

- Smaller distance of needle tip to hottest focus and higher SUVmax at tip corresponded to highest TP vs FN




Guralnik et al. J Nucl Med 2015; 56:518–522

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# Fusion to ultrasound with EM receiver on US probe

# Ultrasound fusion with realtime guidance

Abdominal Imaging

© Springer Science+Business Media New York 2014
Published online: 29 April 2014

Abdom Imaging (2014) 39:1102–1113
DOI: 10.1007/s00261-014-0143-8

## Advantages of percutaneous abdominal biopsy under PET-CT/ultrasound fusion imaging guidance: a pictorial essay

Francesco Paparo,[1] Riccardo Piccazzo,[2] Luca Cevasco,[2] Arnoldo Piccardo,[3] Francesco Pinna,[4] Fiorenza Belli,[5] Lorenzo Bacigalupo,[1] Ennio Biscaldi,[1] Giovanni De Caro,[4] Gian Andrea Rollandi[1]

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[2]School of Radiology, University of Genoa, Via Leon Battista Alberti 4, 16132 Genoa, Italy
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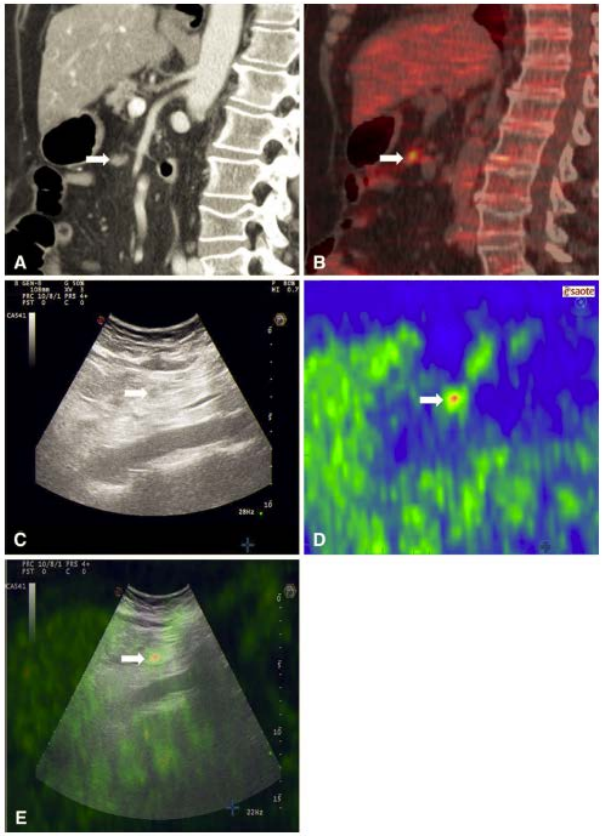
[4]Unit of Interventional Radiology, E.O. Ospedali Galliera, Mura della Cappuccine 14, 16128 Genoa, Italy
[5]Department of General and Hepatobiliary Surgery, E.O. Ospedali Galliera, Mura della Cappuccine 14, 16128 Genoa, Italy




Paparo et al. Abdom Imaging 2014;39:1102–1113

# Fusion to CT with EM tracking system under CT guidance

# EM tracking under CT guidance

Radiology

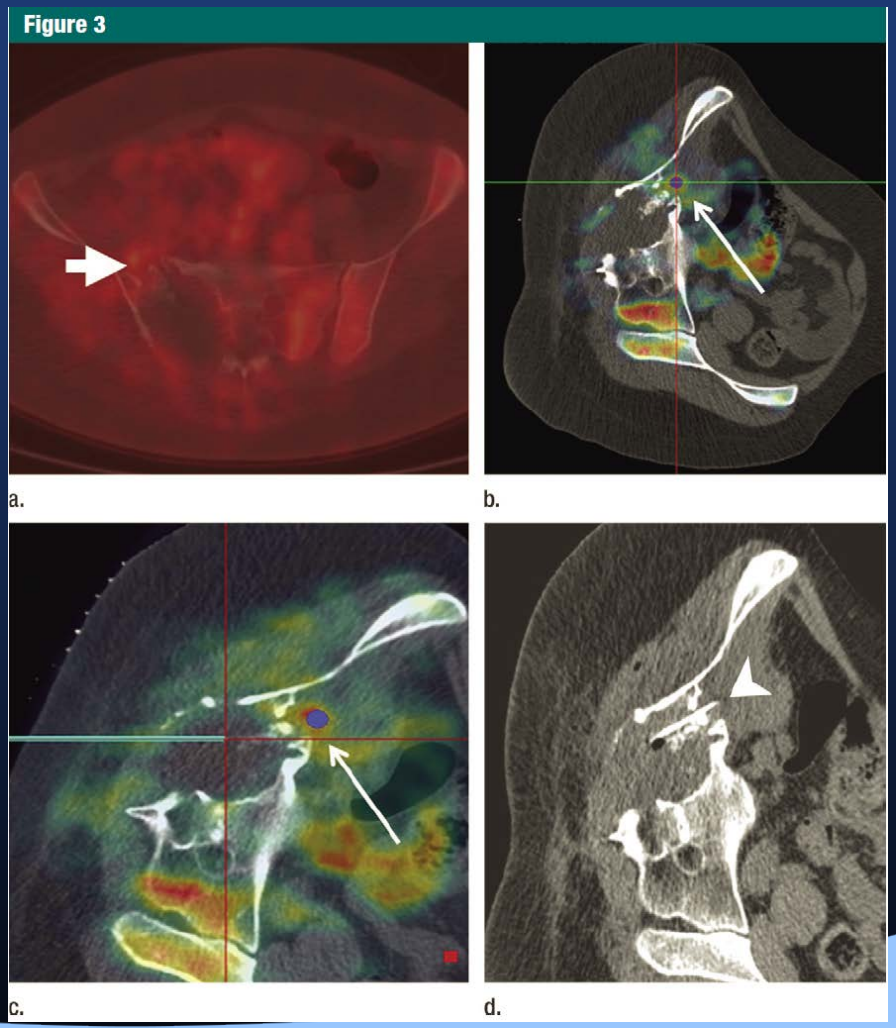
## Real-time FDG PET Guidance during Biopsies and Radiofrequency Ablation Using Multimodality Fusion with Electromagnetic Navigation[1]

Aradhana M. Venkatesan, MD
Samuel Kadoury, PhD
Nadine Abi-Jaoudeh, MD
Elliot B. Levy, MD
Roberto Maass-Moreno, PhD
Jochen Krücker, PhD
Sandeep Dalal, PhD
Sheng Xu, PhD
Neil Glossop, PhD
Bradford J. Wood, MD

**Purpose:** To assess the feasibility of combined electromagnetic device tracking and computed tomography (CT)/ultrasonography (US)/fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) fusion for real-time feedback during percutaneous and intraoperative biopsies and hepatic radiofrequency (RF) ablation.

