SNMMI Satellite Symposium - FAP Ligands for Imaging and Therapy - 06/12/2022

FAP-LIGAND PET UPTAKE ≠ CANCER

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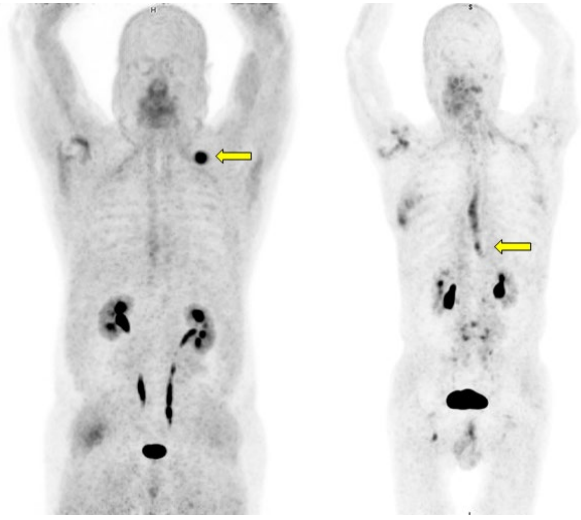


UCLA AHMANSON TRANSLATIONAL THERANOSTICS DIVISION

68GA-FAPI-46 PET CLINICAL RESEARCH PROGRAM

ACADEMIC INVESTIGATOR INITIATED AND SPONSORED

RDRC

Agreement between Heidelberg and UCLA Universities

UCLA
University of California, Los Angeles

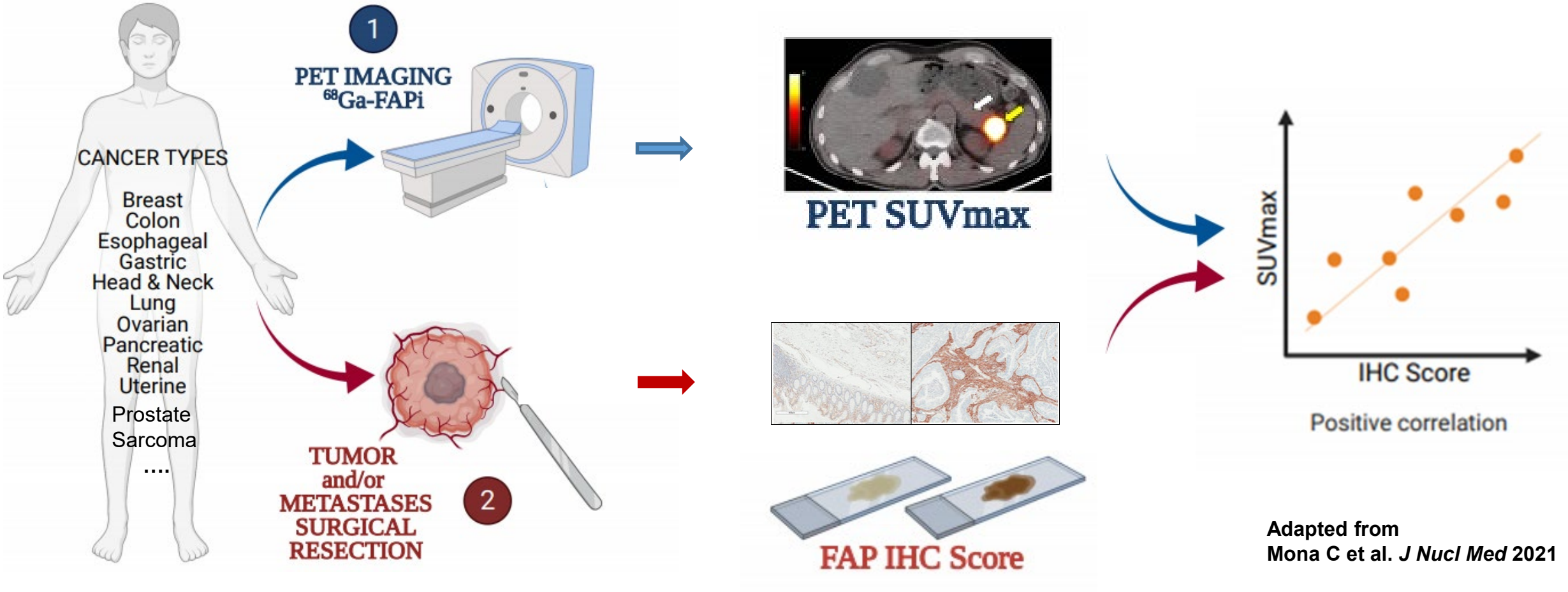
Since Dec. 2019

IRB #	NCT #	Protocol	Acronym	enrollment
19-000756	NCT04147494	FAPI + FDG (+/- PSMA) before surgery in **multiple** cancers	**FAPI PET RDRC 1**	**25 / 30 - Open**
20-000177	NCT04457232	FAPI + PSMA for **Prostate** Cancer before surgery or biopsy	**FAPI PET Prostate**	**21 / 30 - Open**
20-000623	NCT04457258	FAPI + FDG for **Sarcoma** before surgery or biopsy	**FAPI PET Sarcoma**	**13 / 30 - Open**
20-003628	NCT04459273	FAPI + FDG for **multiple** cancers before surgery or biopsy	**FAPI PET RDRC 2**	**16 / 30 - Open**
21-000678	NCT05365802	FAPI for **Lung Interstitial Disease**	**FAPI Lung ILD**	**4 / 30 - Open**

06/08/2022 n=77

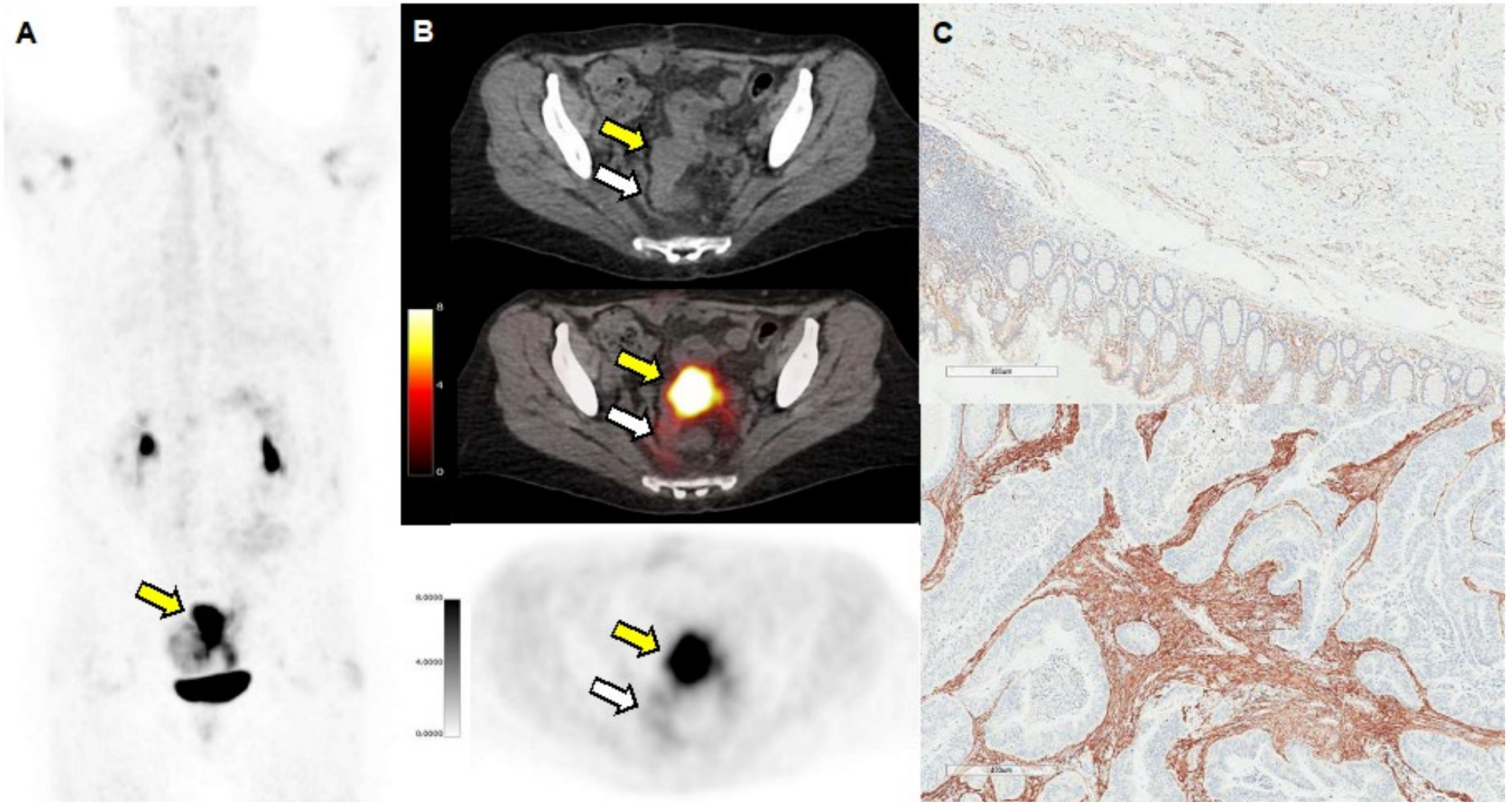
AIM OF THE 68GA-FAPI-46 PET RDRC STUDIES

⇨ TO CORRELATE THE FAPI PET SIGNAL WITH FAP IHC STAINING



Adapted from
Mona C et al. *J Nucl Med* 2021

CASE EXAMPLE #01



sigmoid colon adenocarcinoma

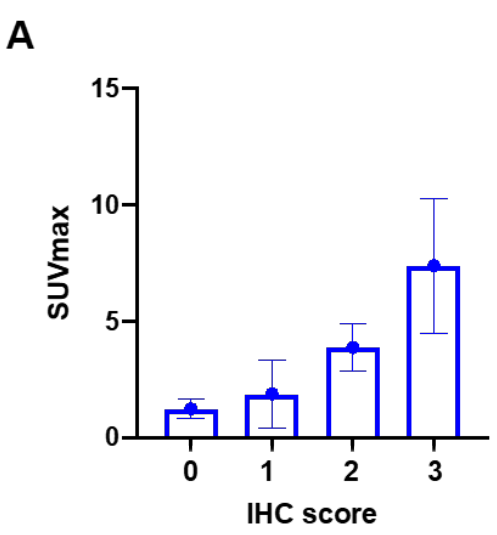
Mona C et al. *J Nucl Med* 2021

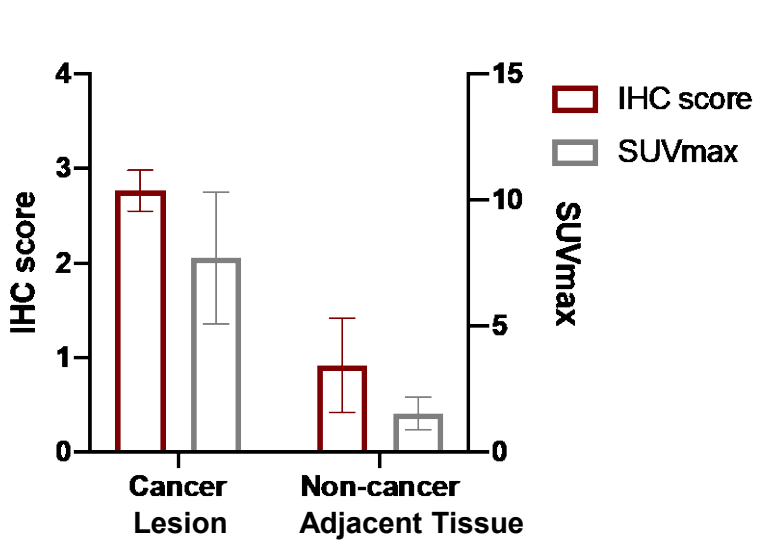
68Ga-FAPI-46 PET STUDY **NCT04147494 BASKET #01** EARLY REPORT

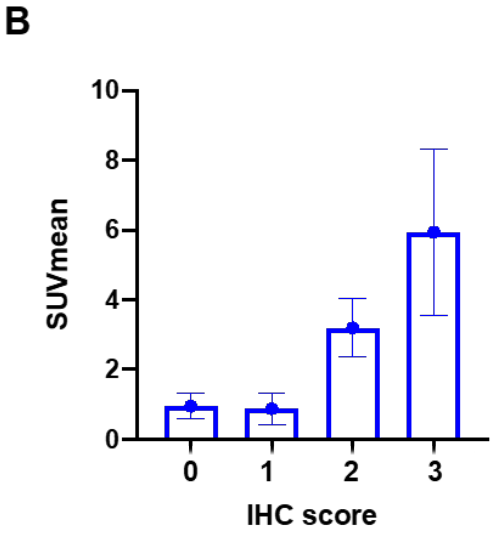
FAPI PET SUV AND IHC SCORE IN CANCER LESIONS

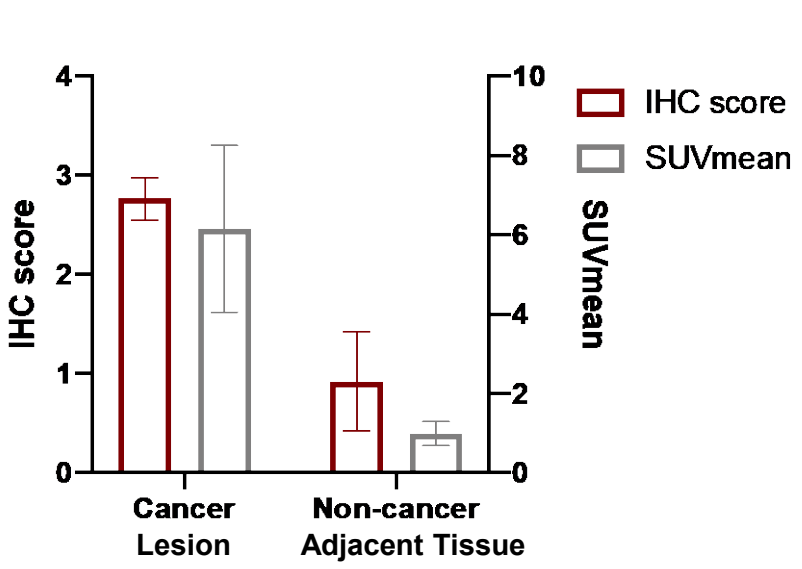
- Early interim report: First 15 patients between December 2019 and May 2020
- 7 different cancer types:
  CCR, HN, PDAC, breast, gastric, esophageal, uterine
- FAPi PET and surgery within 16.1 (range 1–50)

