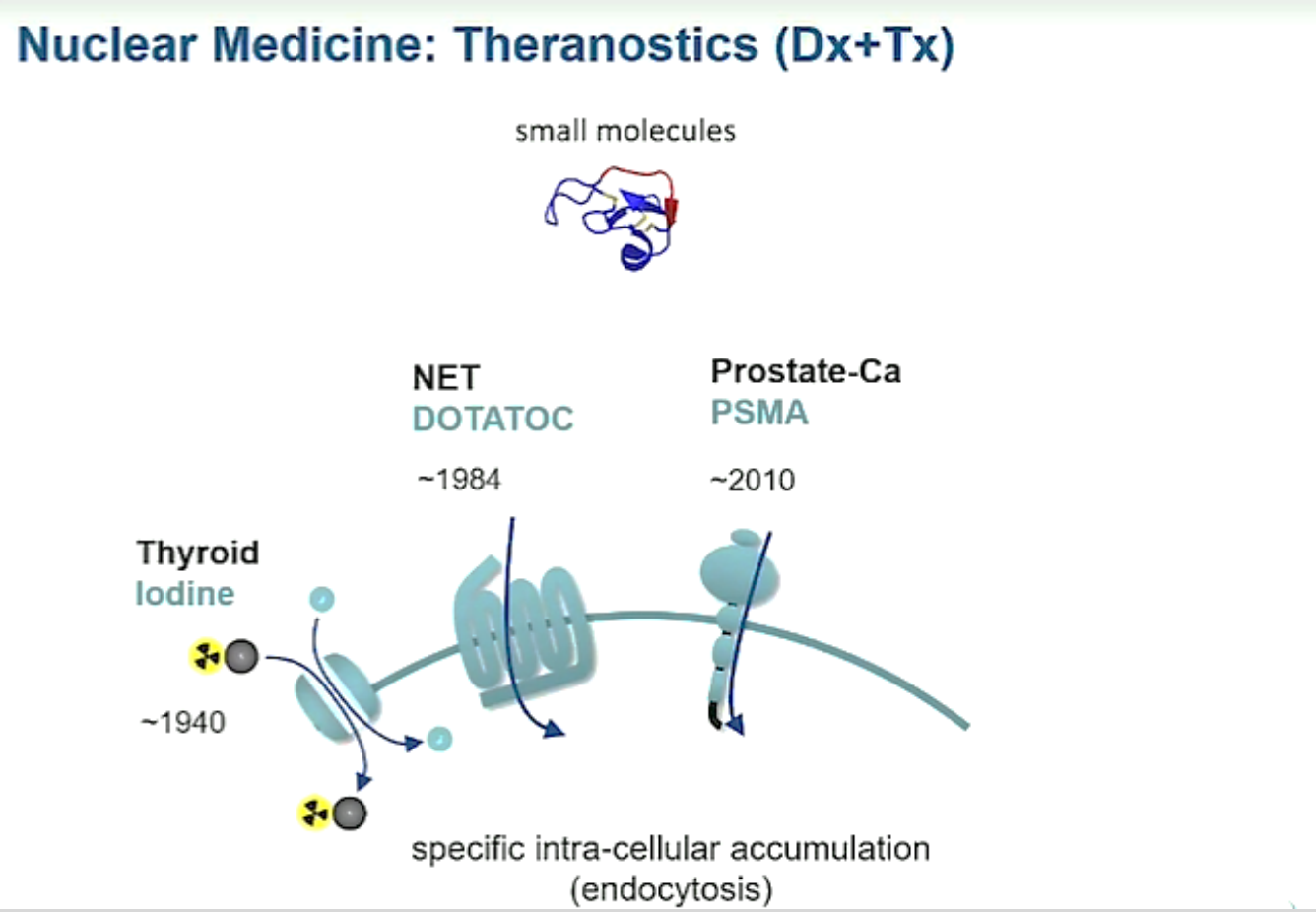
FAPi IMAGING

Haim Golan MD MSc

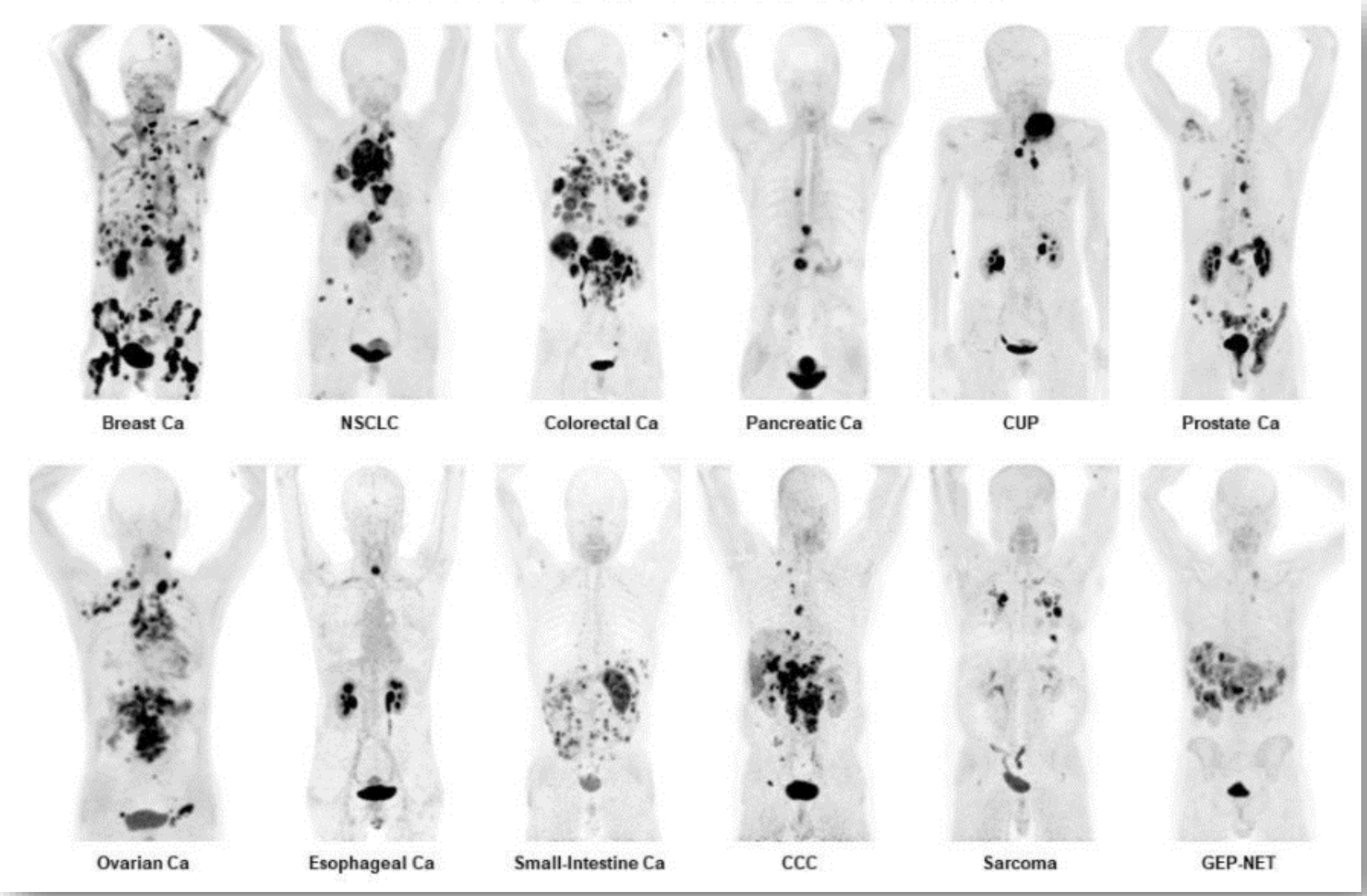
THERANOSTICS

Current Theranostics Molecules



FUTURE THERANOSTICS

2019 SNMMI IMAGE OF THE YEAR.



June 25, 2019

SNMMI Value Initiative
SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

^{68}Ga-FAPi-PET/CT

Novel Radiotracer Detects

28 Cancer Types,

Paving the Way for Development of New Therapies

nuclear medicine at the
University Hospital Heidelberg
Osaka University Japan.

FAPi

Fibroblast **A**ctivation **P**rotein **i**nhibitor

What is FAP

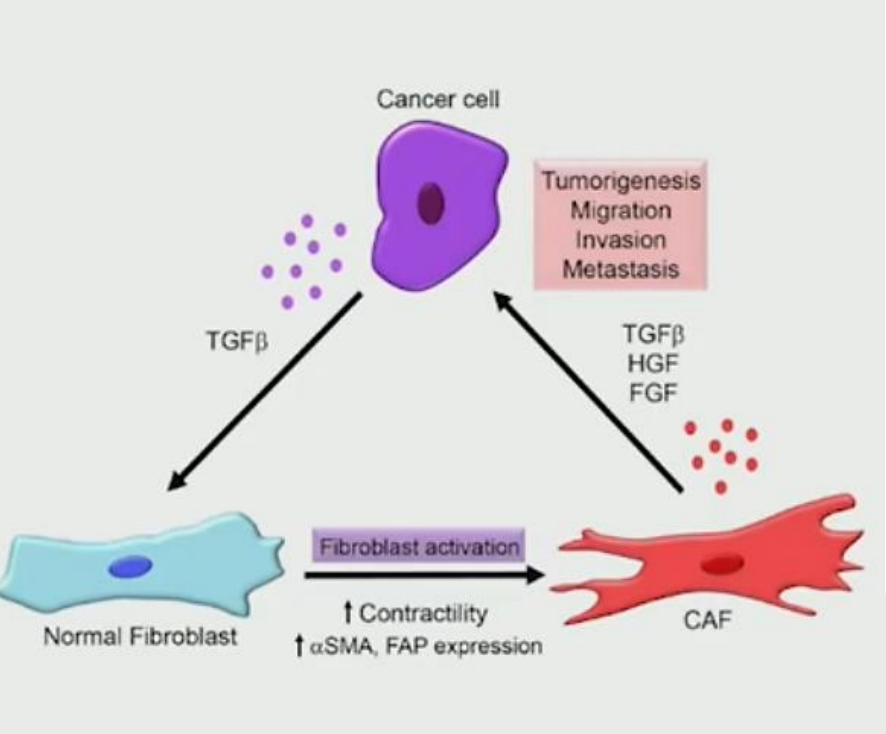
- FAP is a transmembrane cell surface enzyme that degrades proteins of the extracellular matrix and is up-regulated in cancer
- FAP expression:
  - Very low in most adult tissues.
  - High during embryonic development
  - High in pancreatic alpha cells
  - High in multipotent bone marrow stromal cells
  - High in uterine stroma.
  - High in granulation tissue of healing wounds
  - high in reactive stromal fibroblasts of epithelial cancers - CAF
  - High in malignant cells of bone and soft tissue sarcomas.
- FAP is thought to be involved in the control of fibroblast growth or epithelial-mesenchymal interactions during development, tissue repair, and epithelial carcinogenesis.
- FAP expression is seen on activated stromal fibroblasts of more than 90% of all human carcinomas, potentially making it a suitable target across a wide array of tumors.