**Materials and Methods:** In this HIPAA-compliant, institutional review board–approved prospective study with written informed consent, 25 patients (17 men, eight women) underwent 33 percutaneous and three intraoperative biopsies of 36 FDG-avid targets between November 2007 and August 2010. One patient underwent biopsy and RF ablation of an FDG-avid

Venkatesan et al. Radiology 2011; 260:848



# Interventional (Dedicated) PET-CT

# Dedicated system (short breath hold PET acquisitions)

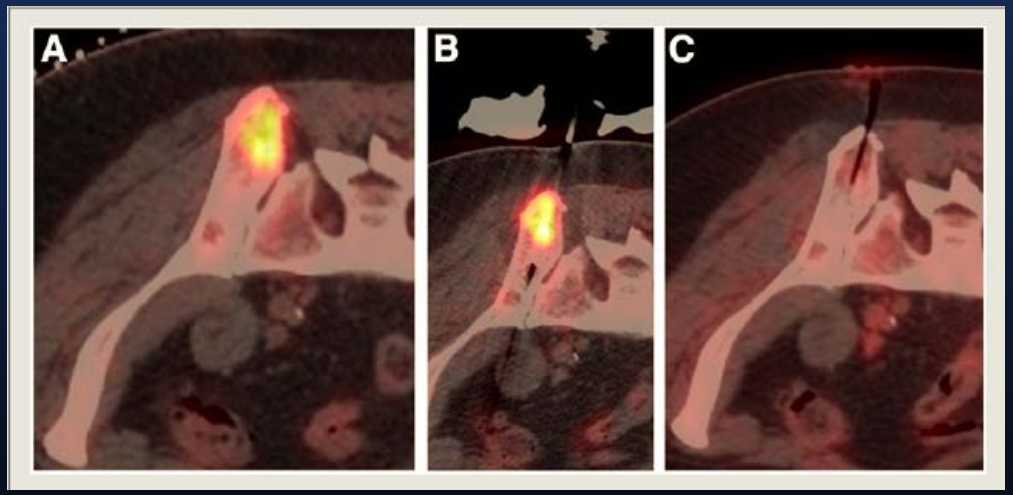
FOCUS ON MOLECULAR IMAGING

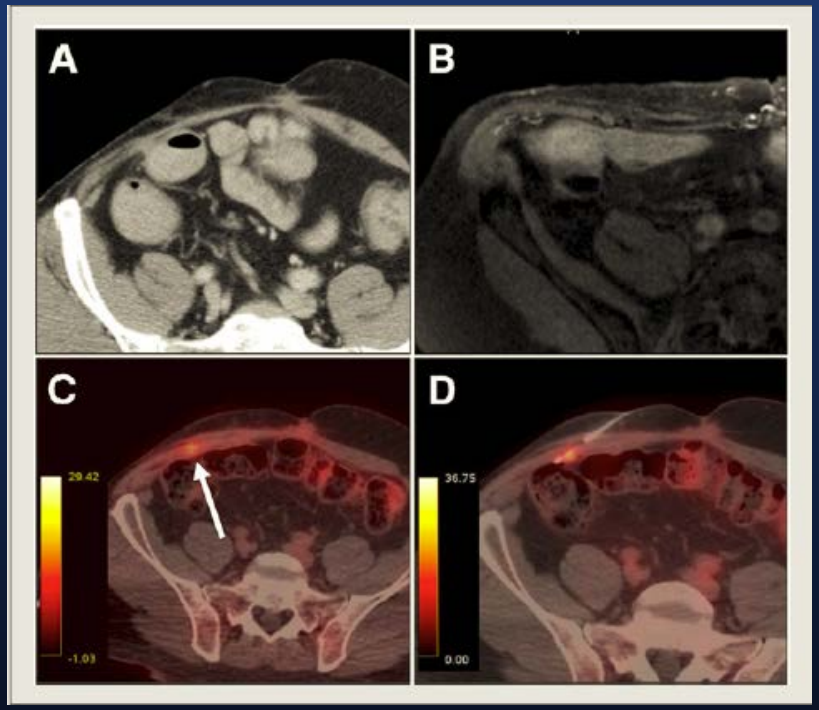
## Interventional Molecular Imaging

Stephen B. Solomon[1] and Francois Cornelis[1,2]

*[1]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York; and [2]Department of Radiology, Pellegrin Hospital, Bordeaux, France*

Although molecular imaging has had a dramatic impact on diagnostic imaging, it has only recently begun to be integrated into interventional procedures. Its significant impact is attributed to its ability to provide noninvasive, physiologic information that supplements conventional morphologic imaging. The four major interventional opportunities for molecular imaging are, first, to provide guidance to localize a target; second, to provide tissue analysis to confirm that the target has been reached; third, to provide in-room, posttherapy assessment; and fourth, to deliver targeted therapeutics. This article will provide an update on the status of interventional molecular imaging.

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Solomon et al. J Nucl Med 2016; 57:493–496

# Work at Emory

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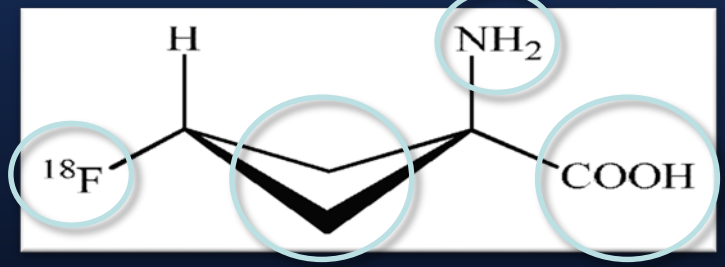
# *anti*-1-amino-3-[$^{18}$F]fluorocyclobutane-1-carboxylic acid *(anti-3-[$^{18}$F]FACBC)*

- Non-natural alicyclic amino acid PET radiotracer
  - – developed at Emory
- Fluciclovine not metabolized