Mona C et al. *J Nucl Med* 2021



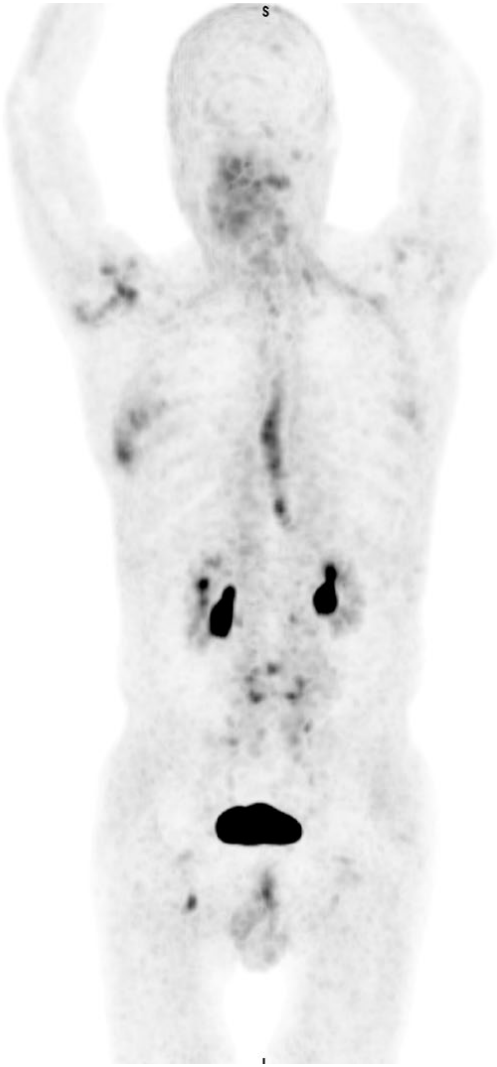






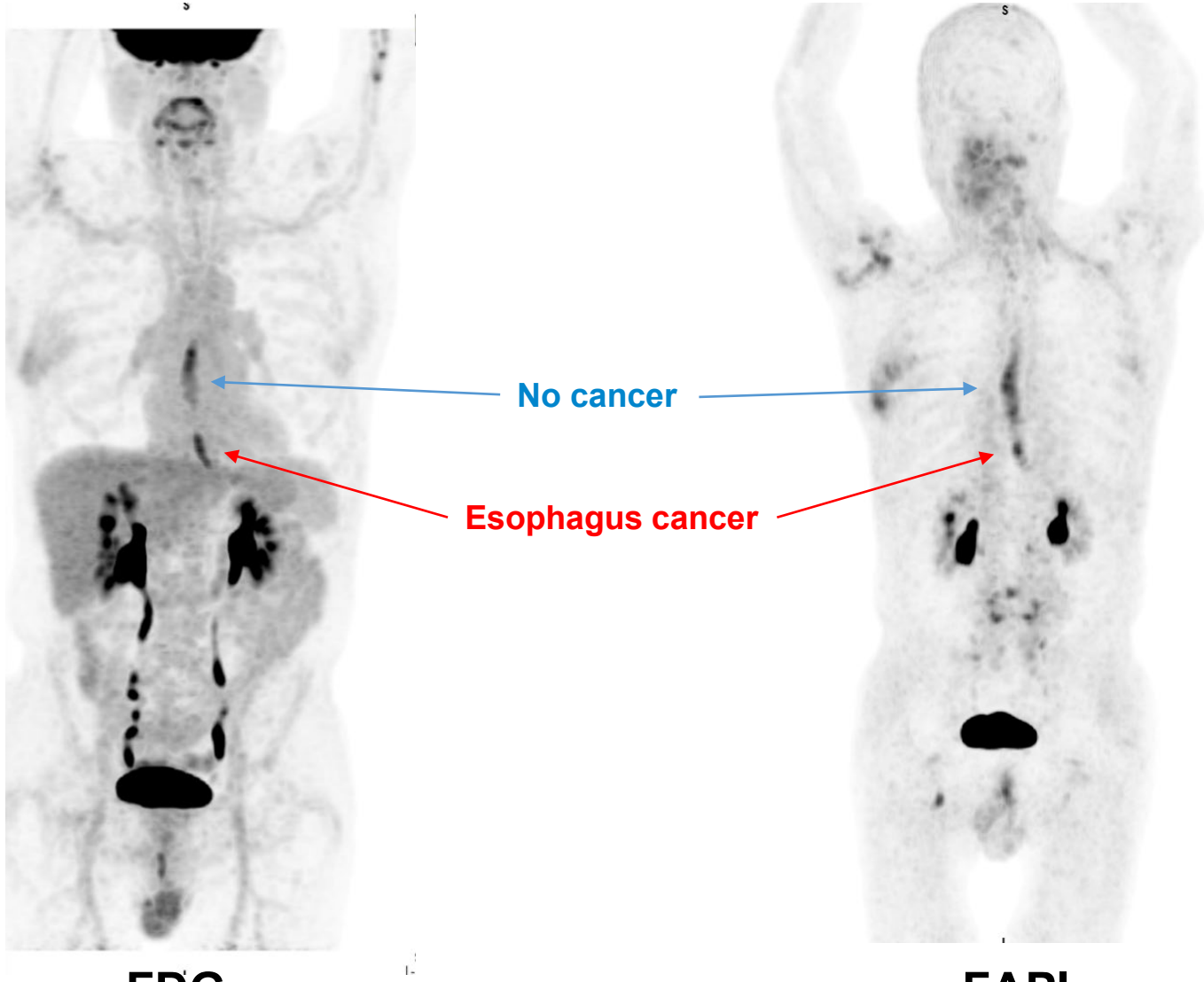
LEARNING CURVE – *"PITFALLS"*

FDG



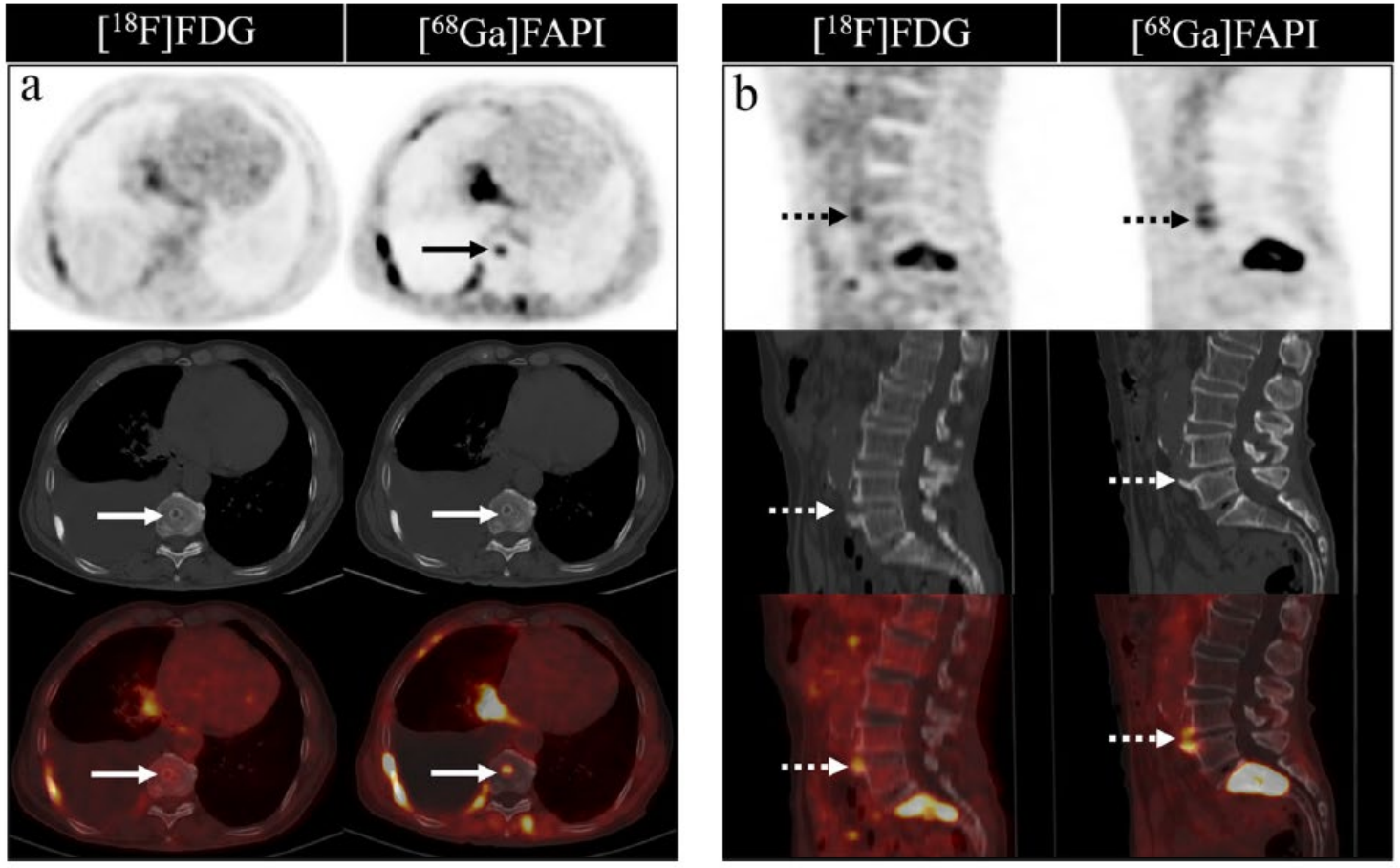
FAPI

LEARNING CURVE – *"PITFALLS"*

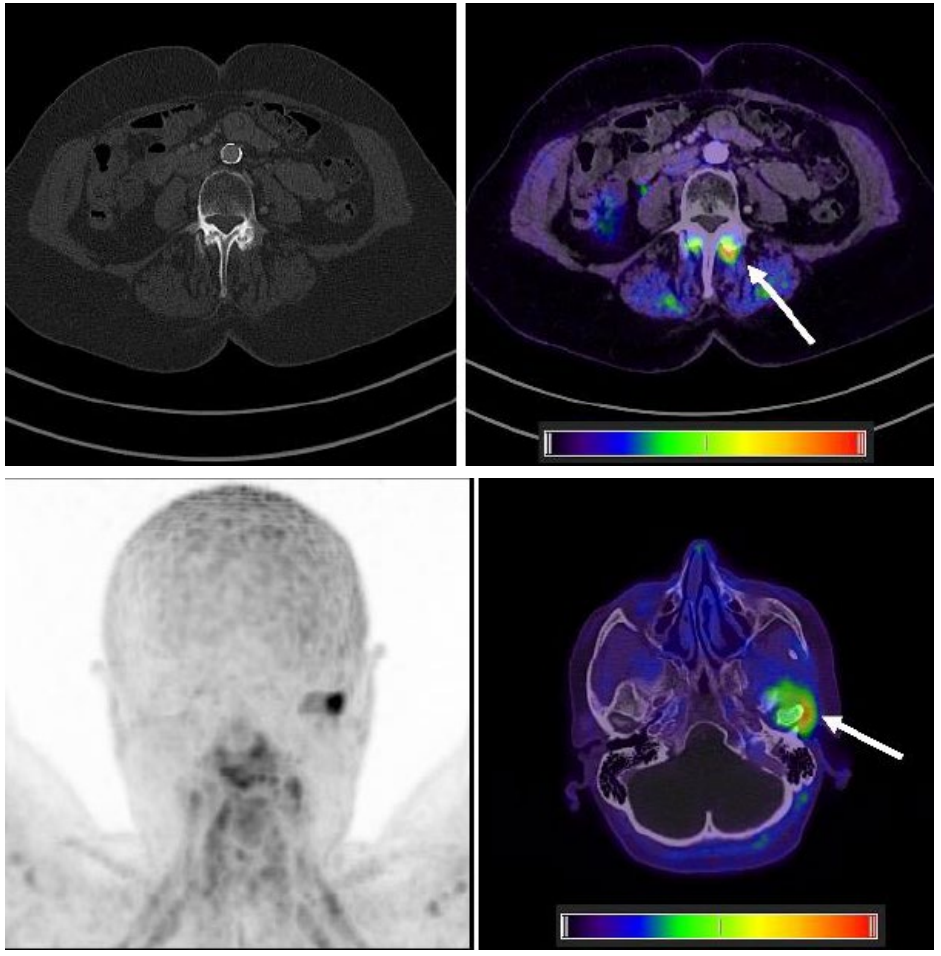


LEARNING CURVE – *"PITFALLS"*