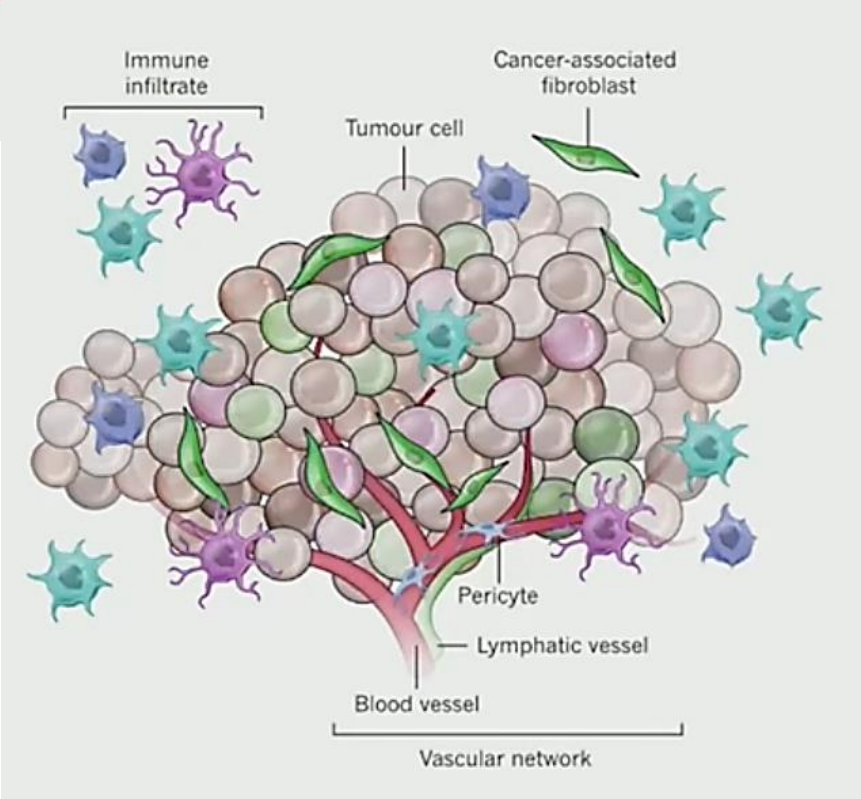
What do we image with FAPi

- Tumors does not contain cancer cells only.
- Up to 90% of a tumor's mass consist of stroma.
- Stroma cells include:
  - Vascular cells
  - Inflammatory cells
  - Fibroblasts - CAF = Cancer Associated Fibroblasts
- CAF differ from normal fibroblasts by their specific expression of the Fibroblast Activation Protein = FAP.
- FAP is overexpressed in CAF .
- FAP-specific inhibitors (FAPi) were first developed as conventional anticancer drugs

CFA

- Cancer-associated fibroblasts (CAFs) is known to be involved in growth, migration and progression of the tumor.
- CAFs have a heterogeneous origin:
  - local fibroblasts
  - circulating fibroblasts
  - vascular endothelial cells via endothelial to mesenchymal transition
  - Adipocytes
  - Bone marrow derived stem cells
- activation of CFA leads to changes in morphology:
  - Stellate shaped as opposed to a spindle shaped form.
  - CFA are able to migrate
  - Proliferate
  - Production of extracellular matrix

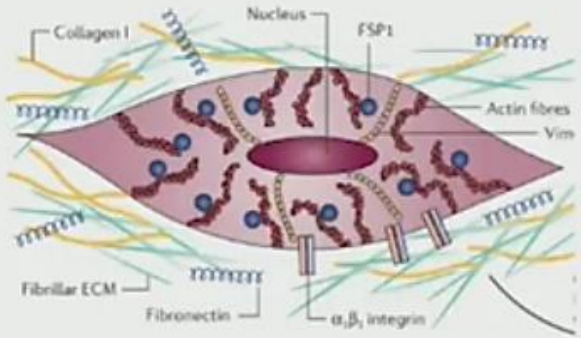




Tumor Microenvironment

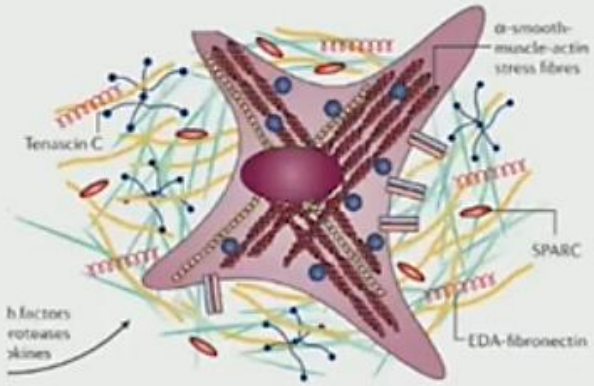
- Fibroblasts
- Immune cells
- Endothelial cells
- Mesenchymal cells
- CAF are produced only when the tumor size is greater than 3mm cell cluster

Normal fibroblast



- connective tissue
- support function by production of collagen
- wound healing

Caner associated fibroblast (CAF)