***FACBC***
***fluciclovine ($^{18}$F)***
***FDA approved:***
***Axumin***

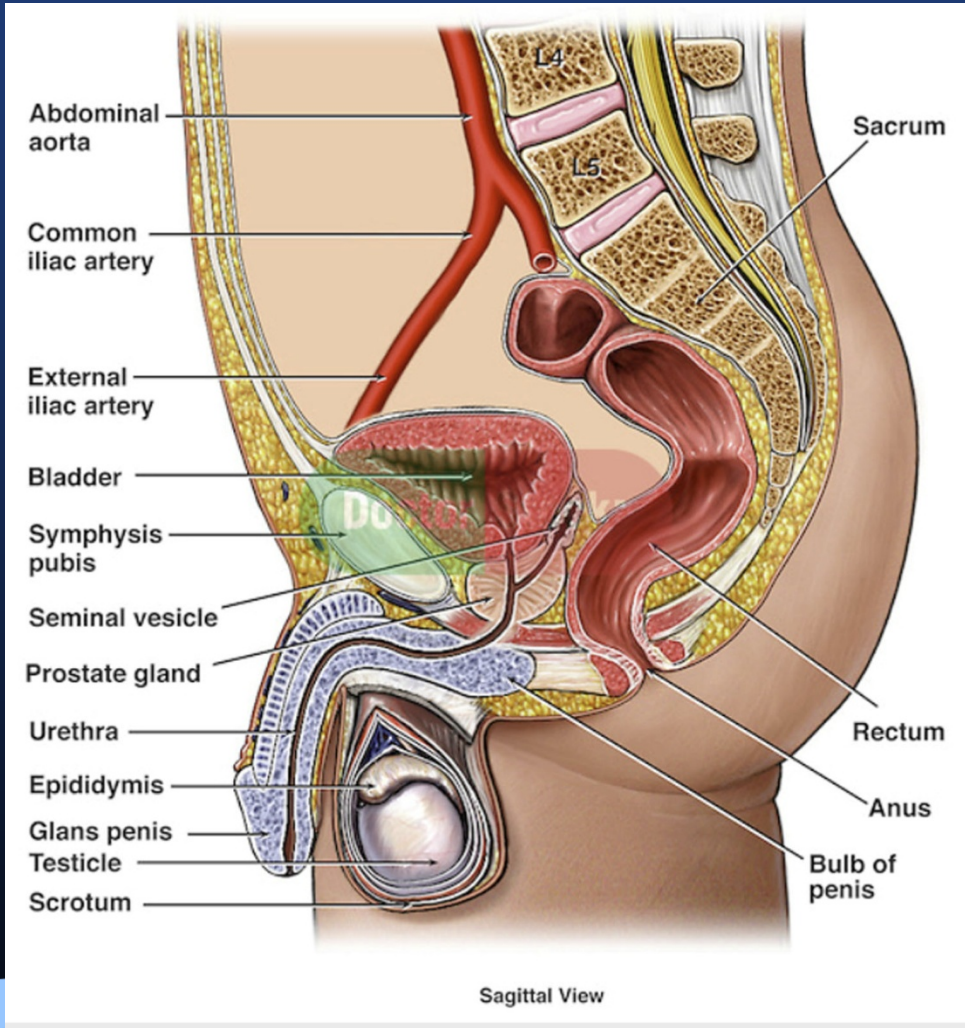


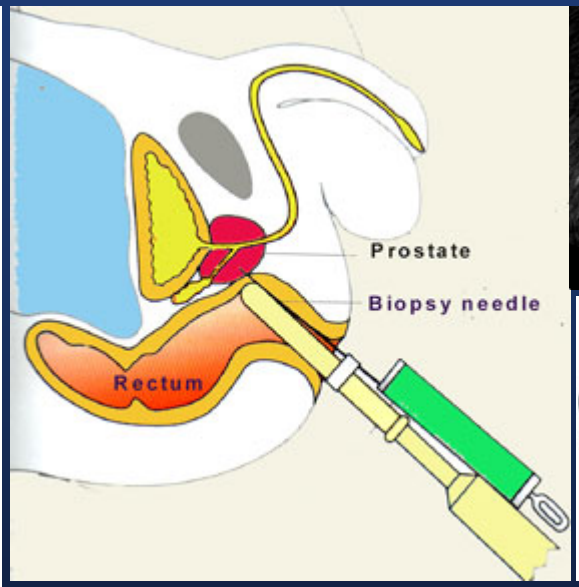
# Early experience

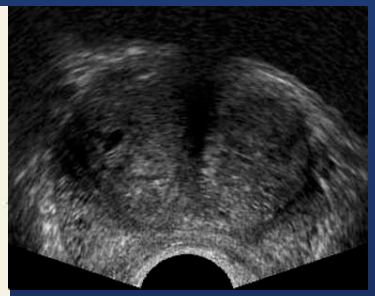
- We had some cases where fluciclovine was positive but biopsy negative
  - yet later proven to have tumor in prostate
- We realized there was non-specificity but also sampling error
    - tease out both elements
  - Approached by Baowei Fei to see if interest in working on a molecular guided ultrasound biopsy system