Schmorl's node



Wu et al. Frontiers Oncol. 2021

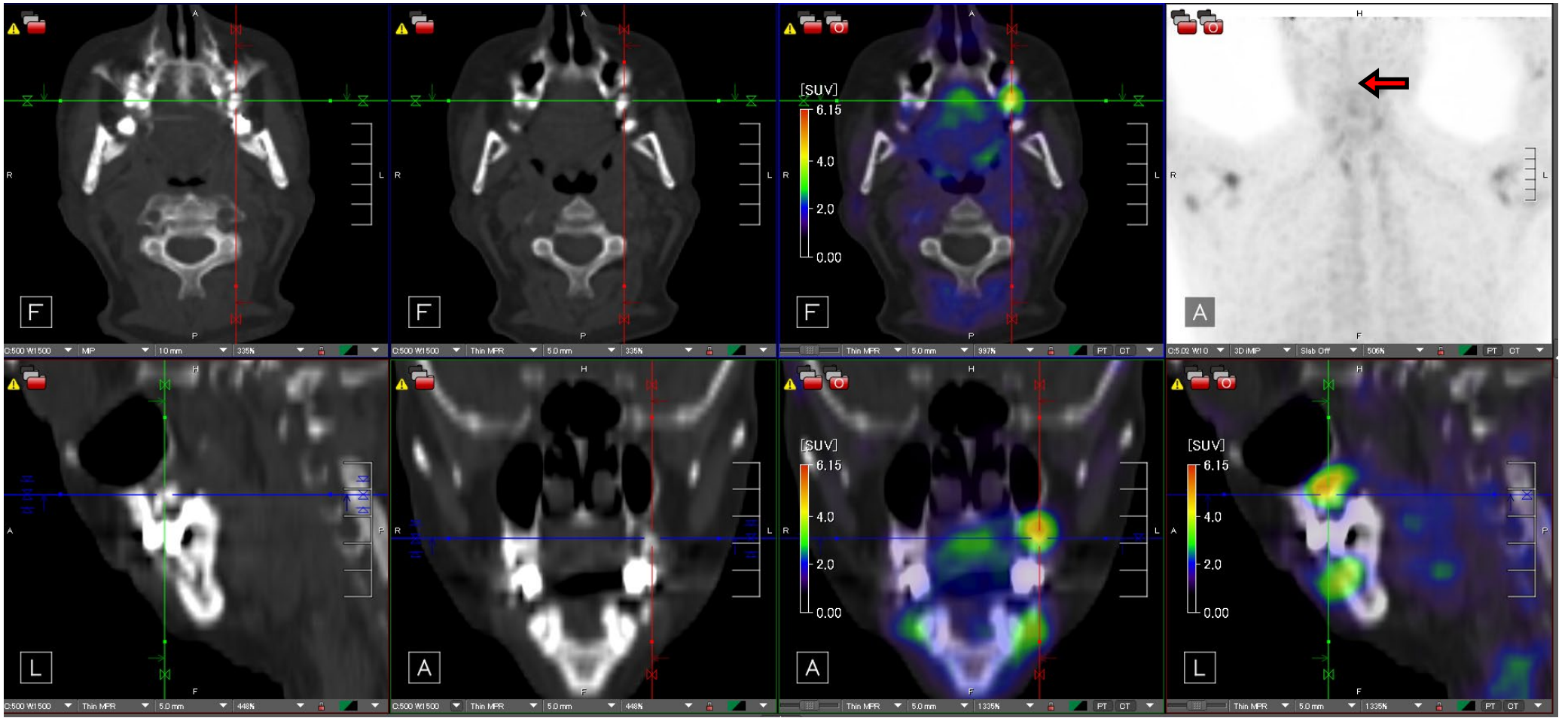


Kessler et al. J Nucl Med 2021

LEARNING CURVE – *"PITFALLS"*

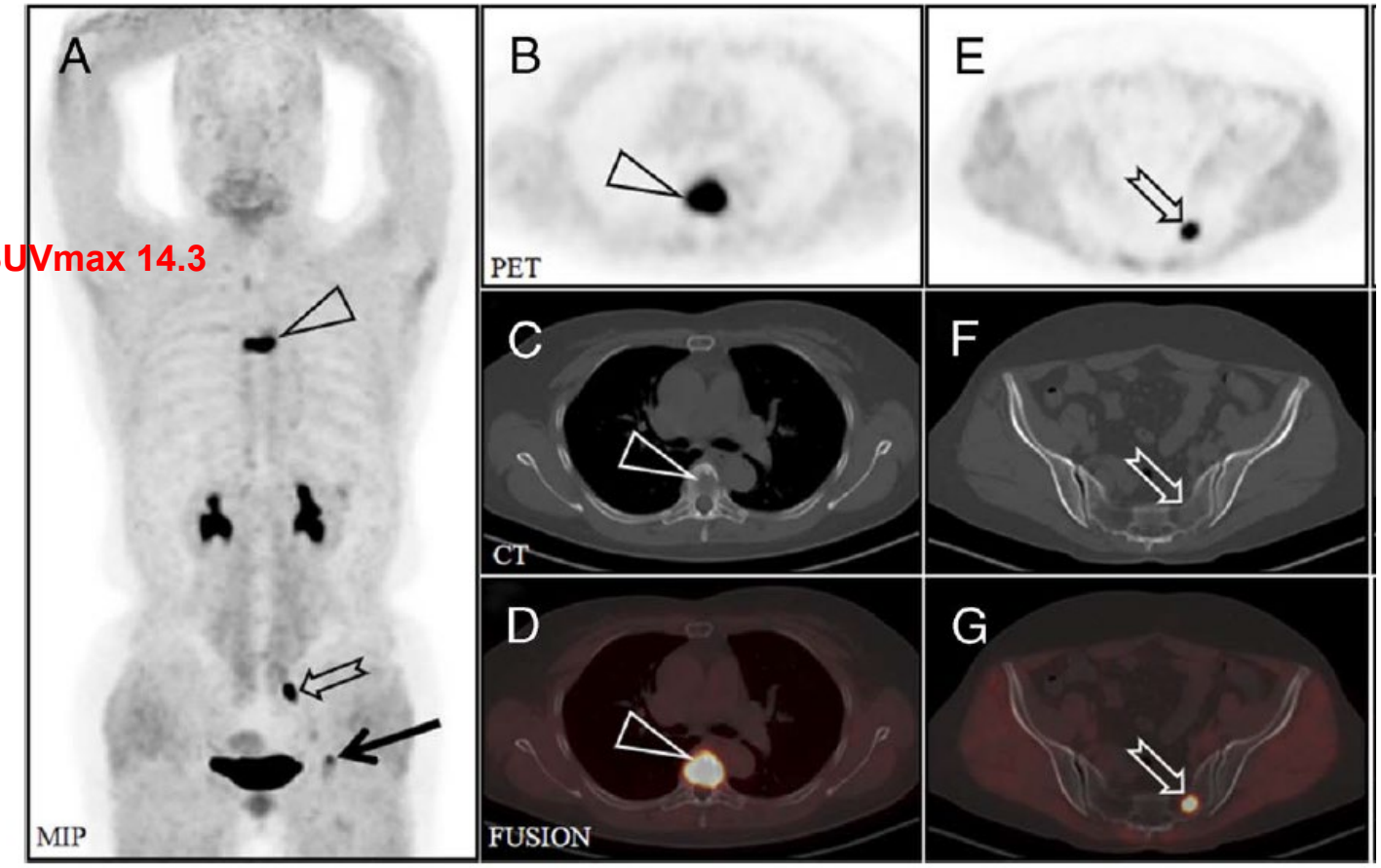
Focal dental uptake representing periodontitis was seen in 4/68 (6%) patients with a median SUVmax of 4.8 (range: 4.4-6.0)