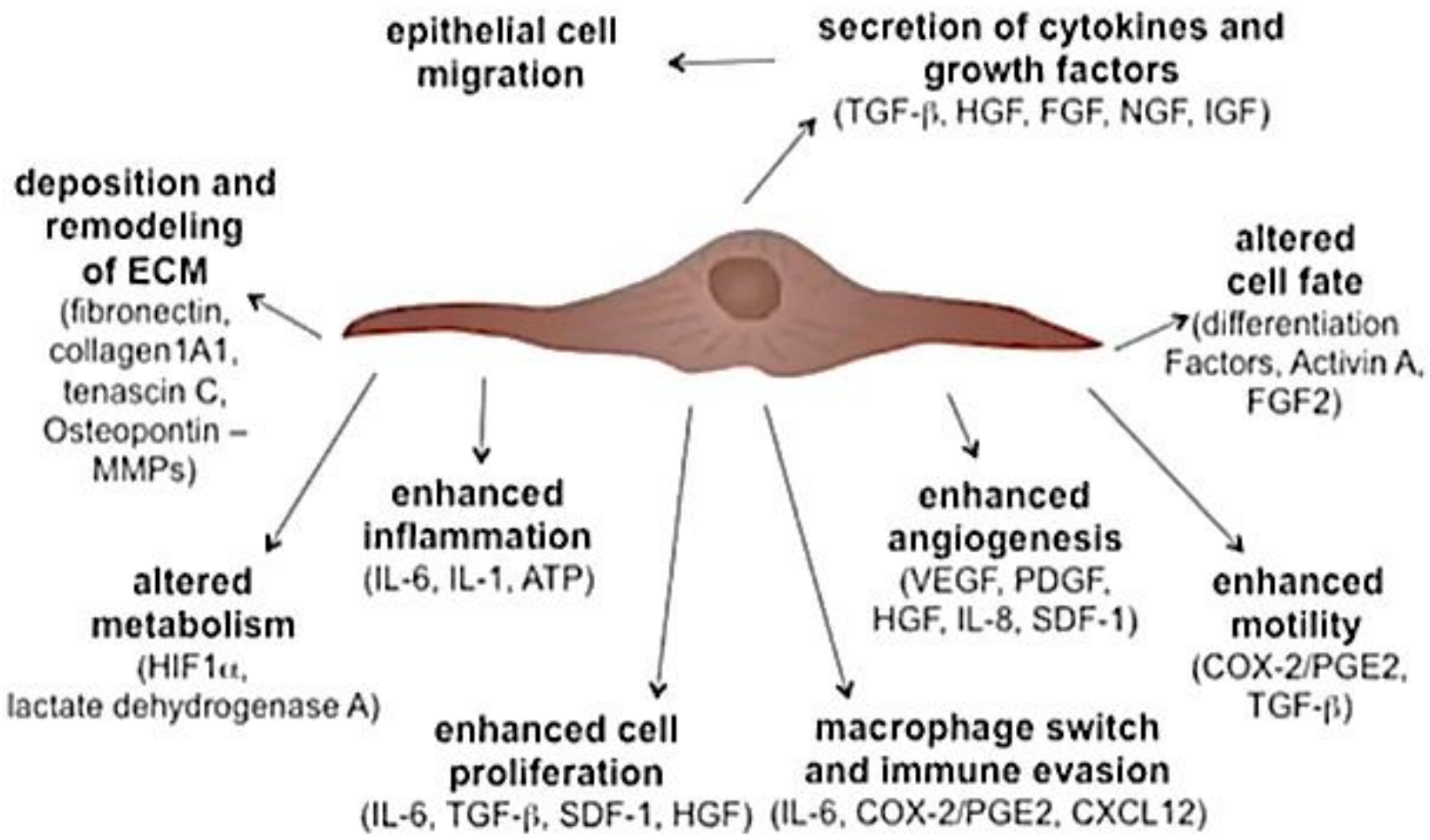


- changed structure
- increased collagen-I secretion
- support for the growth and metastasis of carcinomas

Cancer Associated Fibroblast (CAF)

"Tumor is a never healing wound"

Dvorak 1980



CAF - Cancer Associated Fibroblasts

Secretion of many cancer driving factors.

CAF promotes tumor growth, angiogenesis, invasion and metastasis.

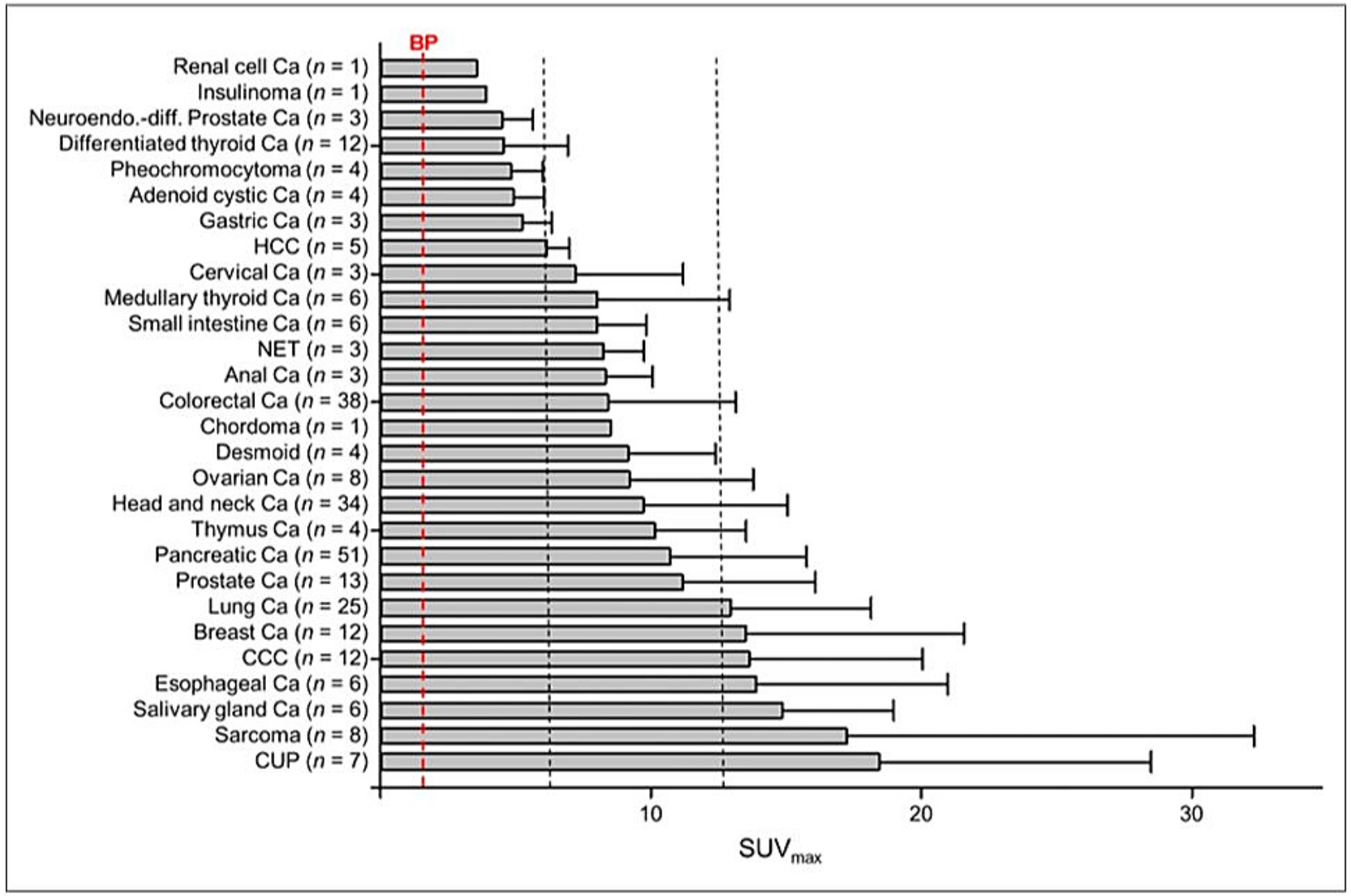


FIGURE 2. Average SUV_{max} of ^{68}Ga-FAPI PET/CT in various tumor entities. Low, intermediate, and high uptake was defined by cutoff at SUVs 6 and 12. By comparison, average background (blood pool) was found to have SUV 1.4. Ca = cancer; CCC = cholangiocellular carcinoma; CUP = carcinoma of unknown primary; HCC = hepatocellular carcinoma; NET = neuroendocrine tumor.