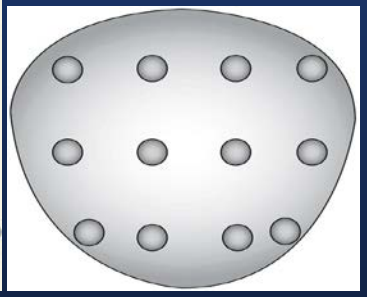
# TRUS-guided Biopsy

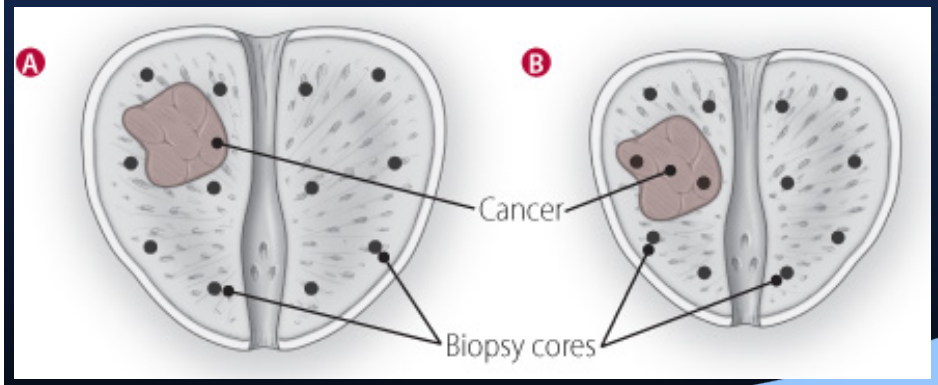
## 12-Core Biopsy





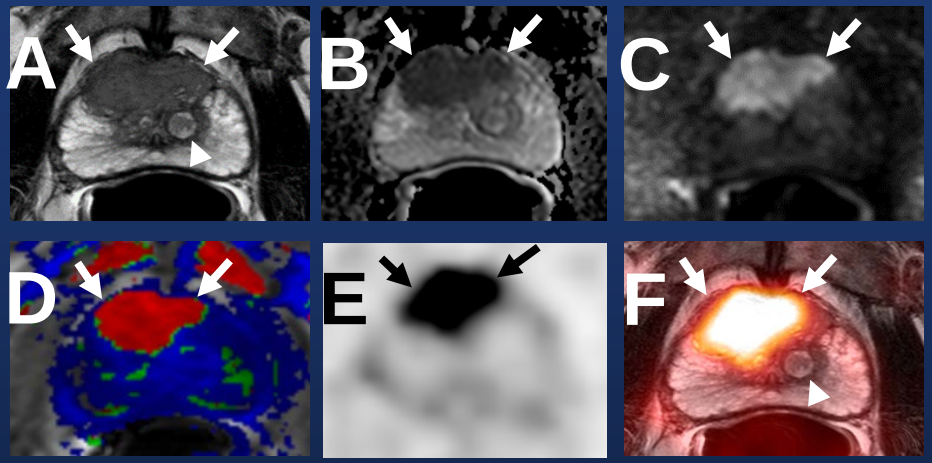


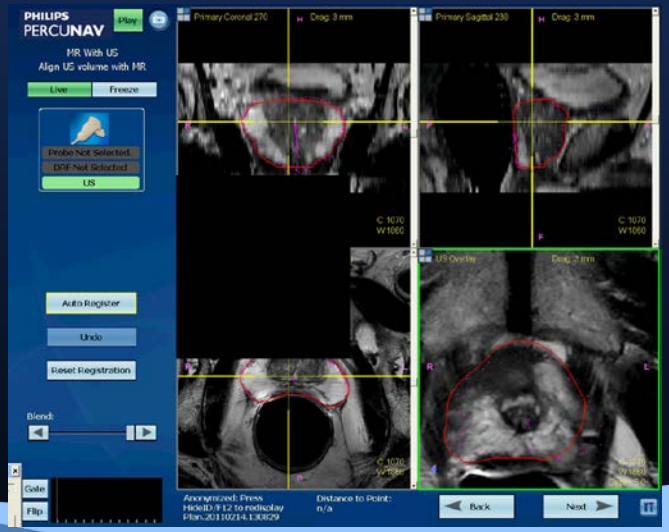
# Current Problems

- Two-dimensional (2D) image guidance
  - difficult to go to the same location for re-biopsy in a follow up examination
- Ultrasound imaging has a low sensitivity for detecting cancer
  - *essentially blind biopsy*

# Ongoing Work with Multimodality TRUS Fusion

- UCLA, NCI, others
- Most with MR-TRUS
- NCI ongoing work with PET-MR-TRUS
- Most work in primary or active surveillance setting



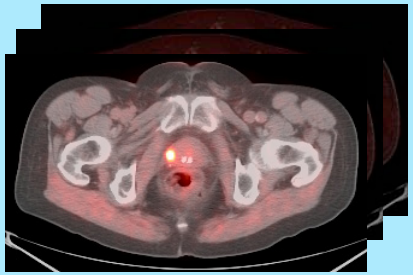




P. Choyke, B. Turkbey, NCI, NIH, Bethesda, MD, USA

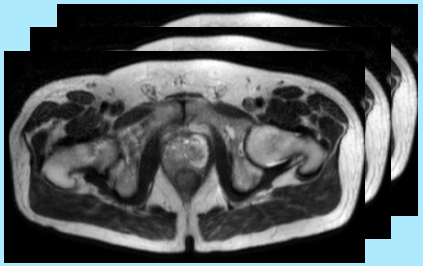
Gleason 4+5 DCFBC mpMR with 2 negative prior biopsies

# Emory - Targeted Biopsy

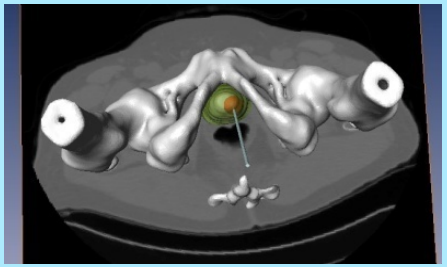
**Molecular Imaging with PET/CT or MRI/MRSI**



PET/CT



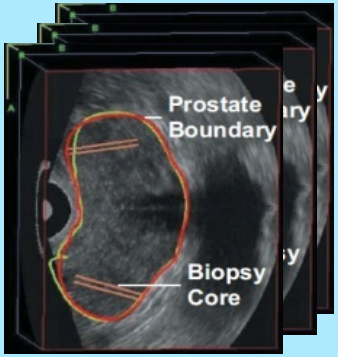
MRI/MRSI



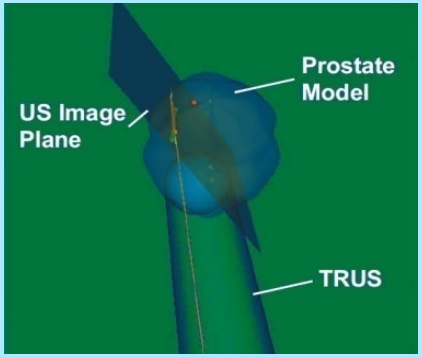
3D Visualization

**Registration** **Fusion** **Visualization**

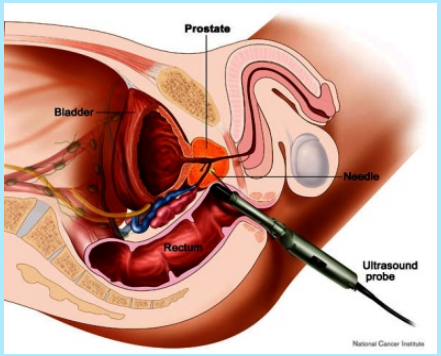
**Real-time 3D ultrasound-guided biopsy**




**Segmentation**




**Planning**




**Biopsy**

**Molecular imaging**

**+**

**3D Ultrasound for real time guidance**

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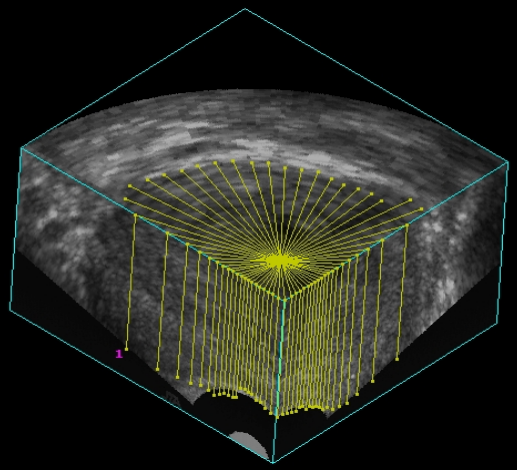
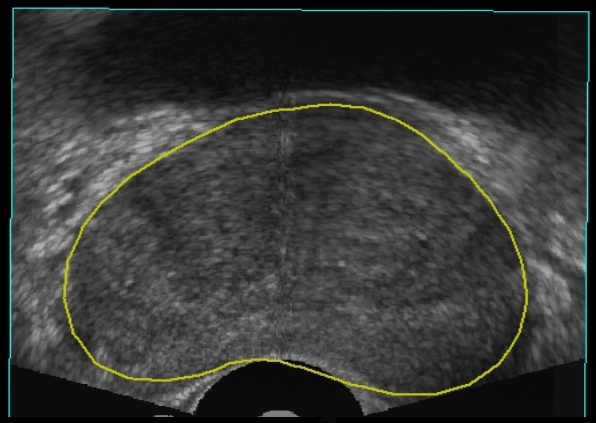
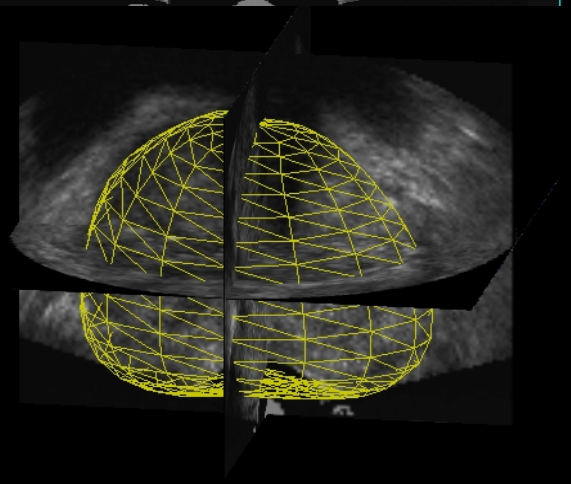
NIH R01CA156775, R21CA176684, PI: Baowei Fei

