UCSF Helen Diller Family Comprehensive Cancer Center

Molecular Imaging in RCC

Arpita Desai MD

Assistant Professor

Medical Director GU Oncology

University of San Francisco California

Molecular imaging

- Non-invasive technique for depicting and quantifying biological processes in tumors at the molecular and cellular level
- PET and SPECT are among the most sensitive molecular imaging techniques

Arpita Desai/UCSF
@ADESAIONCMD

Metabolic profiling and imaging in RCC

Genetic Basis of RCC:

- RCCs are characterized by mutations in metabolic pathway genes, including:
  - **Oxygen sensing**: VHL (von Hippel–Lindau)
  - **Tricarboxylic acid (TCA) cycle**: FH (*fumarate hydratase*), SDHB (*succinate dehydrogenase B*)
  - **Energy & nutrient sensing**: MTOR (*mammalian target of rapamycin*)

Metabolic Differences Between RCC and Benign Tumors:

- Distinct metabolic profiles due to genetic mutations
- Changes in oxygen sensing, energy metabolism, and nutrient signaling

Role of Metabolic Radiotracers in RCC Imaging:

- Radionuclide-labeled metabolites selectively accumulate in tumors
- Enables non-invasive tumor detection and characterization

Clinical Potential of Metabolic Radiotracers:

- Identify tumor proliferation and metabolic heterogeneity
- Improve diagnosis and prognostic assessment of RCC

Arpita Desai/UCSF
@ADESAIONCMD

FDG PET tracers in RCC

18F-FDG PET-CT in RCC

- **Mechanism:** Glucose analogue transported via GLUT proteins
- **Diagnostic Value:**
  - Limited for **primary RCC** (Sensitivity: 47–89%, Specificity: 67–87%)
  - **Comparable** to conventional imaging for **recurrent/metastatic RCC**
- **Clinical Findings:**
  - **104 RCC patients (94 ccRCC):** Sensitivity 74%, Specificity 80%
  - **125 ccRCC patients:** Effective in distinguishing WHO–ISUP high-grade ccRCC
  - **Positive uptake** associated with **high progression risk**
- **Advantages over CT/MRI:**
  - **Low nephrotoxicity**, **no allergy risk** → Suitable for renal insufficiency
  - **Effective for:** FH-deficient RCCs, high-grade ccRCCs, pRCCs

11C-Acetate PET-CT in RCC

- **Mechanism:** Reflects acetate metabolism → Acetyl-CoA synthesis
- **Current Use:** Mainly in **prostate cancer, glioma**
- **Findings in RCC:**
  - **High heterogeneity in uptake** limits differentiation of benign vs. malignant renal masses
  - **70% uptake in RCCs** (13 ccRCCs, 1 pRCC in 20-patient study)
  - **Oncocytomas** show **higher uptake** than RCCs

Arpita Desai/UCSF
@ADESAIONCMD

Wu *et al* Nature Reviews Urology 2024
Schieda, N. *et al.* Radiology 2022
Alongi *et al* 2016
Vogel et al 2019
Zhao *et al* 2021
Schug *et al* 2015
Kim *et al* 2024

FDG PET tracers

Dual-Tracer PET-CT (18F-FDG + 11C-Acetate)

- **Metabolic Profiles (48 RCC Patients + 10 AMLs):**
  - AMLs: 18F-FDG-negative, 11C-acetate-positive
  - High-grade ccRCCs: High 18F-FDG uptake
  - Low-grade ccRCCs: High 11C-acetate uptake
  - chRCC: 11C-acetate uptake only
  - pRCC: 18F-FDG uptake only
- **Potential for RCC Subtype Differentiation**
  - **Combined imaging** could improve diagnosis & classification

Arpita Desai/UCSF
@ADESAIONCMD
Wu *et al* Nature Reviews Urology 2024
Ho *et al* 2012

CD70: A Novel Target for ccRCC Imaging

CD70 Expression in ccRCC:

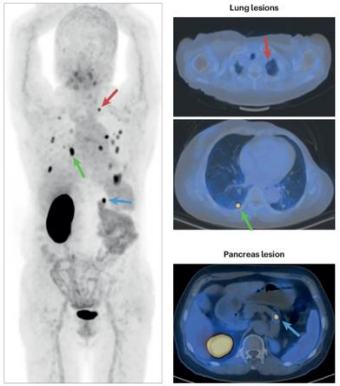
- CD70, a TNF superfamily member, is aberrantly expressed in **~80% of ccRCC cases** but absent in normal kidney tissue.
- High CD70 expression correlates with **tumor differentiation, necrosis, metastasis, and survival outcomes**.
- Immunohistochemistry is the current method for CD70 detection, but whole-body imaging is needed.

Potential Applications:

- **Diagnostic Marker:** Differentiates ccRCC from other RCC subtypes.
- **Therapeutic Target:** CD70 expression enables immune evasion and T cell suppression, making it a promising target.
- **Theranostic Approach:** Molecular imaging can guide CD70-targeted treatments.

Flieswasser, T. et al. 2022
O'Neill, R. E. et al. 2017
Ruf et al 2015
Huang, R. R. et al 2024

CD70: A Novel Target for ccRCC Imaging



Advantages of CD70-targeted Imaging:

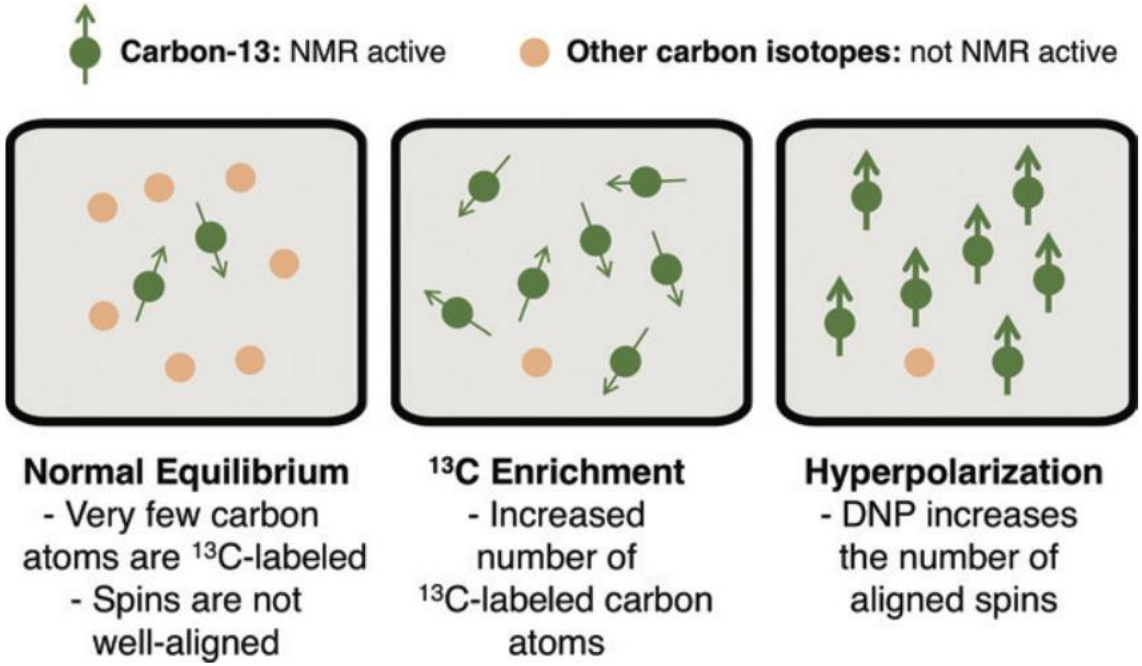
- **Non-invasive & Whole-body Detection:** Overcomes immunohistochemistry limitations.
- **Uses Single-Domain Antibody (sdAb) Tracers:** Small size (~15kDa), high affinity, rapid clearance.
- **Preferred Radiolabels:** 68Ga (T½ = 68 min) & 18F (T½ = 109.8 min) for efficient clinical imaging.