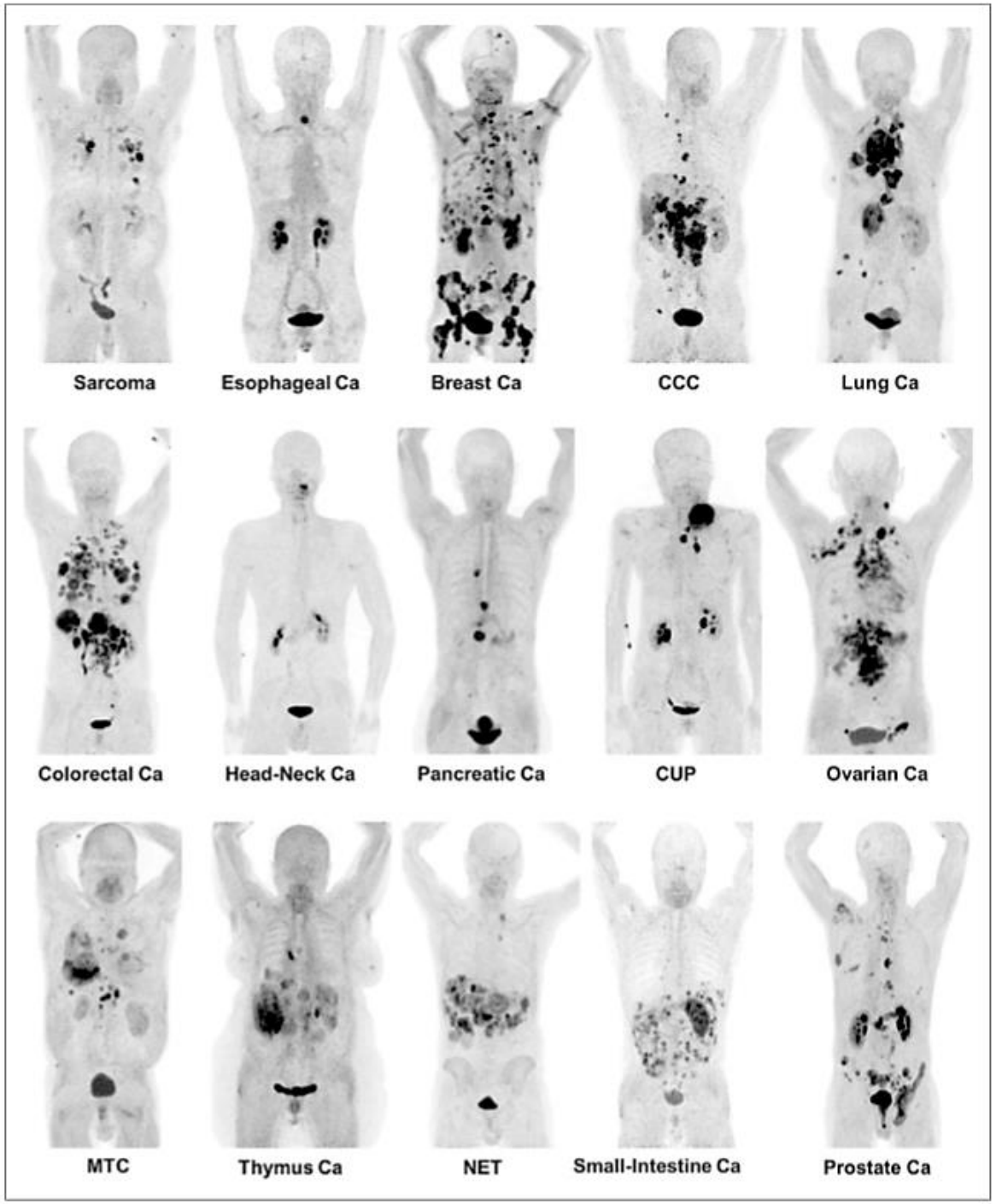
68-Ga-FAPi-04 PET/CT

Expression of CAF in various tumors

Tracer Uptake in 28 Different Kinds of Cancer

68Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. J Nucl Med 2019; 60:801–805

Sarcoma is a malignant tumor, that arises from connective tissue. Connective tissue is a broad term that includes bone, cartilage, fat, vascular, or hematopoietic tissues.