# 3D Prostate Model



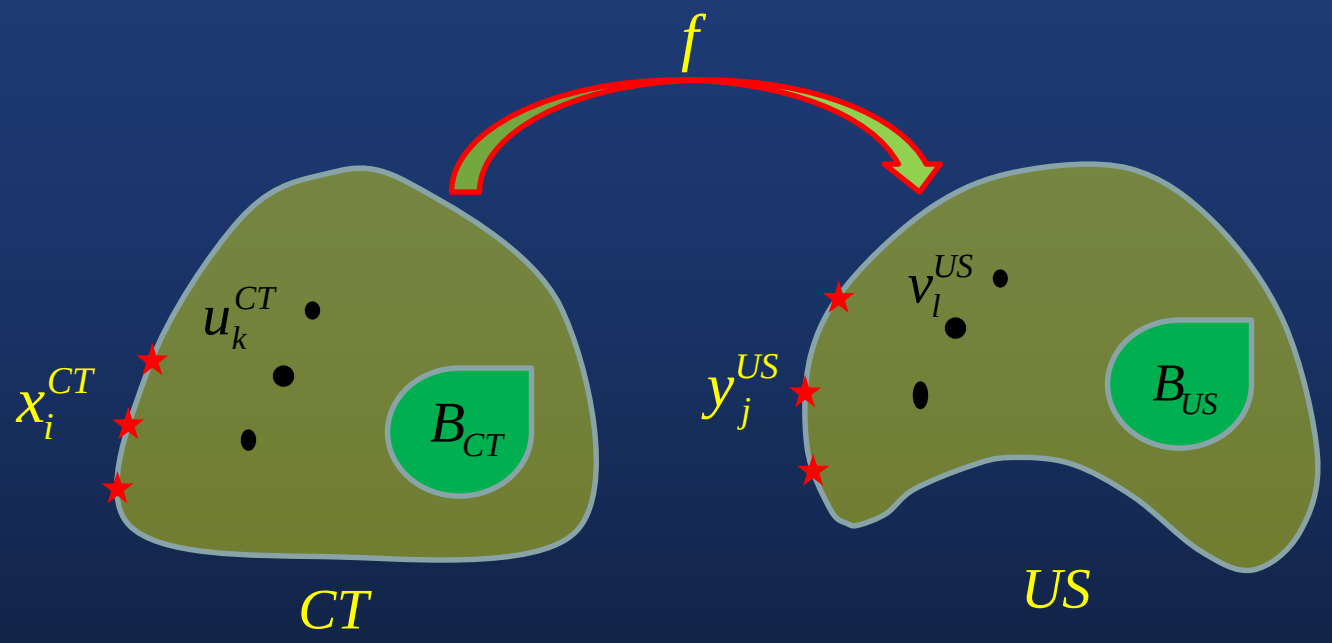




3D Ultrasound Image Segmentation

Once we get the 3D images, we can segment the prostate and build a 3D model of the organ.