Key Findings from Clinical Studies:

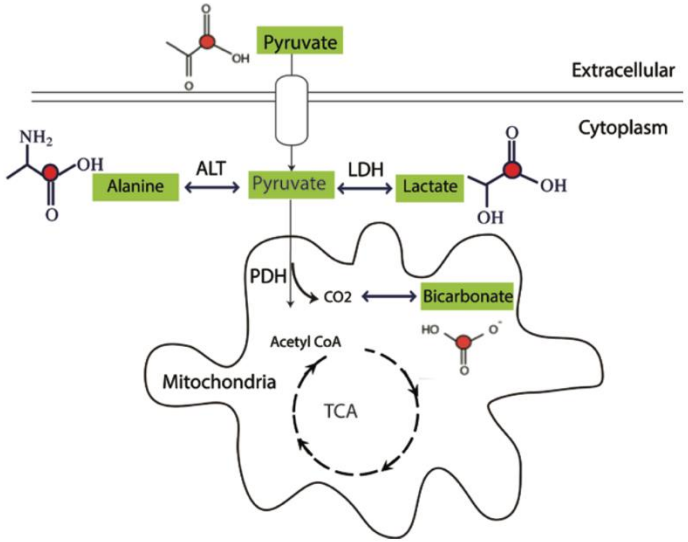
- **[18F]RCCB6 PET-CT:** Higher tumor-to-background ratio, detected more metastases than CT/18F-FDG PET-CT.
- **[68Ga]Ga-NOTA-RCCB6:** Accurately identified metastases in various organs.
- **Clinical Utility:** Staging, restaging, metastasis identification, therapy response monitoring, and post-treatment surveillance.

Hyperpolarized C13 MRI in RCC

- HP ^{13}C MRI is a novel tool allowing **rapid, noninvasive**, and **pathway-specific investigation of dynamic metabolic** and **physiologic processes** that were previously inaccessible to imaging.
- Hyperpolarization increases sensitivity (>10,000-fold signal increase) for imaging ^{13}C-enriched biomolecules that are endogenous, nontoxic, and nonradioactive.
- ^{13}C pyruvate is the most widely studied HP probe to date given its position at a critical branch point of multiple pathways, including glycolysis, the tricarboxylic acid cycle, and amino acid biosynthesis



Processes for increasing MRI signal of carbon 13 *(13C)* nuclei.
DNP = dynamic nuclear polarization, *NMR* = nuclear magnetic resonance.



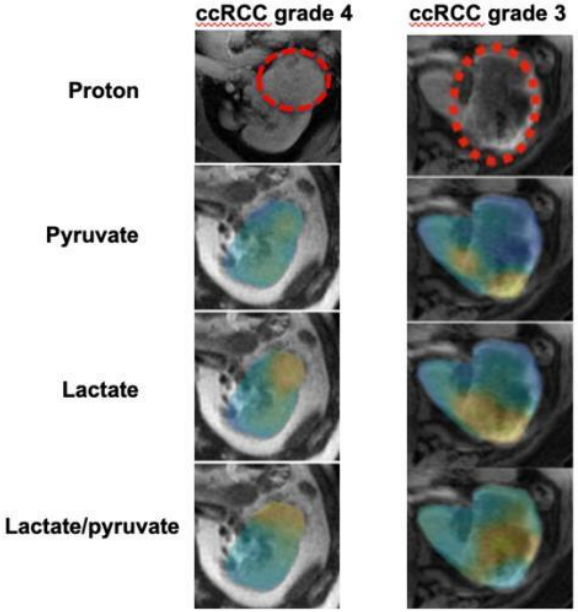
Multiple preclinical studies have shown the ability of HP ^{13}C pyruvate MRI to monitor the increased pyruvate-to-lactate conversion that occurs with aggressive cancers and to provide a rapid assessment of treatment response