Hotta M et al. 2022



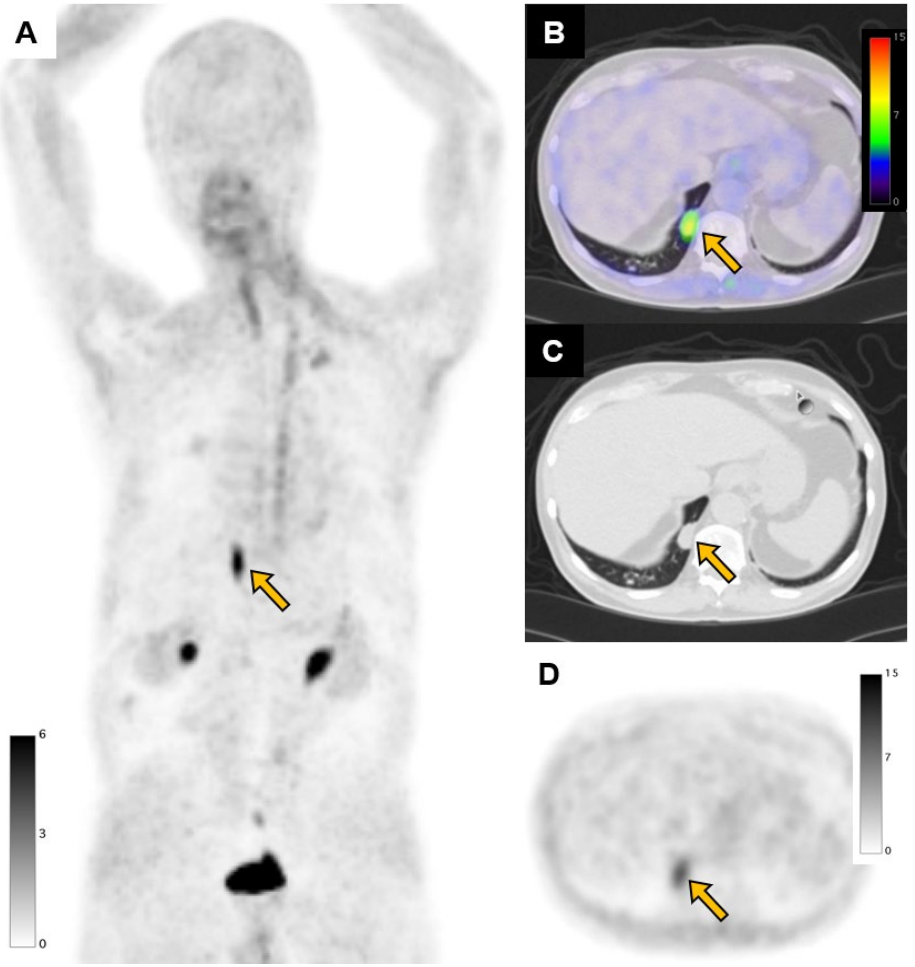
LEARNING CURVE – *"PITFALLS"*

SUVmax 14.3



tuberculous granulomatous inflammation

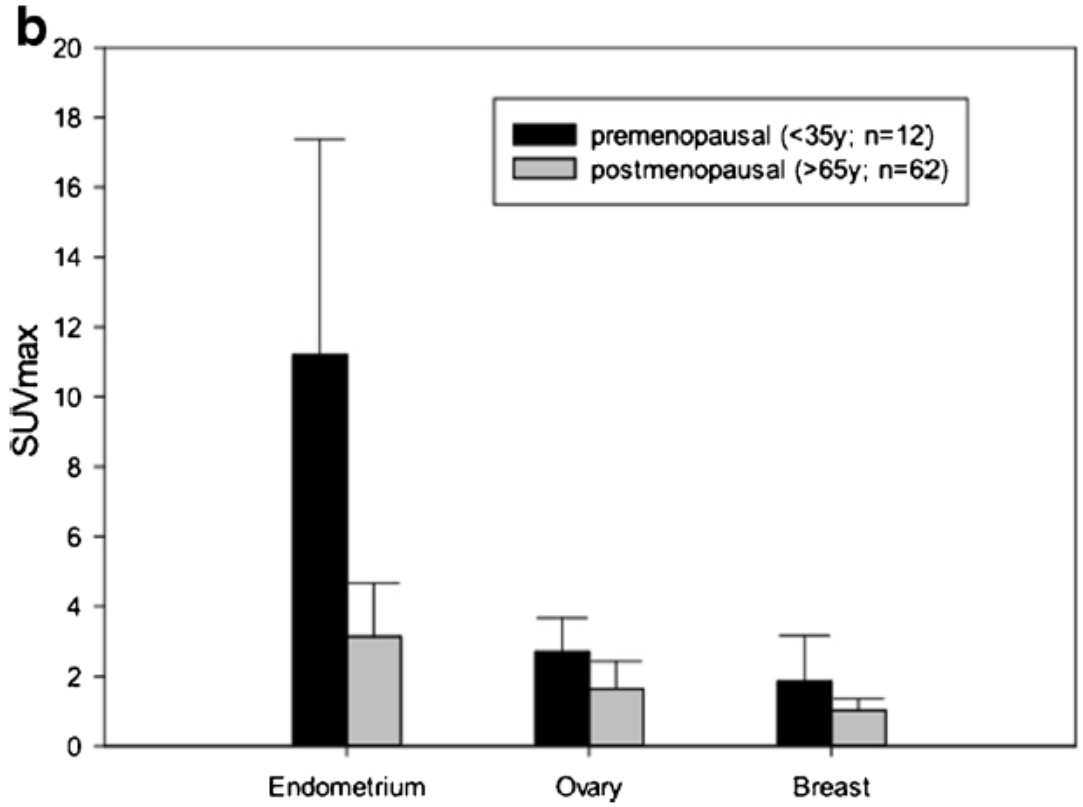
Gong et al. Clin Nucl Med 2022



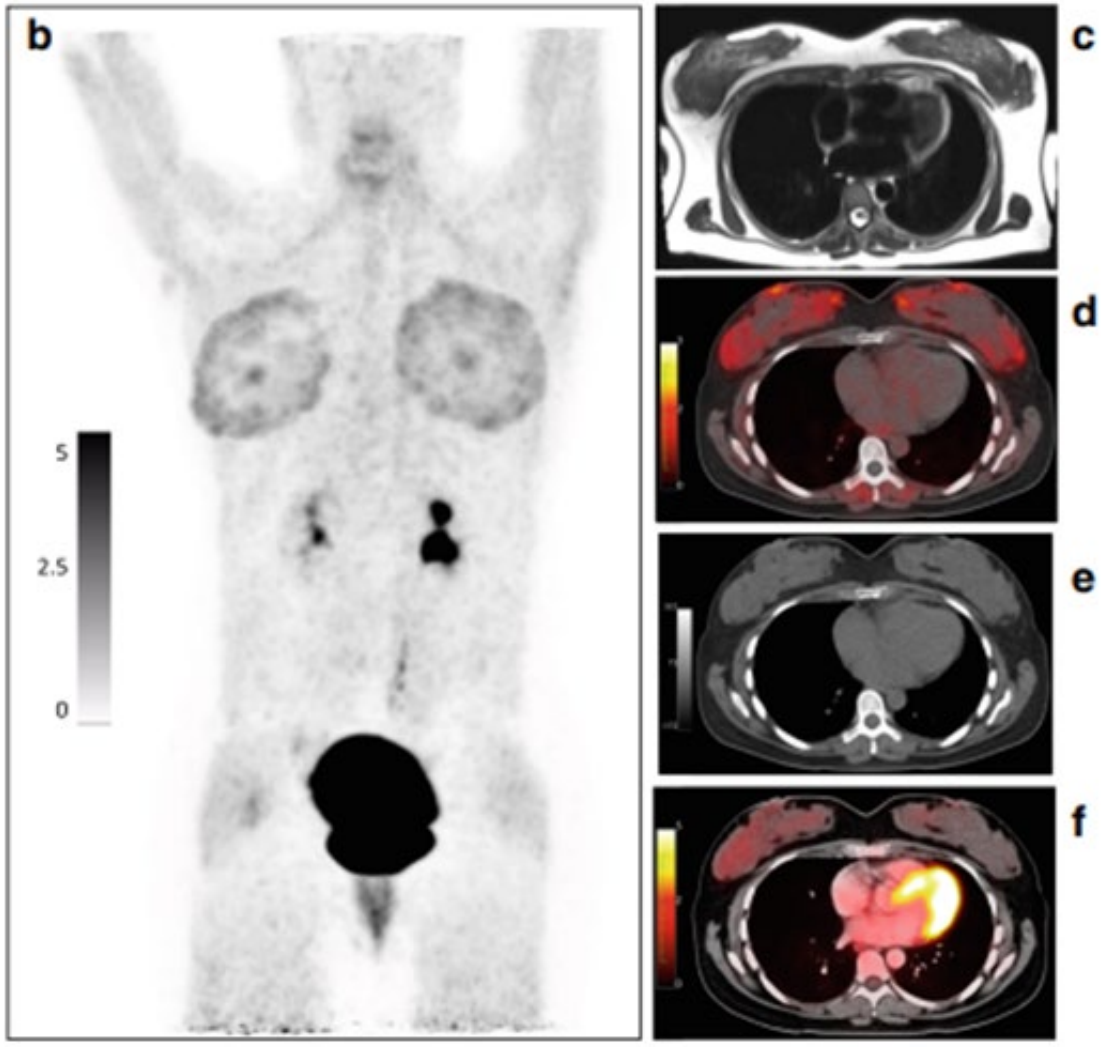
necrotizing granuloma

Hotta M et al. Eur J Nucl Med Mol Imaging 2021

LEARNING CURVE – *"PITFALLS"*

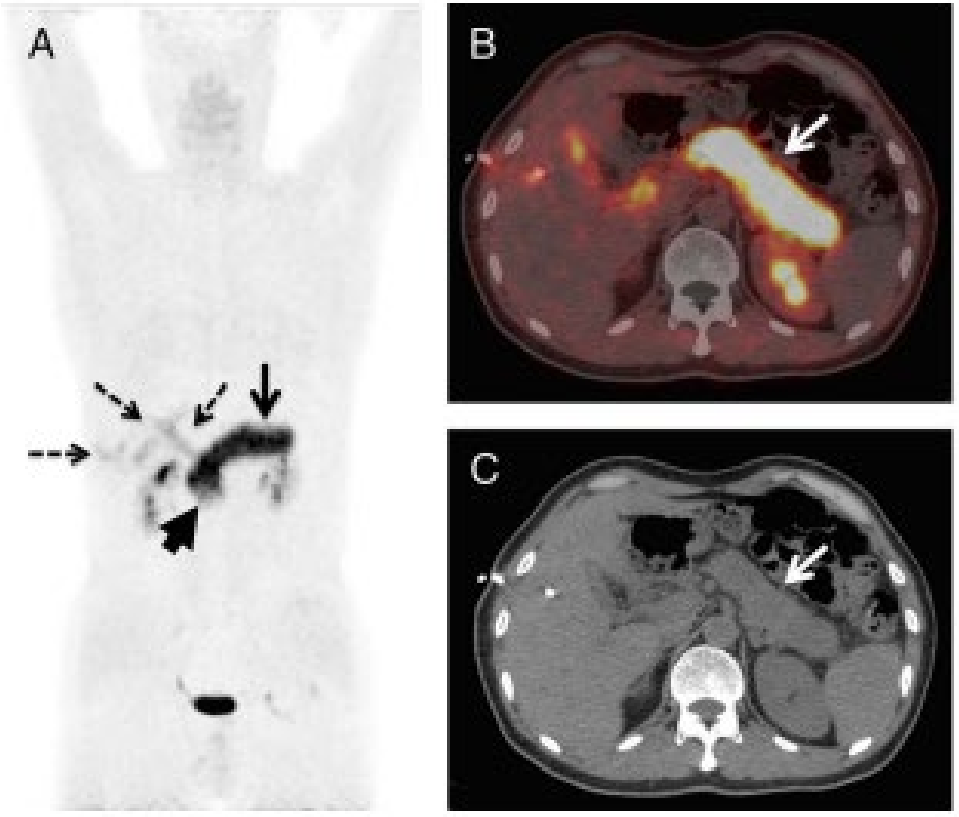


Dendl K et al. Eur J Nucl Med Mol Imaging 2021

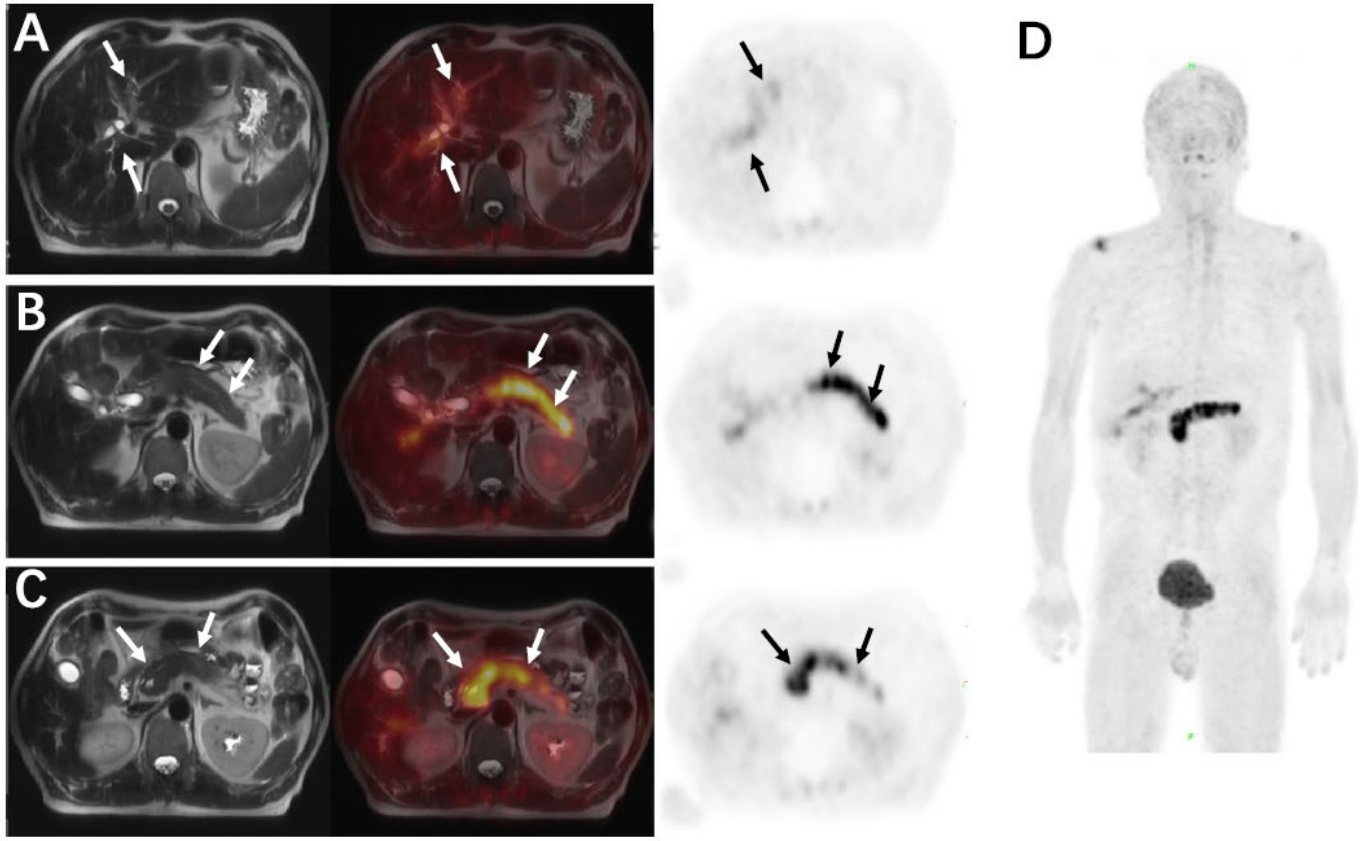


Sonni et al. Eur J Nucl Med Mol Imaging 2021

LEARNING CURVE – *"PITFALLS"* – PANCREATITIS



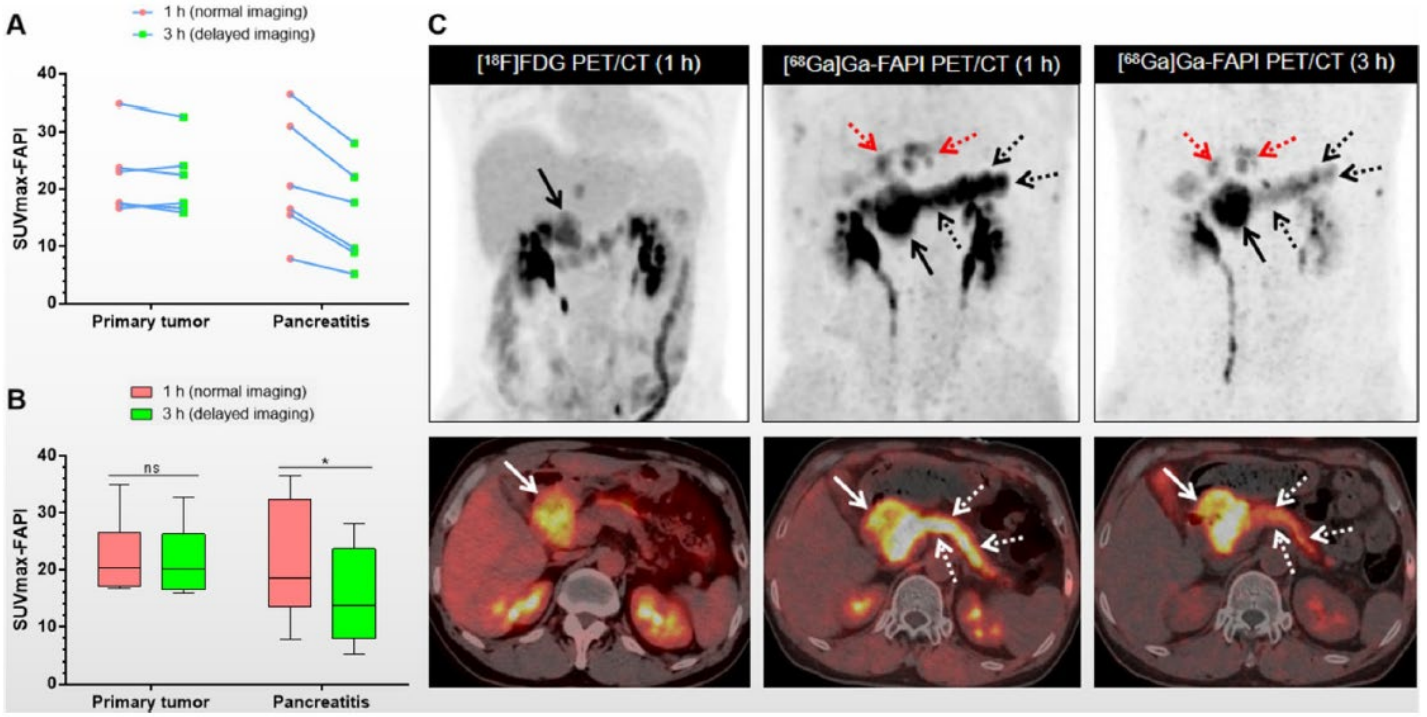
Luo et al. Clin Nucl Med 2020



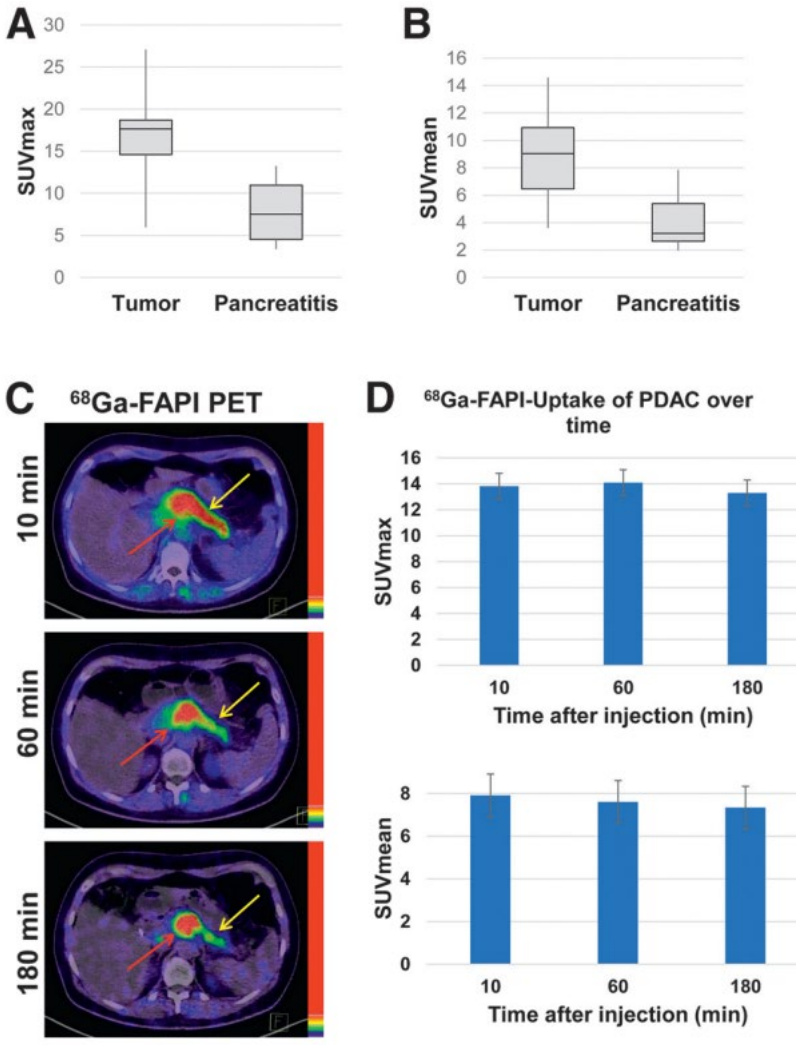
Shou et al. European Journal of Hybrid Imaging 2021

LEARNING CURVE – *"PITFALLS"* – PANCREATITIS

Intense FAPI uptake throughout the pancreas in 12/26 (46%)