High CAF

Medium CAF

Low CAF

68-Ga-FAPI-04 PET/CT

Tracer Uptake in 15 Different Kinds of Cancer

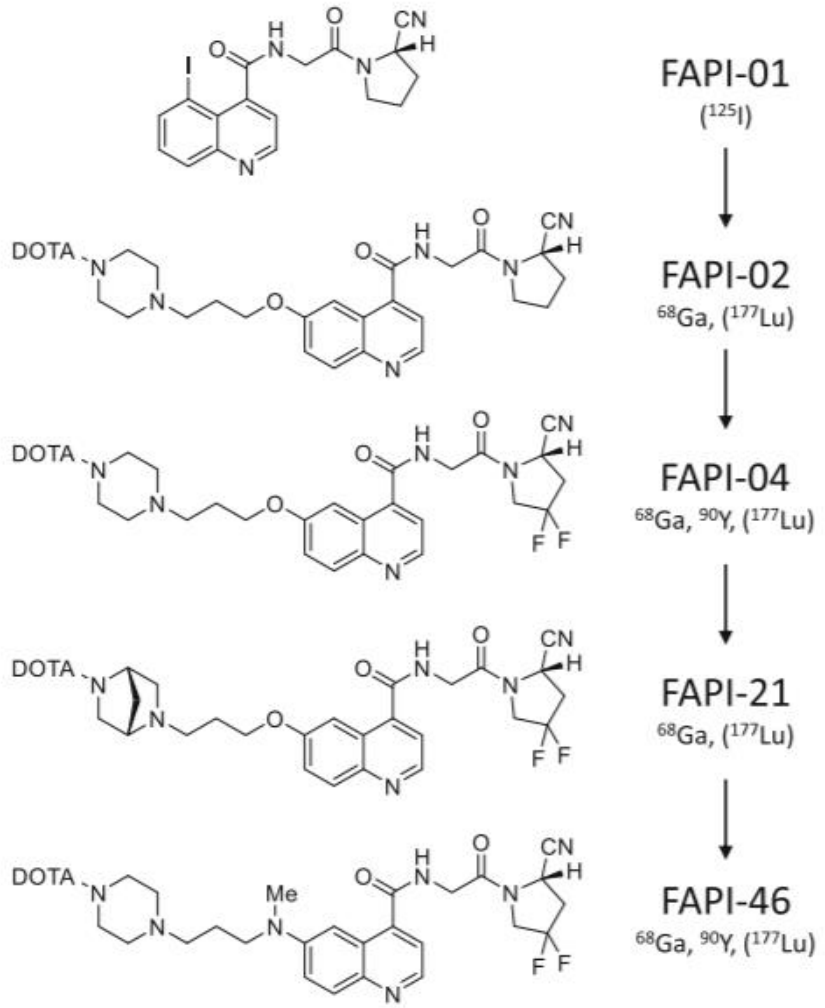
uptake in descending order

68Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. J Nucl Med 2019; 60:801–805

FAPi Theranostics

- FAPi have been advanced into tumor-targeting radiopharmaceuticals.
- FAPI tracers contain the universal NOTA/DOTA-chelator that binds 68-Ga and 18-Fal.
- NOTA/DOTA-chelators enables FAPi labelling with therapeutic radionuclides.

http://jnm.snmjournals.org/content/early/2020/06/26/jnumed.120.245084.abstract



developement of FAP-targeted theranostics,
nuclides in brackets were only used for preclinical experiments

Fig. 4 Development of FAP-targeted theranostics. Chemical structures are shown for selected compounds which were investigated in detail preclinically and/or clinically. Radionuclides in brackets were only used for preclinical experiments

FAPi-01

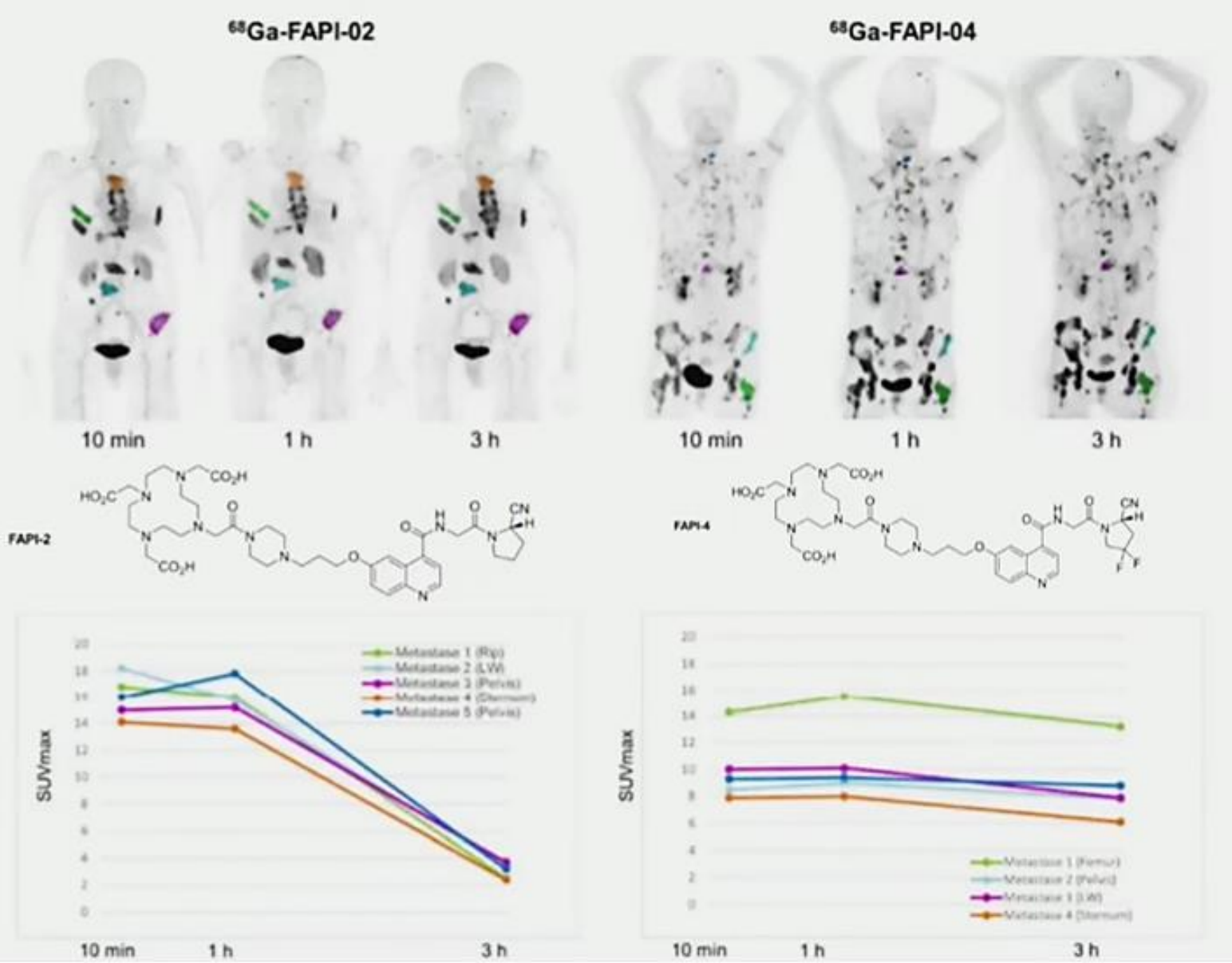
FAPI-01 proved to be suboptimal due to enzymatic deiodination with efflux of

free iodine and consequently a lower intracellular radioactivity after longer incubation

intervals.