Studies in localized RCC

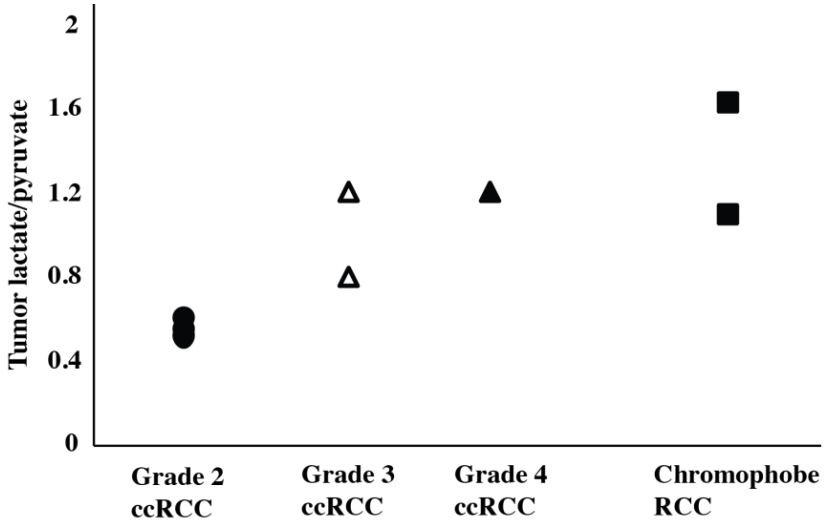
Metabolic Imaging With Hyperpolarized ^{13}C Pyruvate Magnetic Resonance Imaging in Patients With Renal Tumors—Initial Experience

Shuyu Tang, PhD [1,2]; Maxwell V. Meng, MD[3]; James B. Slater, RPh, PhD[1]; Jeremy W. Gordon, PhD [1]; Daniel B. Vigneron, PhD[1,2]; Bradley A. Stohr, MD, PhD[4]; Peder E. Z. Larson, PhD [1,2]; and Zhen Jane Wang, MD[1]

- Feasibility of using HP 13C in localized kidney cancer
- There was a trend toward a higher lactate-to-pyruvate ratio in high-grade ccRCCs compared with low-grade ccRCCs.
- Chromophobe RCCs had relatively high lactate-to-pyruvate ratios.



AUC images from HP^{13}C pyruvate MRI of patients with high grade (grade 3 and 4) ccRCC demonstrate increased tumoral lactate-to-pyruvate ratio



Tumor lactate-to-pyruvate ratio in 8 patients, stratified by tumor histology and grade.

Applications in metastatic RCC

- Assess treatment response of a TKI in metastatic kidney cancer
  - Regimens with high primary Progressive disease (belzutifan, Ipi/nivo)
  - HLRCC –Reliance on glycolytic pathway
  - Chromophobe RCC
- Pilot study at UCSF to access early treatment response in metastatic RCC

Pilot study evaluating early treatment response in RCC

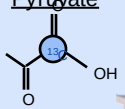
- To determine whether there is an early (4–6-week post treatment initiation with a TKI) change in tumor ^{13}C pyruvate metabolism when compared to baseline HP ^{13}C MRI scans
- To compare changes in tumor ^{13}C pyruvate metabolism between patients with disease control versus those with disease progression as defined by RECIST criteria on subsequent clinical CT scan at 3 months and this will be exploratory in nature

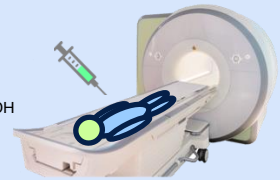
Systemic Therapies

Week 0 | Week 3-4 | Week 12-14

HP $^{13}C/^{1}H$ MRI of Advanced Renal Cancer (Baseline)