dual-time point may differentiate pancreatitis from malignancy.



Pang et al. Eur J Nucl Med Mol Imaging 2021

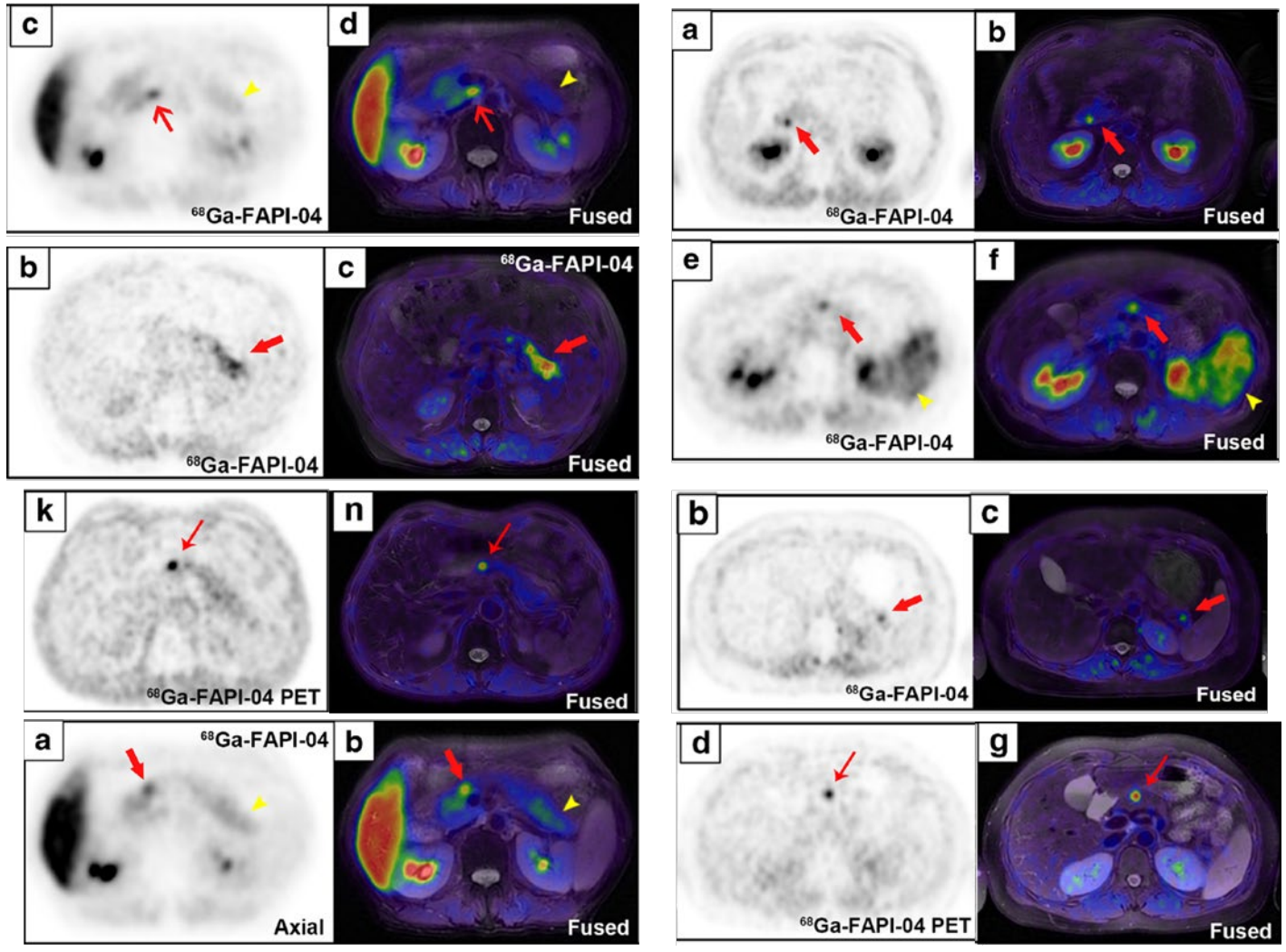


M Röhrich et al. J Nuc Med. 2021

LEARNING CURVE – *"PITFALLS"* – PANCREAS

- retrospectively analysis of 103 patients with cancer or liver fibrosis who had a 68Ga-FAPI-04 PET/MR
- **7/103 (7%) patients had focally elevated uptake in the pancreas**
- SUVmax range 3.1–9.1.
- **All the pancreatic lesions were proven to be non-neoplastic** by pathology confirmation or follow-up imaging.

Differential diagnosis:
- pancreatic pseudocysts,
- sites of prior pancreatitis,
- foci of IgG 4-related disease

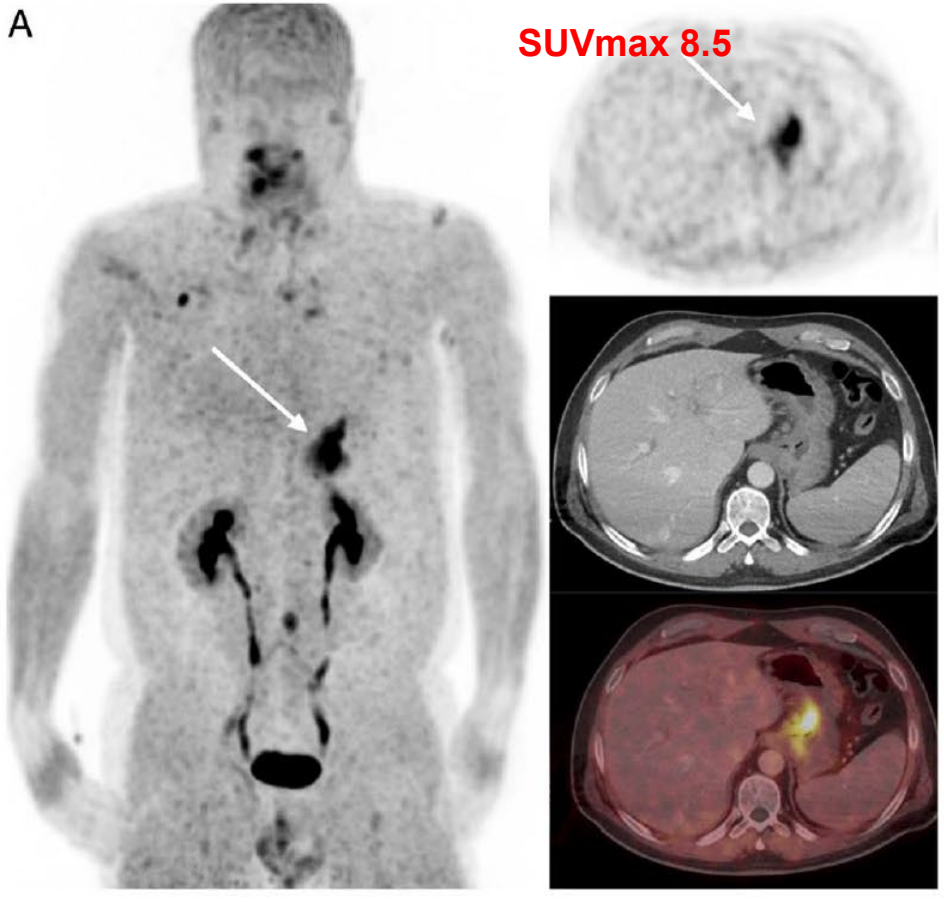


Zhang X et al. Eur J Nucl Med Mol Imaging 2021

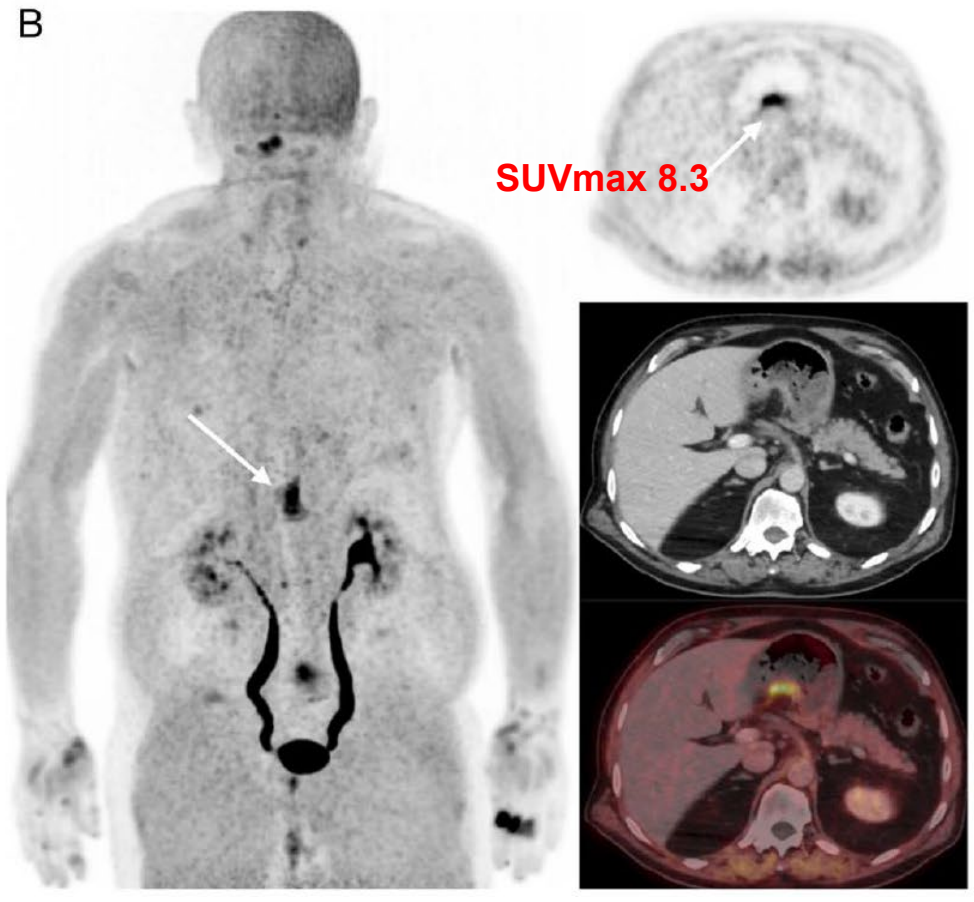
LEARNING CURVE – *"PITFALLS"*

Gastric cancer post-neoadjuvant therapy (4 cycles)
Residual disease ?