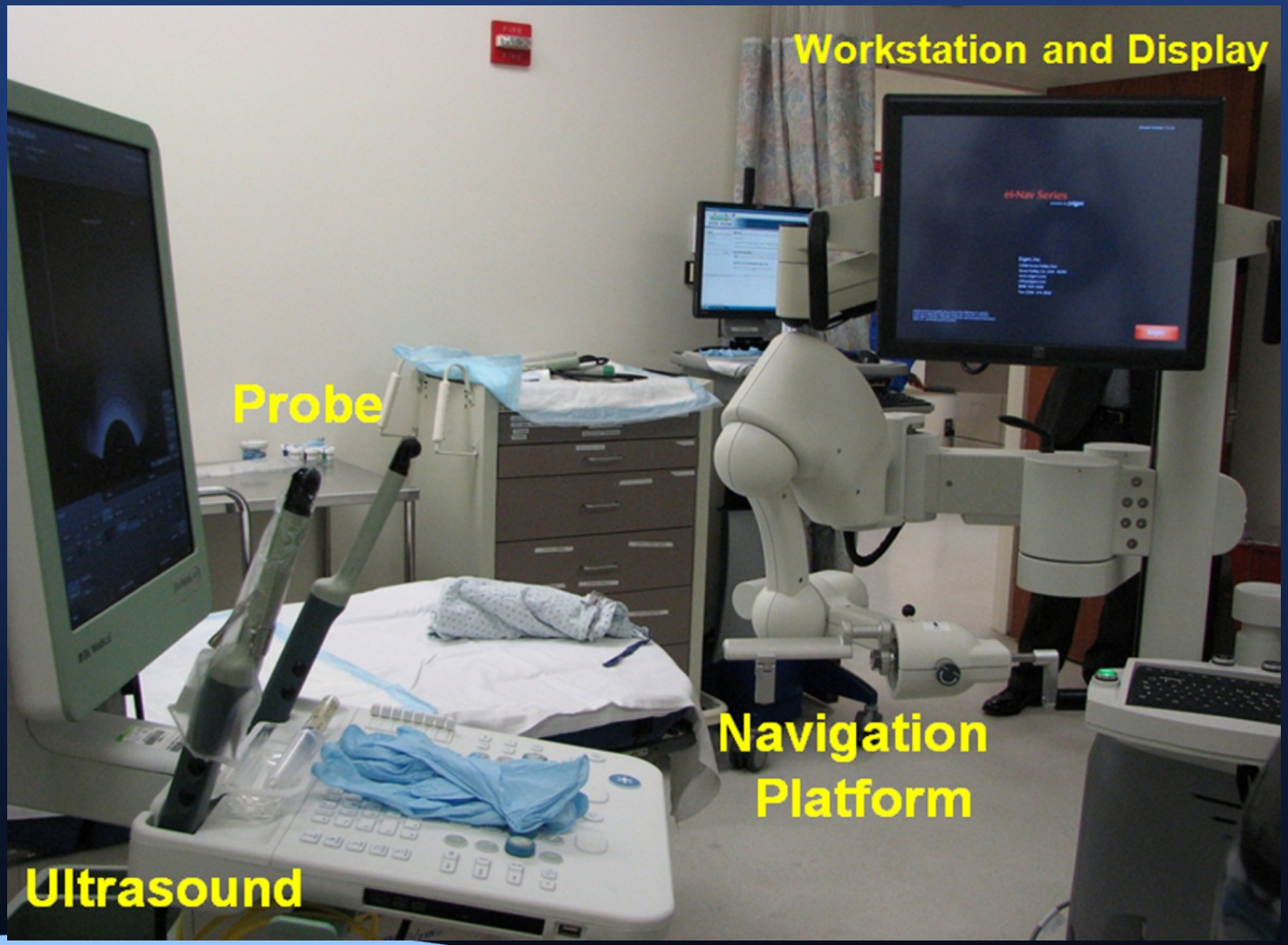
# Deformable Image Registration



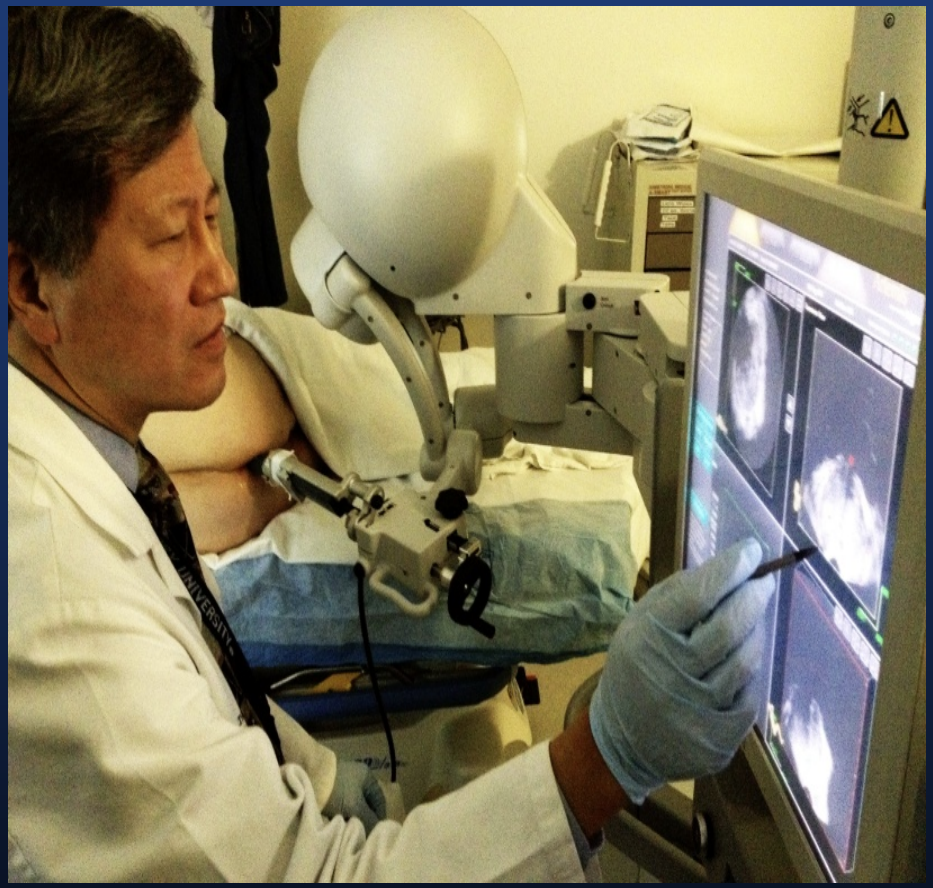

**To incorporate PET-CT into ultrasound guided biopsy, we use CT as the bridge.**

**If register CT with ultrasound, also able to register PET with ultrasound.**

# Clinical Setup for Biopsy



# Targeted Biopsy in Patients



# Clinical Trial

- Suspected recurrence with “intact” prostate
  - non-prostatectomy
- Fluciclovine PET-CT
  - Manually draw regions including prostate
    - *working to automate this process*
- Patients get planning ultrasound before or after PET

# Clinical Trial

- Next session undergoes 12 core template biopsy
  - Locations of the 12 cores are randomly generated by the computer according to the template
    - Urologist does not pick the locations of the 12 cores and blinded to targeted lesions
  - Then target lesions are revealed

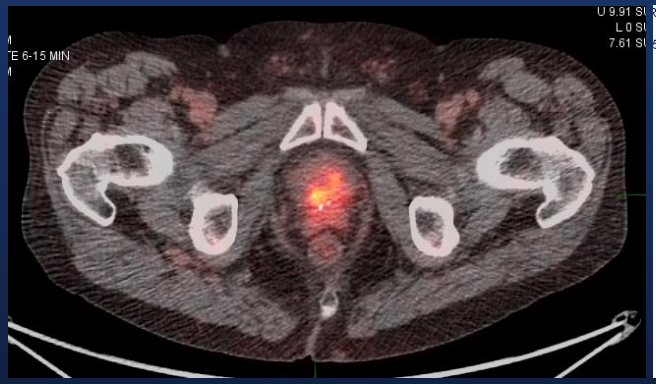
# Clinical Trial

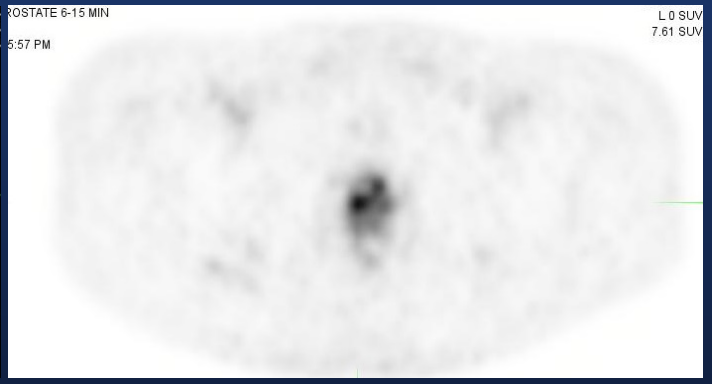
- Standard 12-core biopsy only has a ***7%*** positivity
  - 1 in 12 cores is positive.
- In our preliminary study of 39 patients (primary and recurrent), our MRI/TRUS fusion biopsy improved the detection rate to 29.3% (27 of 92 cores).
- For our 10 patients with positive lesions on PET, our PET/ultrasound targeted biopsy further improved the detection rate to 60% (9 of 15 targeted cores).

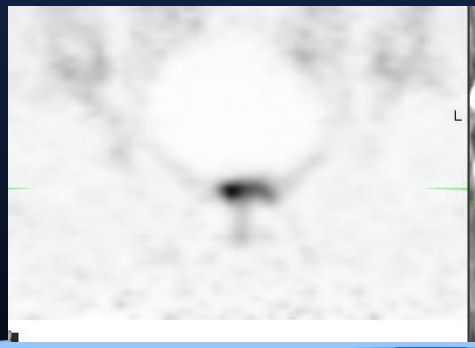
# Molecular Guidance

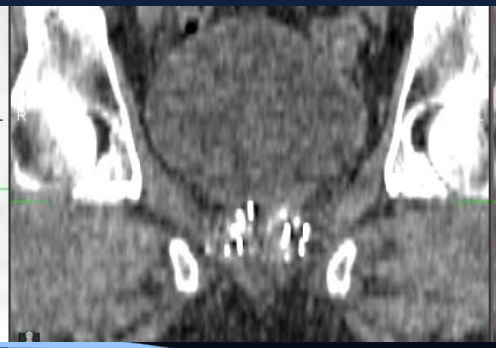
- Direct needle to lesion with confidence and document location
- Determine if lesion outside of normal local field such as seminal vesicle
- Help completely stage the patient before considering salvage therapy

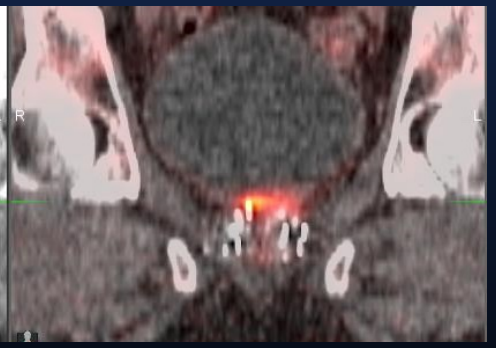
# Post local therapy.
# Positive fluciclovine in prostate with negative biopsy x 2 in past (deemed FP).
# Now PSA rising to 17.8ng/ml.