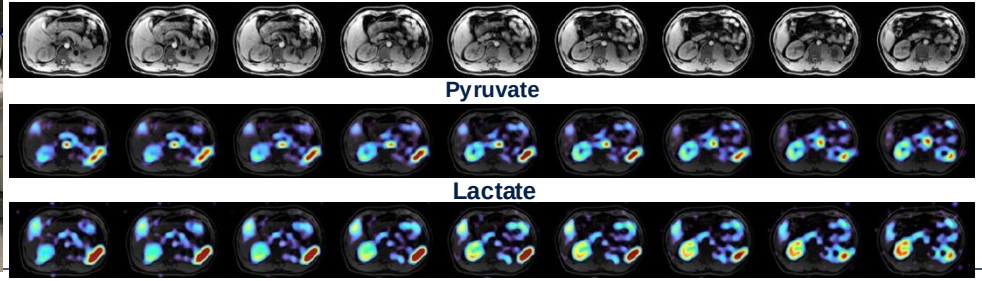
HP ^{13}C Pyruvate



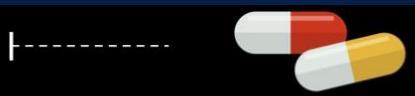


HP $^{13}C/^{1}H$ MRI (Early Follow Up)

Clinical Restaging Scan

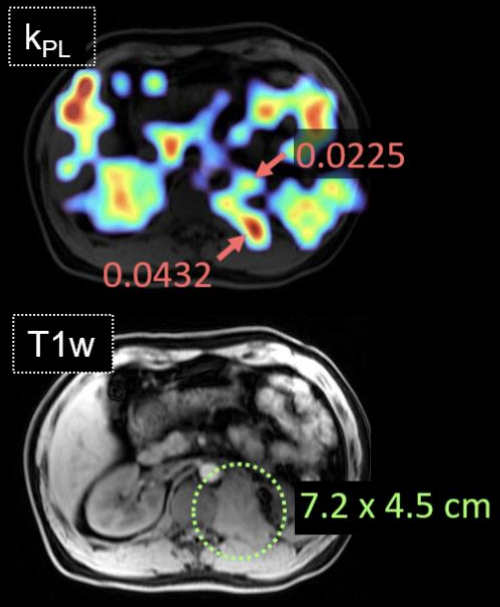


Workflow diagram to detect early treatment response in RCC

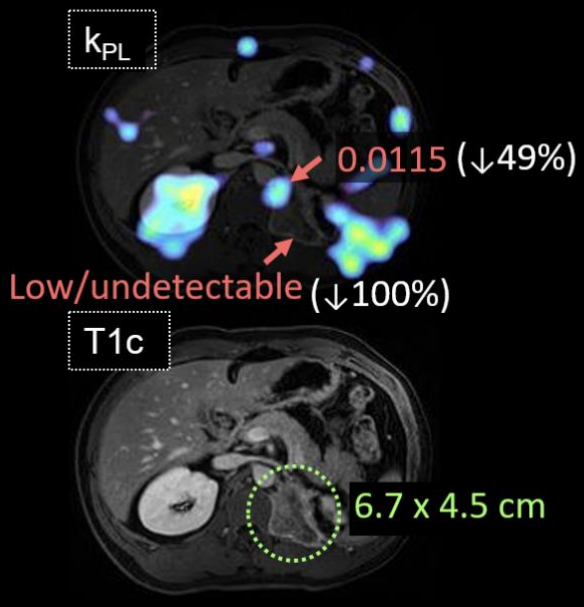


Week 0 | Week 4 | Week 14

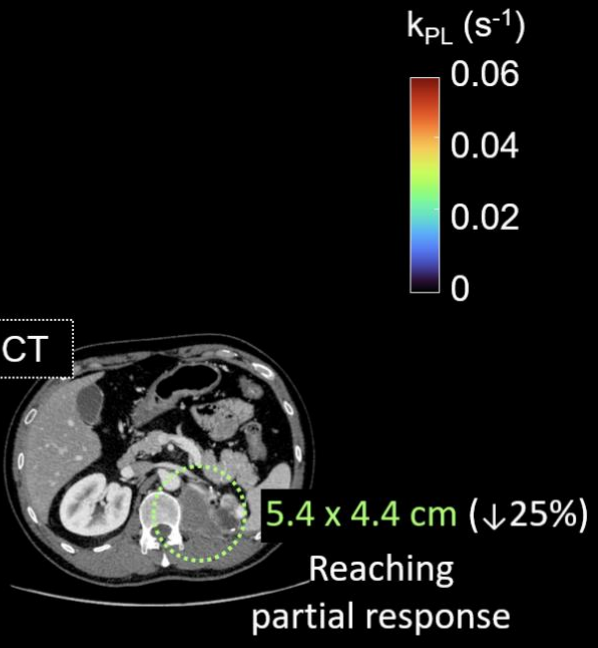
Baseline HP ^{13}C MRI



Follow-Up HP ^{13}C MRI

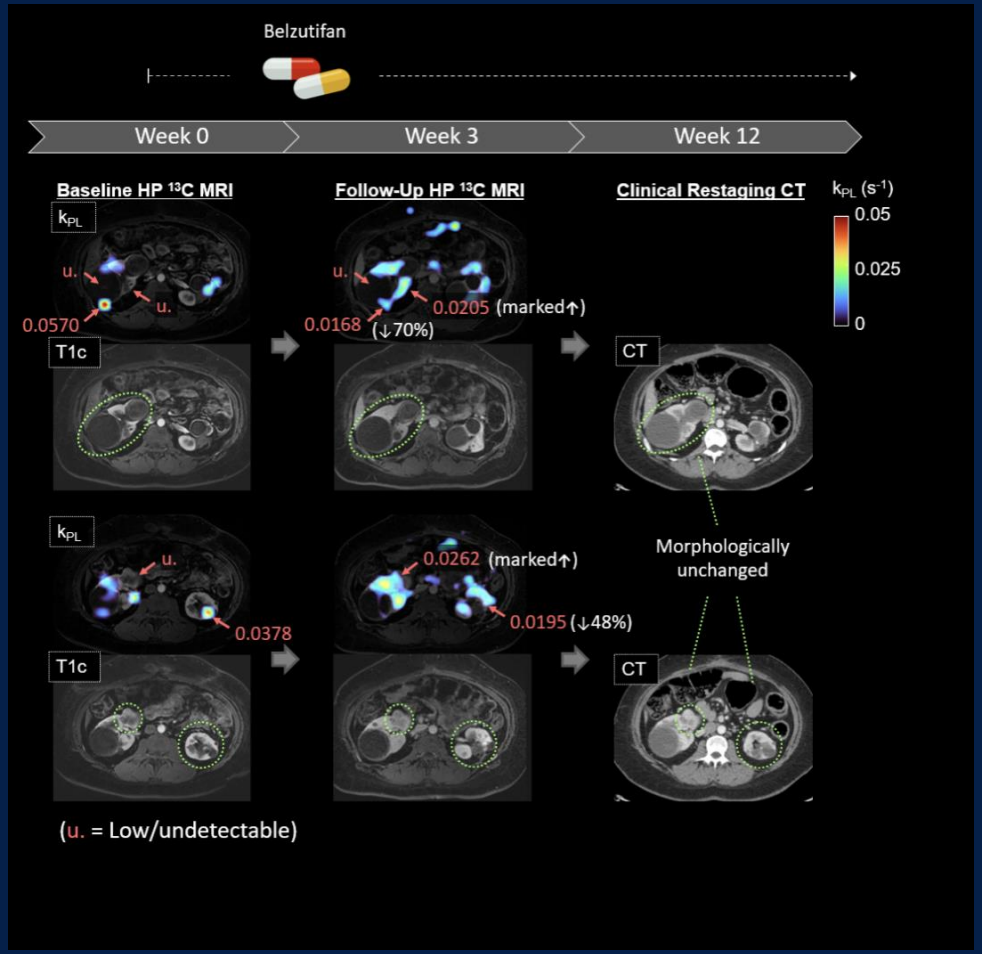


Clinical Restaging CT