Patient #001



Patient #002



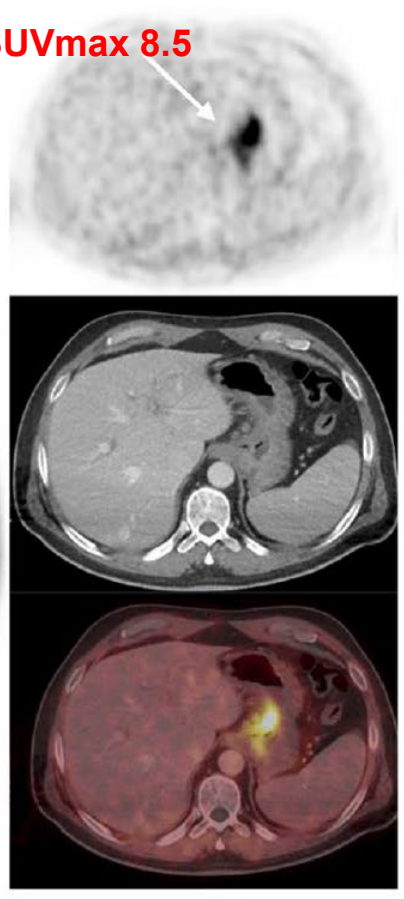
Buren et al. Clin Nucl Med 2022

LEARNING CURVE – *"PITFALLS"*

Gastric cancer post-neoadjuvant therapy (4 cycles)
Residual disease ?

Patient #001

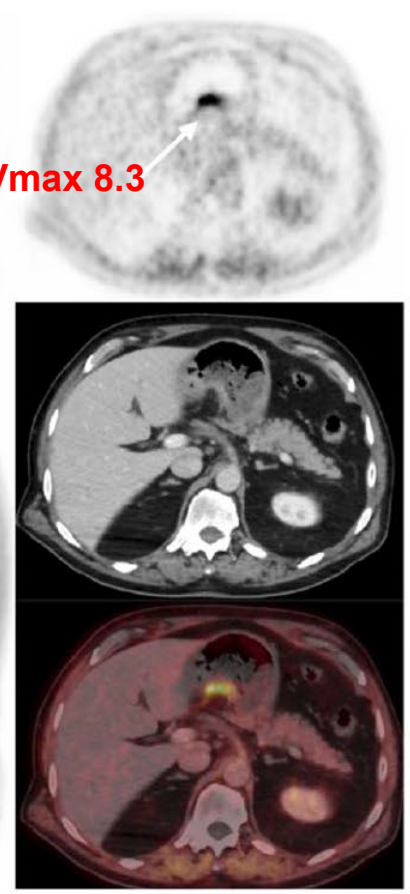
SUVmax 8.5



RESIDUAL CANCER

Patient #002

SUVmax 8.3

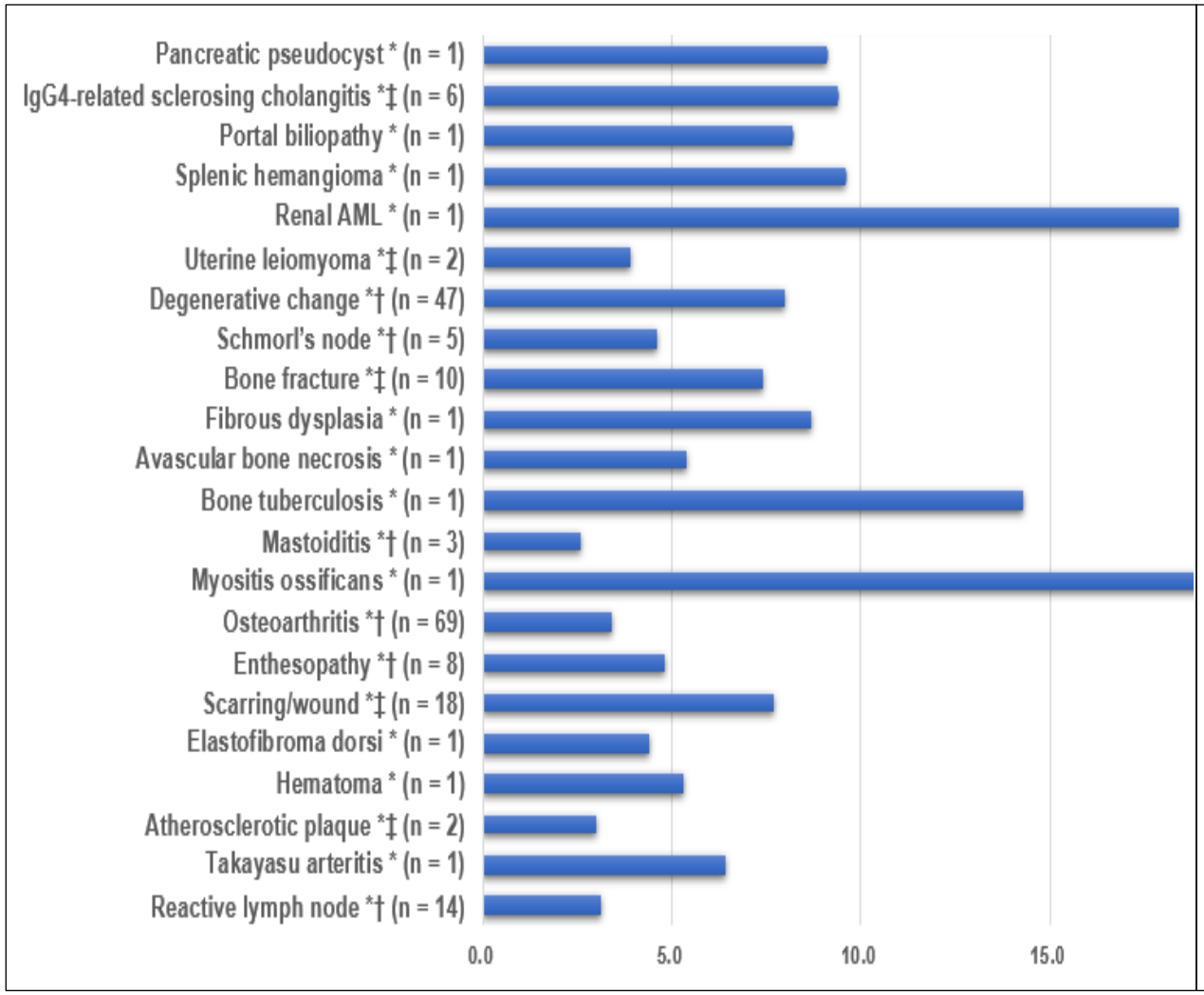


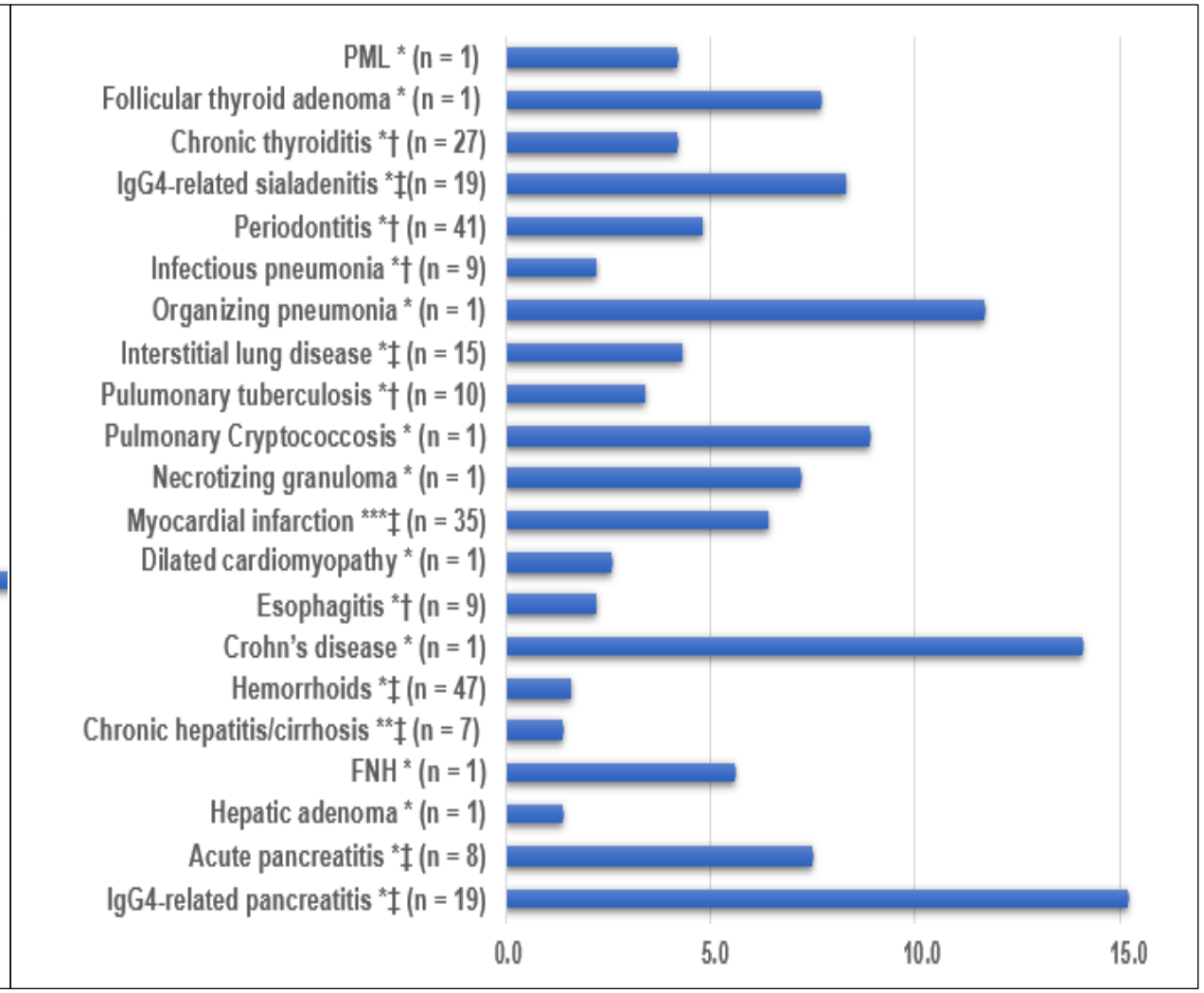
NO RESIDUAL CANCER !