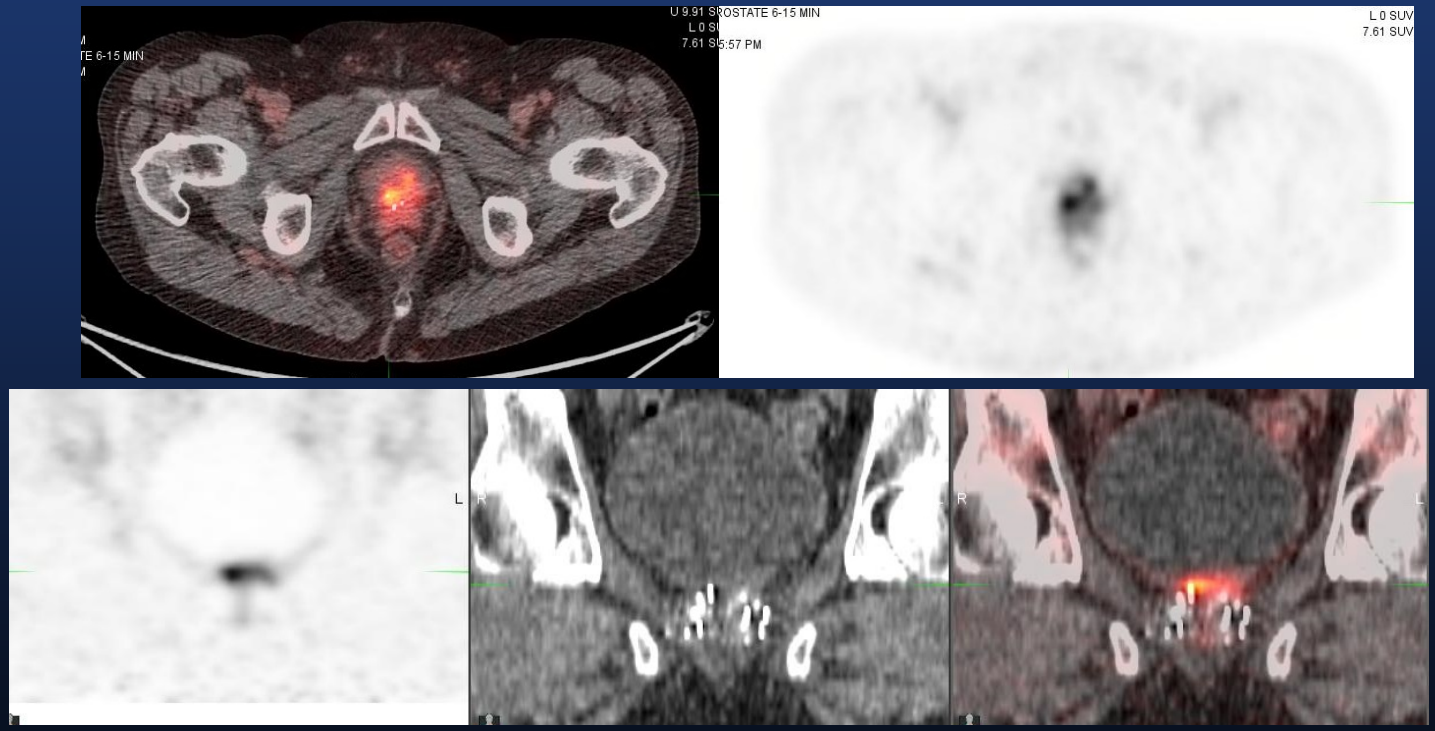


3rd fluciclovine on peripheral ADT.

Uptake in right posterior base and less so in left anterior base.
Equivocal apex.

But now we had guided biopsy…

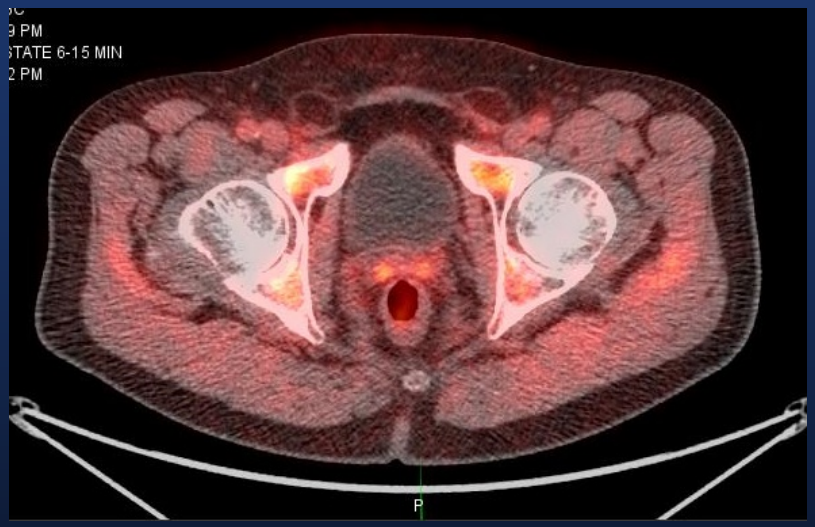
# Standard TRUS: Negative “treatment effect” PET guided: Positive in right posterior and left anterior base. Negative in apex.