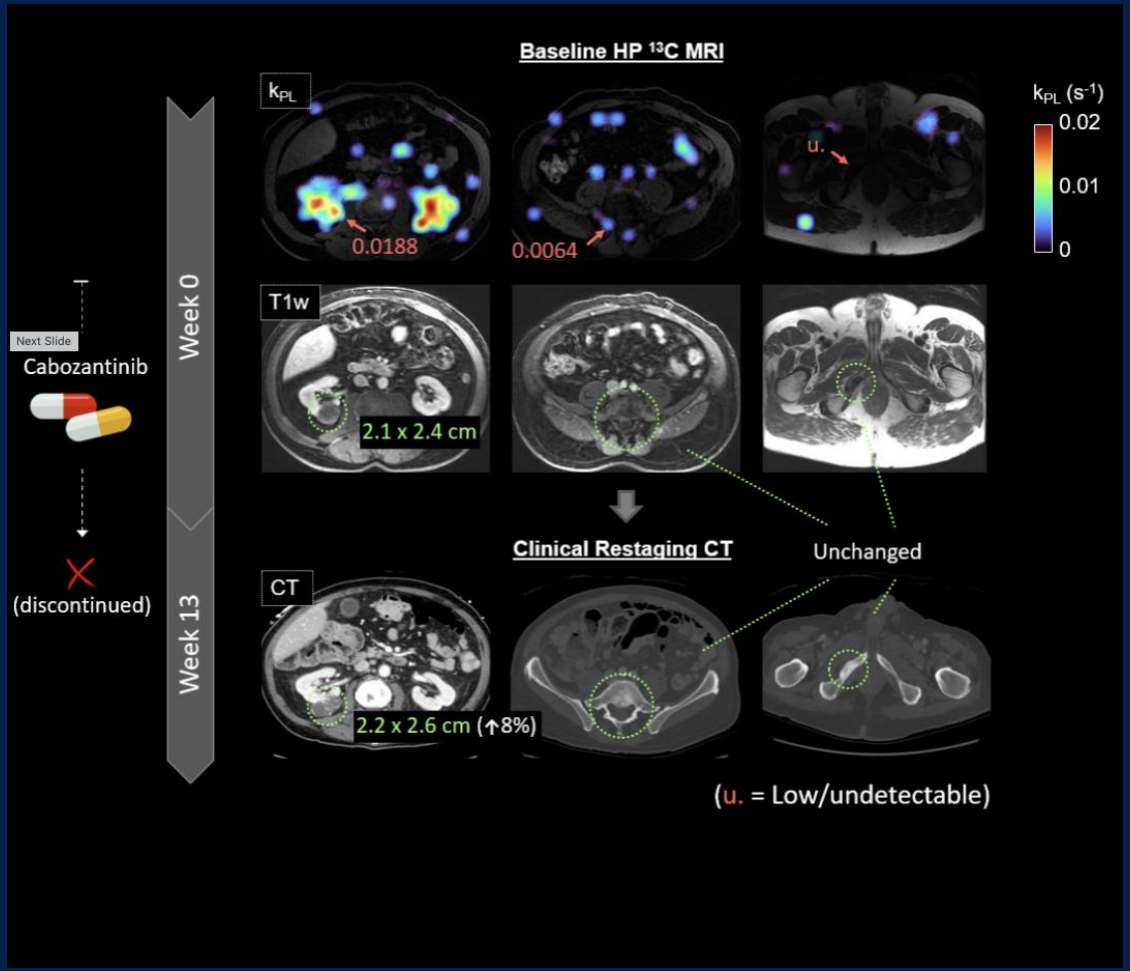
* Unpublished. Please do not post

Arpita Desai/UCSF
@ADESAIONCMD



* Unpublished. Please do not post

Arpita Desai/UCSF
@ADESAIONCMD



* Unpublished. Please do not post

Arpita Desai/UCSF
@ADESAIONCMD

Key Takeaways:

- **Molecular Imaging vs. Conventional Imaging:**
  - Nuclear medicine imaging detects biomarker expression and metabolic processes, providing **cellular & molecular-level insights**.
  - Enables **better diagnosis, staging, stratification, and therapy response assessment** in ccRCC.

Clinical Evidence & Future Needs:

- **CD70-targeted imaging** shows promise in diagnosis, surveillance, and treatment monitoring.
- **Further clinical trials** are needed to validate diagnostic and therapeutic applications.
- **Optimizing radiopharmaceuticals** will improve RCC detection and enable theranostic applications.
- **Collaborative efforts** are crucial to integrating molecular imaging into clinical guidelines and advancing RCC management.


UCSF
Helen Diller Family
Comprehensive
Cancer Center