inflammatory processes
fibrotic remodeling

Buren et al. Clin Nucl Med 2022

LEARNING CURVE – *"PITFALLS"*





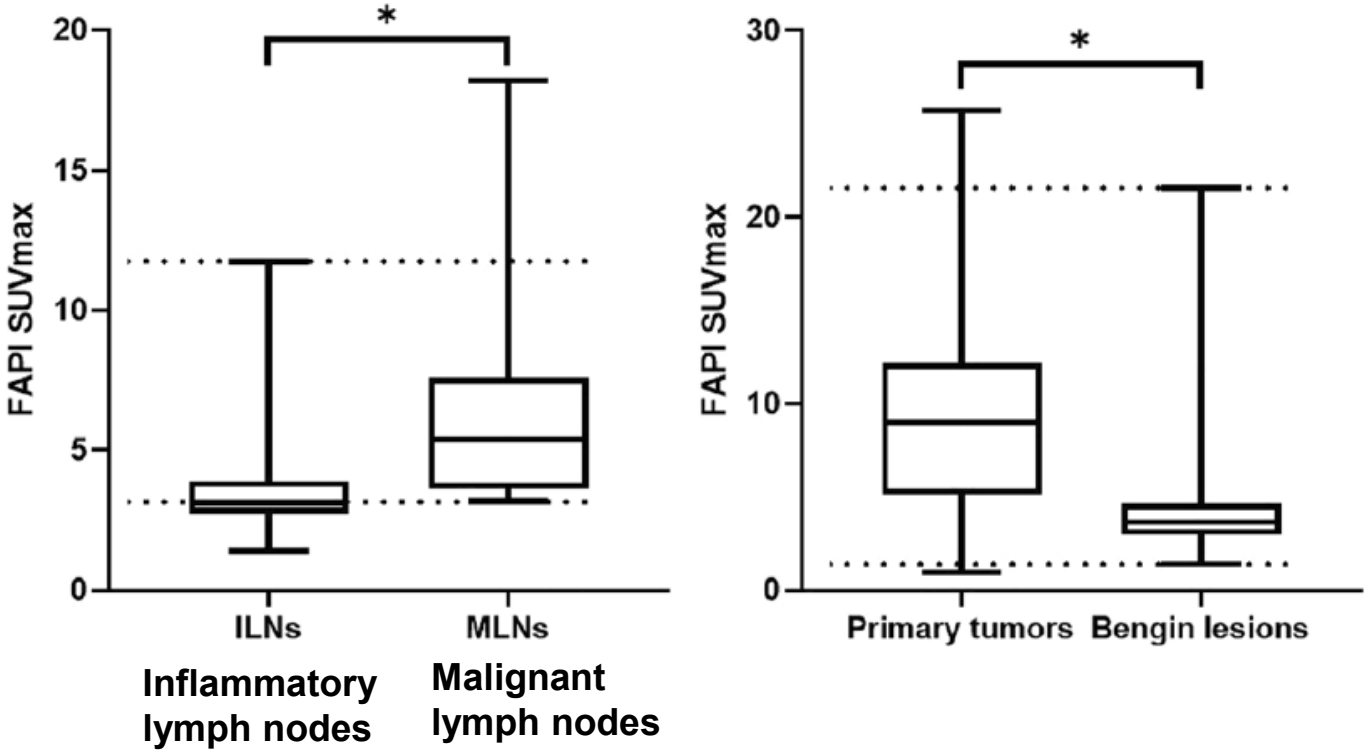
Hotta M et al. Br J Radiol (*In Press*) 2022

LEARNING CURVE – *"PITFALLS"*

Table 2 Benign lesions shown on ^{68}Ga-FAPI PET/CT

Lesions	*N*	Median SUV_{max}	Range of SUV_{max}
Inflammatory lymph nodes	69	3.13	1.39–11.74
Osteoarthritis	55	3.44	2.03–5.91
Exostosis	54	3.39	2.12–6.95
Hemorrhoid	47	3.66	2.49–5.4
Periodontitis	41	4.77	2.38–11.18
Fracture	17	3.76	1.9–6.08
Postoperative changes	10	4.93	3.16–13.79
Obsolete Tb	10	3.42	2.52–7.48
Esophagitis	9	3.01	2.13–9.29
Pneumonia	9	2.24	1.53–3.75
Enthesopathy	8	4.75	2.19–8.73
Tumor-induced pancreatitis	6	10.12	6.63–21.56
Chronic pancreatitis	6	3.7	2.07–4.24
Schmorl's node	5	4.59	3.71–6.69
Liver cirrhosis	4	3.95	3.29–6.75
Mastoiditis	3	2.58	2.45–3.33
Prostatitis	3	3.97	2.62–8.68
Appendicitis	2	4.17	3.12–5.21
Hypersplenism	1	4.05	NA
Renal AML	1	4.39	NA
Total	360	3.65	1.39–21.56

182 patients



significant overlap
Cancer vs Benign

Shan Zheng et al. Annals of Nuclear Medicine (2021)

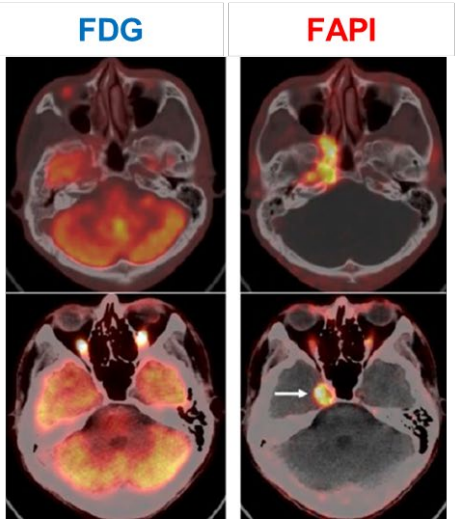
INDICATIONS
for FAP-targeted PET IMAGING ?

1. Cancer Detection / Staging
2. Target expression assessment for FAP-targeted Therapy
3. Non-oncologic Diagnostic Applications

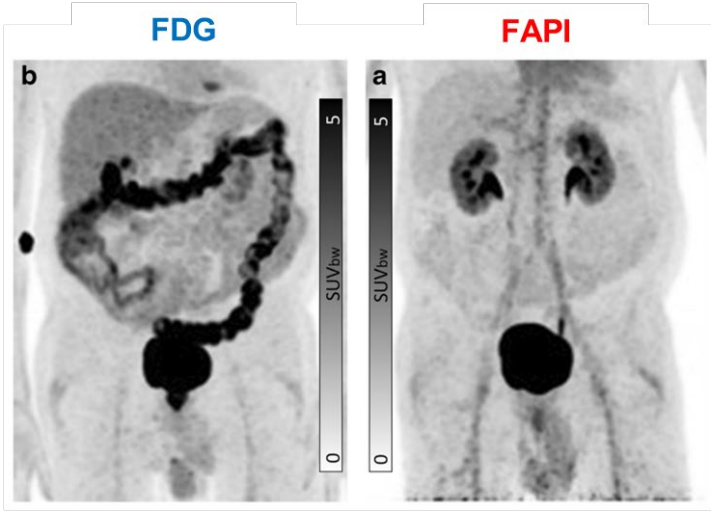
FAPI VS FDG, PAN-CANCER HEAD-TO-HEAD STUDIES

Higher Tumor-to-background-ratio of FAPI over FDG

- brain
- oral mucosa
- liver
- gastrointestinal / digestive /colon
- Bone



Chen H et al.
Eur J Nucl Med Mol Imaging 2020



Giesel et al.
Eur J Nucl Med Mol Imaging 2021

Potential Superiority of FAPI over FDG for ?

Primary Tumor detection

- Breast cancer
- Cancer of Unknown Primary
- Cholangiocarcinoma
- Gastrointestinal tumors
- Gastric signet ring cell tumors
- Head and neck cancer
- Mucinous tumors
- Nasopharyngeal carcinoma
- Pancreatic cancer

Metastasis detection

- Bone metastases
- Brain metastases
- Liver metastases
- Peritoneal carcinomatosis

FAP-TARGETED PET STUDY DESIGN

FAP-targeted PET
=

1. **High sensitivity for specific cancer types / stages**
2. **Low specificity**

+++ Importance of the Specific Clinical question +++

- Diagnosis: Detecting a target for biopsy in patients with a suspected cancer
- Initial staging: detecting M1 disease to exclude patient from unnecessary surgery
- Recurrence: Detecting a target for biopsy in patients with suspected recurrence

Design of Clinical Trial of Diagnostic Accuracy for each specific clinical question

Ex: primary diagnosis in PDAC too much FP in pancreas but good for M1 staging
Therapy response or residual disease detection after neo-adjuvant therapy impossible because of fibrosis

FAP-targeted PET INDICATION(S) FOR IMAGING/DIAGNOSTIC ?

1. Cancer Detection / Staging
2. Target expression assessment for FAP-targeted Therapy
3. Non-oncologic Diagnostic Applications

PET Biomarker Indication is Possible

Multiple Approved ER-targeted therapies for ER+ breast cancer:

Tamoxifen, Raloxifen, Toremifene, Fulvestrant …

Haines CN et al Essays Biochem 2021

Articles

THE LANCET Oncology

Diagnostic accuracy and safety of 16α-[^{18}F]fluoro-17β-oestradiol PET-CT for the assessment of oestrogen receptor status in recurrent or metastatic lesions in patients with breast cancer: a prospective cohort study

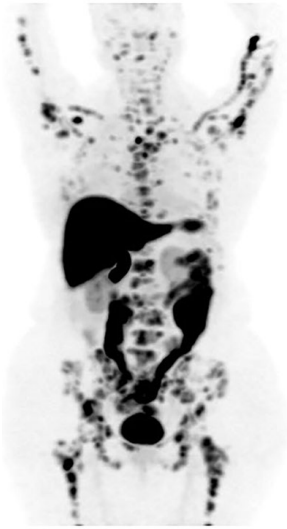
Sun Young Chae, Sei Hyun Ahn*, Sung-Bae Kim*, Sangwon Han, Suk Hyun Lee, Seung Jun Oh, Sang Ju Lee, Hee Jeong Kim, Beom Seok Ko, Jong Won Lee, Byung Ho Son, Jisun Kim, Jin-Hee Ahn, Kyung Hae Jung, Jeong Eun Kim, Seog-Young Kim, Woo Jung Choi, Hee Jung Shin, Gyungyub Gong, Hyo Sang Lee, Jung Bok Lee, Dae Hyuk Moon*

Chae SY et al. Lancet Oncol. 2019

Vaalavirta et al.
J Diag Imaging Ther. 2014

Jager A et al.
Breast Cancer Res 2020

Liu C et al.
Front. Oncol. 2020



Ulaner et al.
J Nucl Med 2021

FES PET was FDA approved for the detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.

FAP PET IN CANCER PATIENTS

FAP PET TO SELECT FOR FAP-TARGETED MRT ?

Y90-FAPI-46 / FAPi-04

n ~ 12 patients
dose 2.9 – 7.4 GBq
number of cycles: 1-4
Kidney Dose 0.52 Gy/GBq

Kratochwil et al. *J Nucl Med.* 2018
Lindner T et al. *J Nucl Med* 2018
Ferdinandus J et al. *J Nucl Med* 2021
Rathke H et al *Clin Nucl Med* 2021

Lu177-FAPI-46 / FAPI-04

n ~ 27 patients
dose 3.7 - 7.4 GBq
number of cycles: 1-4
Kidney Dose 0.9 Gy/GBq

Jokar N et al *Clin Nucl Med* 2021
Assadi M et al *Clin Nucl Med* 2021
Kuyumcu S et al. *Clin Nucl Med* 2021
Fu K et al. *Eur J Nucl Med Mol Imaging* 2021
Barashki S et al. *Clin Nucl Med* 2022
Kaghazchi et al. *Clin Nucl Med* 2022

Lu177-FAPI-2286

n= 11 patients
dose 5.8 GBq
number of cycles: 1-3
Kidney Dose 1.0 Gy/GBq

Baum P et al. *J Nucl Med* 2022

Lu177-DOTAGA.SA.FAPI$_2$

n= 16 patients
dose 5.5 -14 GBq
number of cycles: 1
No acute Grade 3-4 AE

Ballal S et al *Eur J Nucl Med Mol Imaging* 2021
Ballal S et al. *Thyroid*. 2022

FAP-targeted
Radiopharmaceutical Therapy

Early Experience
~65 patients

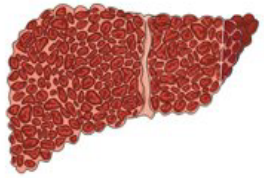
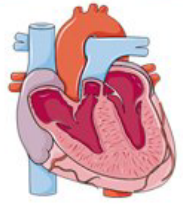
02.14.2022

FAP-targeted PET INDICATION(S) FOR IMAGING/DIAGNOSTIC ?