FAPi-02

- FAPI-02 - a DOTA-linked compound, showed better pharmacokinetic and biochemical properties:
  - Much slower uptake than FAPI-01
  - Approximately 10-fold higher retention after 24 h
  - Rapid internalization (complete internalization after 1 h)
  - No renal parenchyma retention
- High uptake (SUVmax >12) :
  - Sarcoma
  - Esophageal
  - Breast
  - Cholangiocarcinoma
  - Lung cancer
- Medium uptake (SUVmax 6-12) :
  - Hepatocellular
  - Colorectal
  - head-neck
  - ovarian
  - Pancreatic
  - prostate cancer
- Low upatake (SUVmax < 6) :
  - Pheochromocytoma
  - renal cell
  - differentiated thyroid
  - adenoid-cystic and gastric cancer



FAPi for Therapy

- FAPi-02 vs FAPi-04
- Low washout
- Tumor Internalization

http://jnm.snmjournals.org/content/early/2018/08/02/jnumed.118.215913.full.pdf

Which FAPi

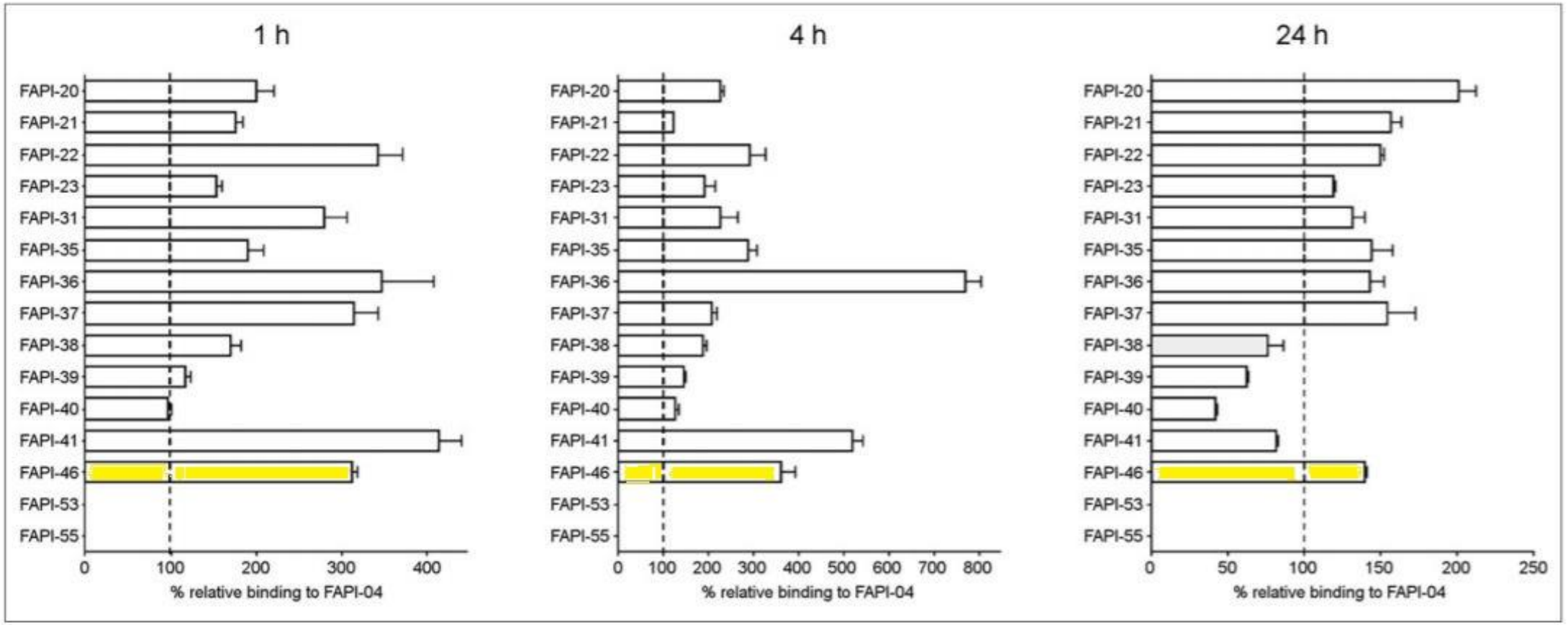


FIGURE 1. Relative binding rates of ^{177}Lu-labeled FAPI derivatives compared with FAPI-04 (set to 100%) using FAP-expressing HT-1080 cells ($n = 3$).