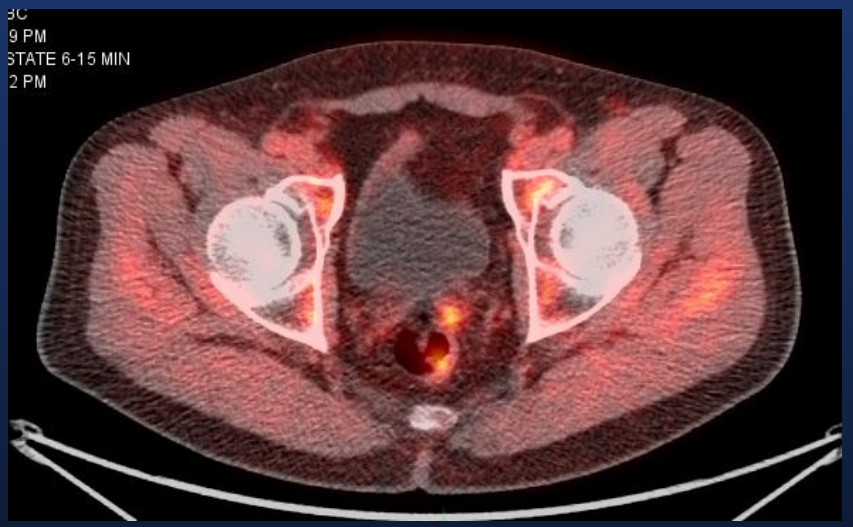


# Molecular Guidance

- Direct needle to lesion with confidence and document location
- Determine if lesion outside of normal field such as seminal vesicle
- Help completely stage the patient before considering salvage therapy

# HIFU and subsequent recurrence treated with salvage cryotherapy. Now rising PSA to 4.3 ng/ml.



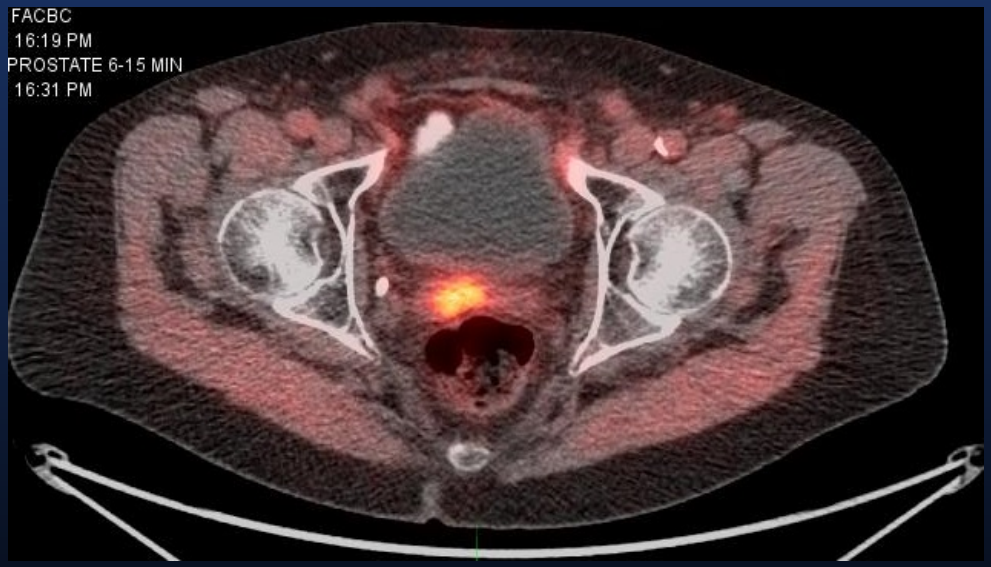

Fluciclovine PET: Positive in right base/SV and higher up in left SV
Urologist can direct biopsies to SVs

# Molecular Guidance

- Direct needle to lesion with confidence and document location
- Determine if lesion outside of normal field such as seminal vesicle
- Help completely stage the patient before considering salvage therapy

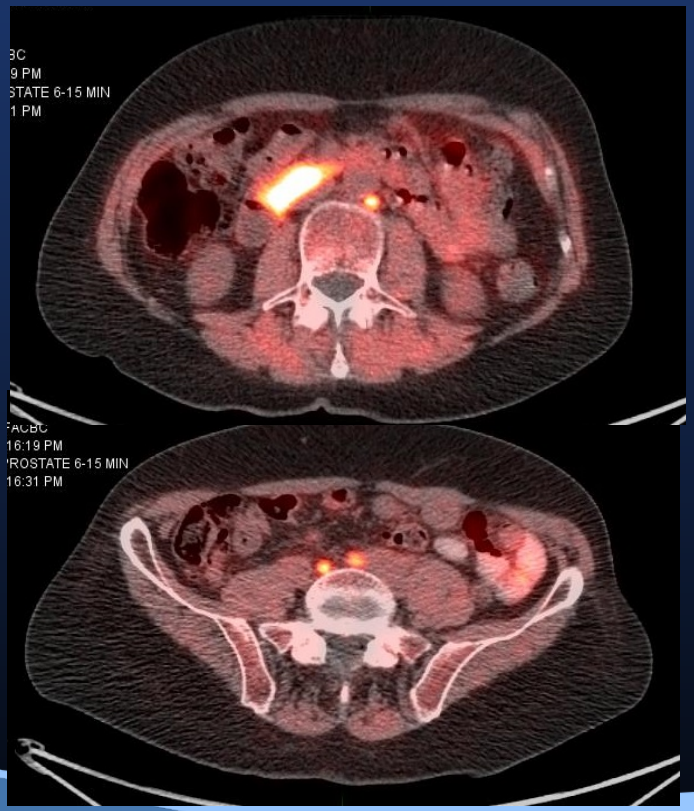
PSA recurrence after proton therapy.
Fluciclovine 2 years earlier with uptake in right SV (and negative MR), but elected no biopsy or therapy. Now PSA 18.8.
Bone scan and mpMR negative.

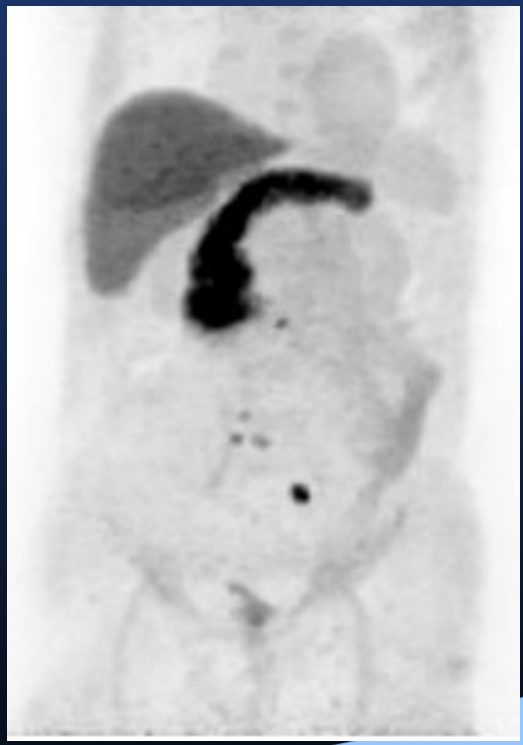
**Right SV hotter.**



# PSA recurrence after proton therapy. Bone scan and mpMR negative.

**But new pelvic and retroperitoneal nodes.**



# From the visible to the invisible to the visible…

| | Availability | Expense | Accuracy |
|---|---|---|---|
| **Eyeball** | Widely | Least | Least |
| **Dedicated** | Limited | Most | Highest |
| **Multimodality** | Mostly | Modest | High |

# Future Plans

- Continue to work on technique and workflow
  - Especially automation
    - *e.g. line up brachytherapy seeds*
  - May be great application for PET-MR
- Use data to refine criteria for positivity in bed
- Plan to incorporate other radiotracers such as PSMA
- Active surveillance trial
  - perhaps combination of radiotracers

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