1. Cancer Detection / Staging
2. Target expression assessment for FAP-targeted Therapy
3. Non-oncologic Diagnostic Applications

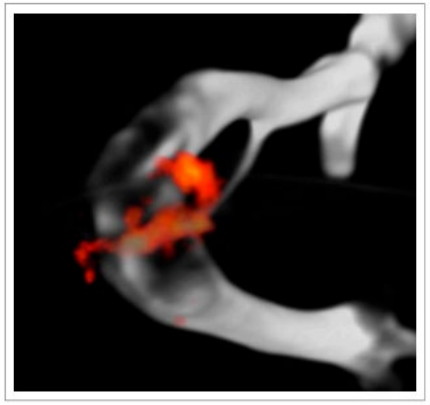
FAPI PET IN **NON-**CANCER PATIENTS

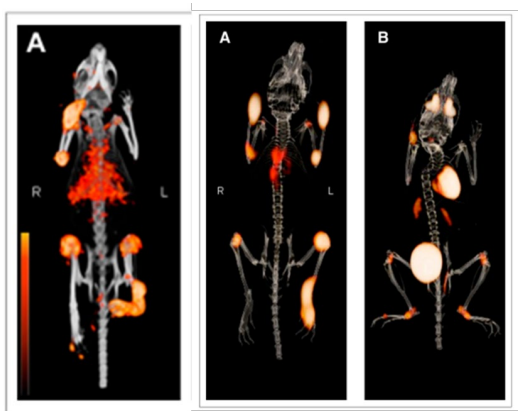
FAPI PET HYPE

Initiating triggers		Resulting changes
- Autoantibodies - Drug-induced - Genetic predisposition - Idiopathic		- Inflammation - Connective tissue alterations - Muscle weakness - Systemic organ involvement
- Viral hepatitis - Alcoholic liver disease - Non-alcoholic fatty liver disease - Biliary disease		- Inflammation - Hepatic stellate cell activation - Pathological angiogenesis - ECM deposition
- Nephrolithiasis - Hypertension - Allograft nephropathy - Glomerular disease		- Inflammatory cell influx - Tubular atrophy - Glomerulosclerosis - ECM deposition
- Idiopathic pulmonary fibrosis - Treatment (radiotherapy) - Pneumoconiosis - Hypersensitivity pneumonitis		- Abundant wound healing - Fibroblastic foci - Leukocyte infiltration - Architectural distortion
- Myocardial infarction - Cardiomyopathy - Hypertension - Aortic stenosis		- Systolic and diastolic dysfunction - Cardiac arrhythmia - Increased stiffness - Chamber dilation

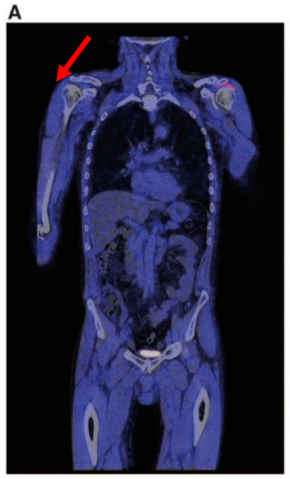
Baues et al. Adv Drug Deliv Rev (2017)

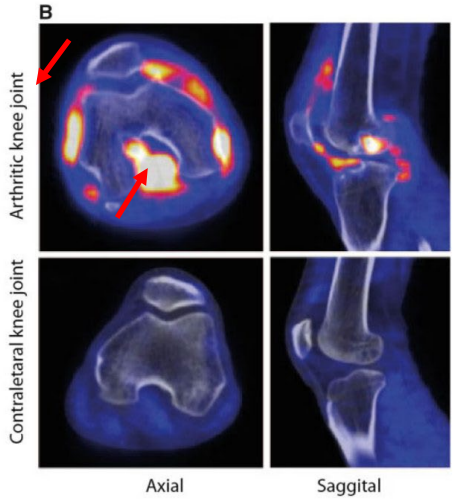
Indium-111/ Zirconium-89-Anti-FAP-mAb-28H1





Laverman P et al. J Nucl Med 2015

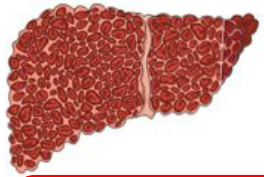
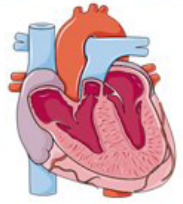




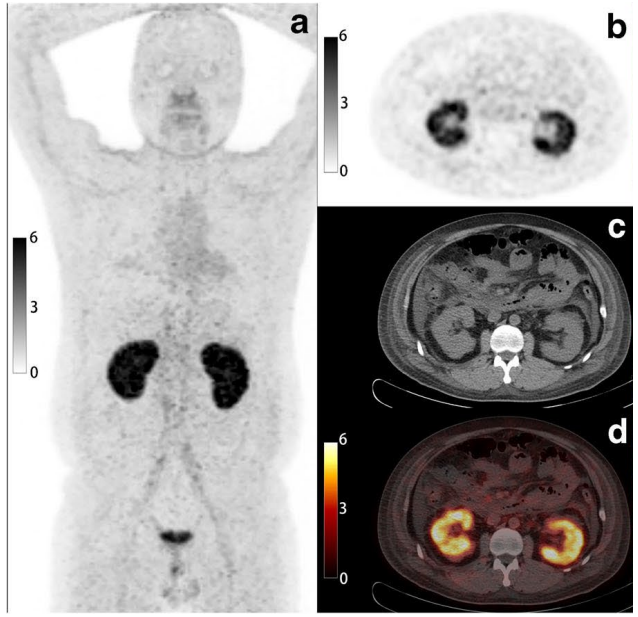
Dorst et al. Rheumatology 2021;0:1-11

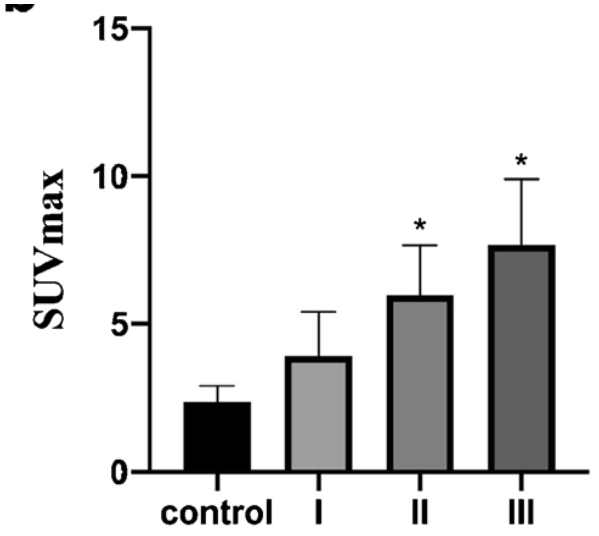
FAPI PET IN **NON-**CANCER PATIENTS

FAPI PET HYPE

Initiating triggers		Resulting changes
- Autoantibodies - Drug-induced - Genetic predisposition - Idiopathic		- Inflammation - Connective tissue alterations - Muscle weakness - Systemic organ involvement
- Viral hepatitis - Alcoholic liver disease - Non-alcoholic fatty liver disease - Biliary disease		- Inflammation - Hepatic stellate cell activation - Pathological angiogenesis - ECM deposition
- Nephrolithiasis - Hypertension - Allograft nephropathy - Glomerular disease		- Inflammatory cell influx - Tubular atrophy - Glomerulosclerosis - ECM deposition
- Idiopathic pulmonary fibrosis - Treatment (radiotherapy) - Pneumoconiosis - Hypersensitivity pneumonitis		- Abundant wound healing - Fibroblastic foci - Leukocyte infiltration - Architectural distortion
- Myocardial infarction - Cardiomyopathy - Hypertension - Aortic stenosis		- Systolic and diastolic dysfunction - Cardiac arrhythmia - Increased stiffness - Chamber dilation

Baues et al. Adv Drug Deliv Rev (2017)





Degree of renal fibrosis

Zhou Y, et al. Eur J Nucl Med Mol Imaging. 2021.

FAPI PET IN **NON-**CANCER PATIENTS

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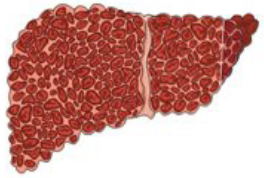
- Viral hepatitis - Alcoholic liver disease - Non-alcoholic fatty liver disease - Biliary disease		- Inflammation - Hepatic stellate cell activation - Pathological angiogenesis - ECM deposition
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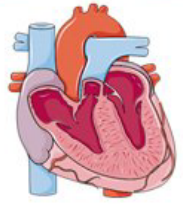
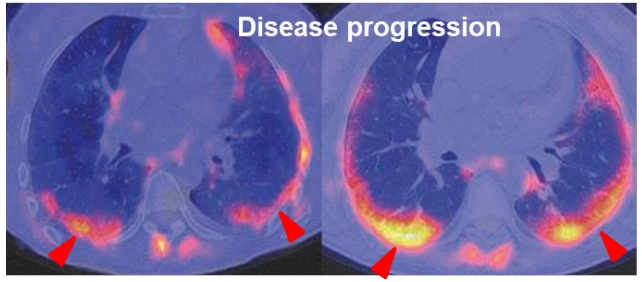
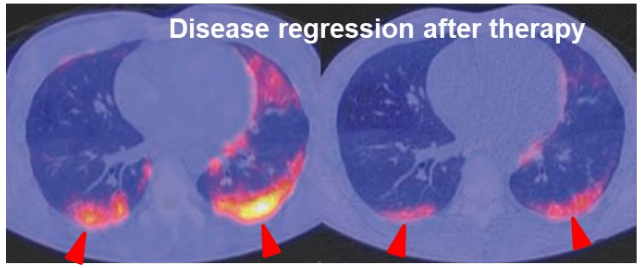
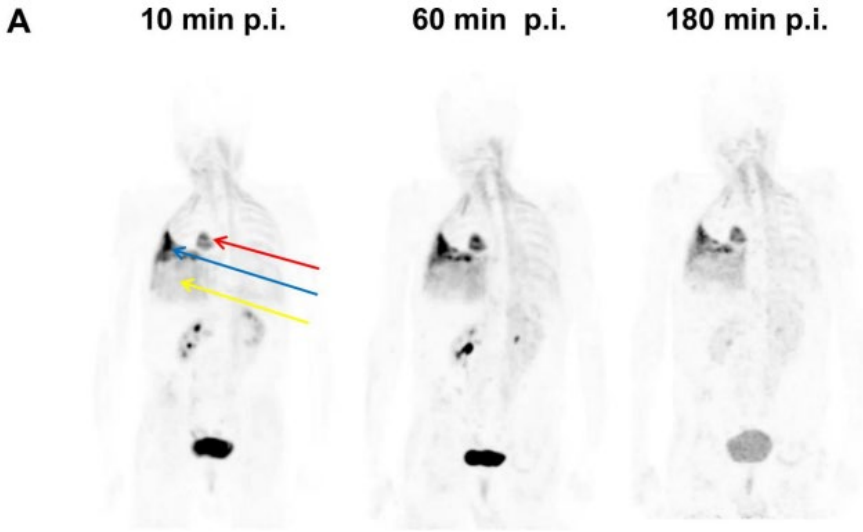
- Myocardial infarction - Cardiomyopathy - Hypertension - Aortic stenosis		- Systolic and diastolic dysfunction - Cardiac arrhythmia - Increased stiffness - Chamber dilation

Baues et al. Adv Drug Deliv Rev (2017)





Bergmann et al. Lancet Rheumatol (2021



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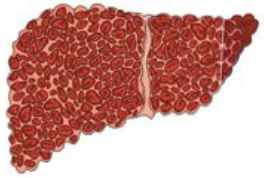
- Viral hepatitis - Alcoholic liver disease - Non-alcoholic fatty liver disease - Biliary disease		- Inflammation - Hepatic stellate cell activation - Pathological angiogenesis - ECM deposition
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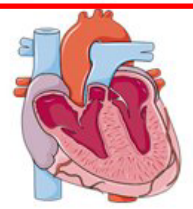
- Myocardial infarction - Cardiomyopathy - Hypertension - Aortic stenosis		- Systolic and diastolic dysfunction - Cardiac arrhythmia - Increased stiffness - Chamber dilation

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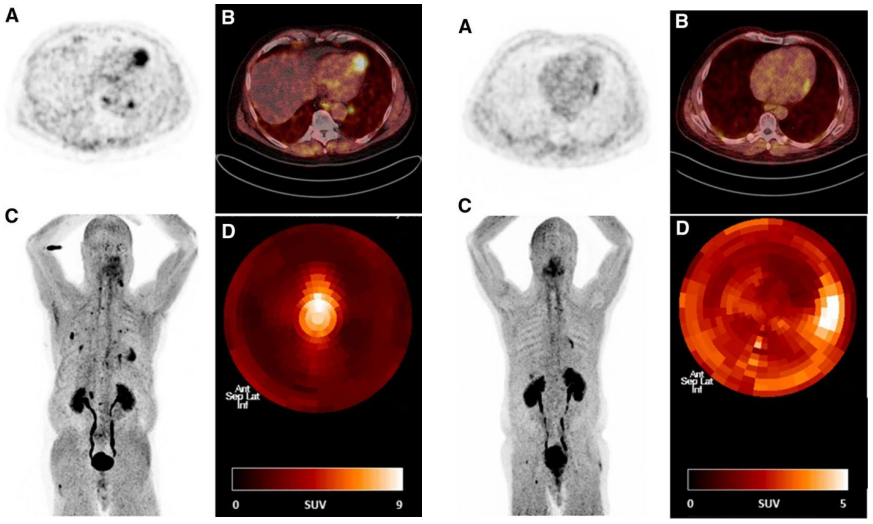
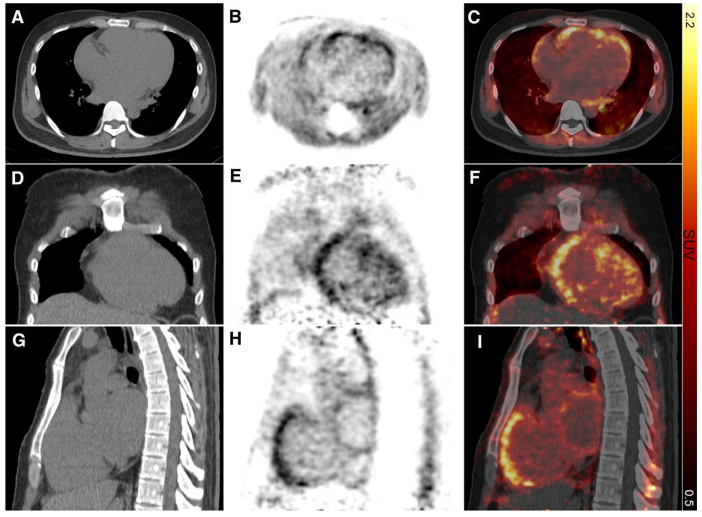


Siebermair et al. J Nucl Cardiol (2020)



Wang et al. J Nucl Cardiol (2020)

FAP-LIGAND PET UPTAKE ≠ CANCER

THANK YOU FOR YOUR ATTENTION

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