J Nucl Med 2019; 60:1421–1429 DOI: 10.2967/jnumed.118.224469

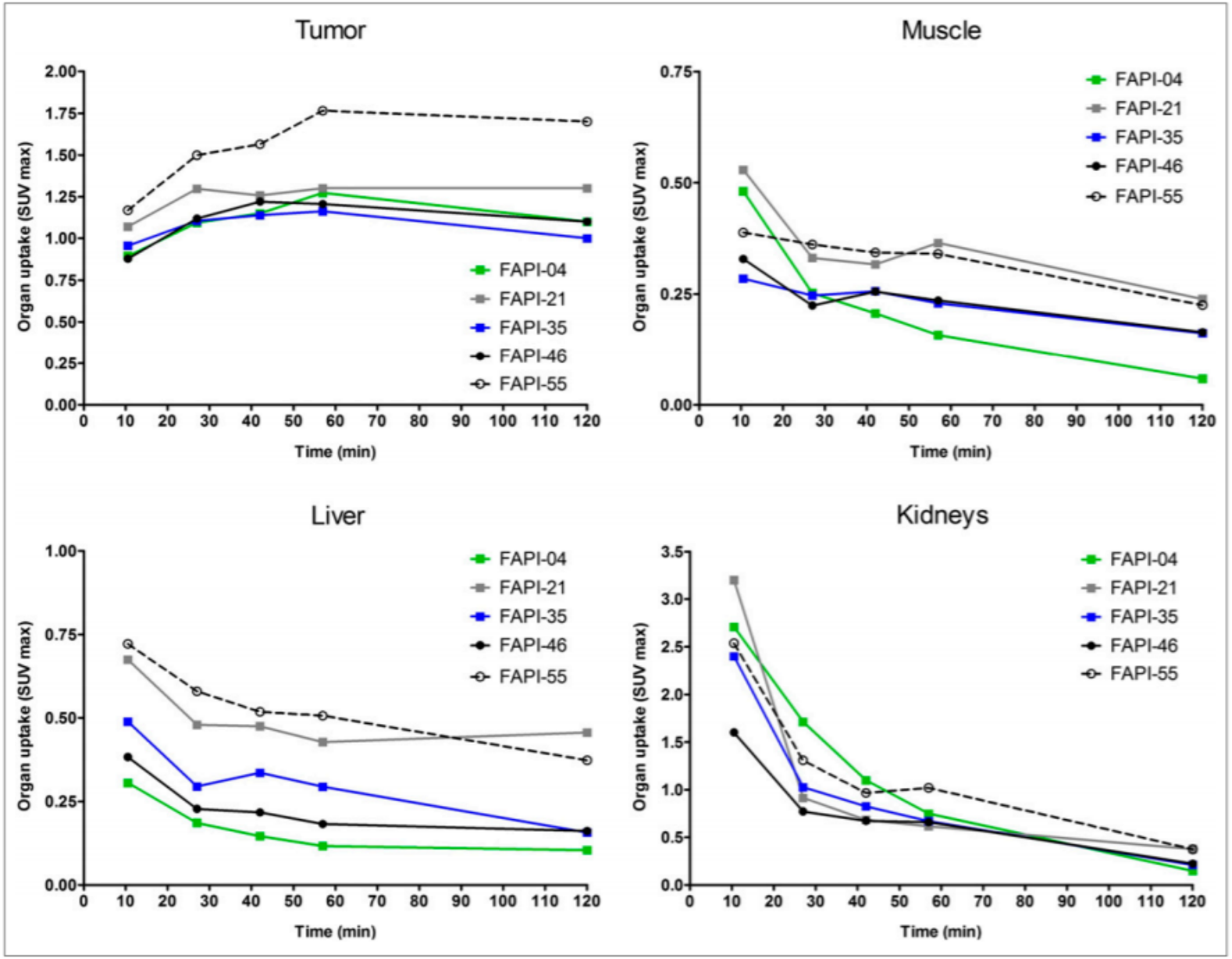


FIGURE 2. Organ SUV_{max} of ^{68}Ga-labeled FAPI derivatives in HT-1080-FAP tumor–bearing mice determined by small-animal PET imaging ($n = 1$).

Which FAPi

J Nucl Med 2019; 60:1421–1429 DOI: 10.2967/jnumed.118.224469

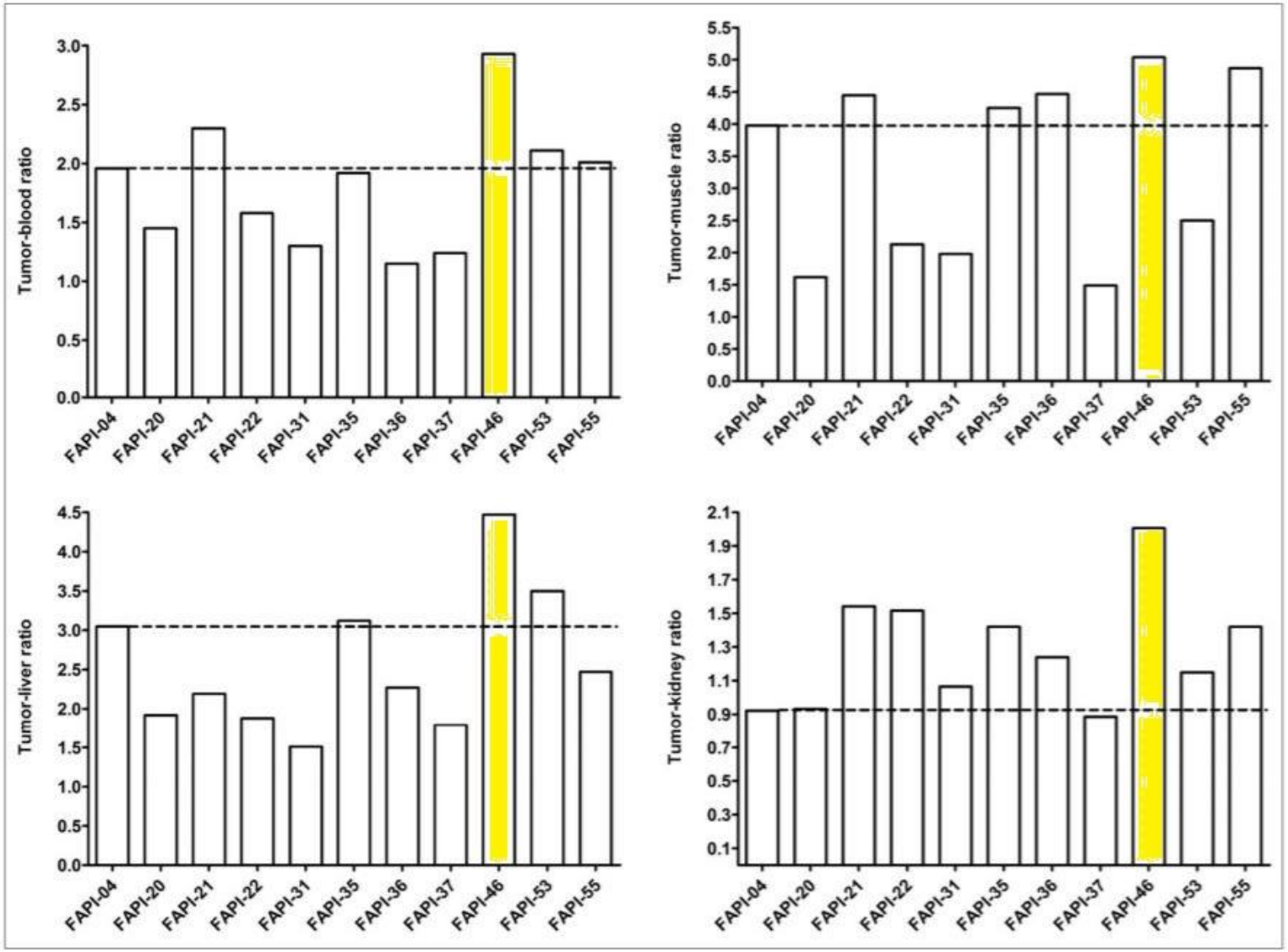


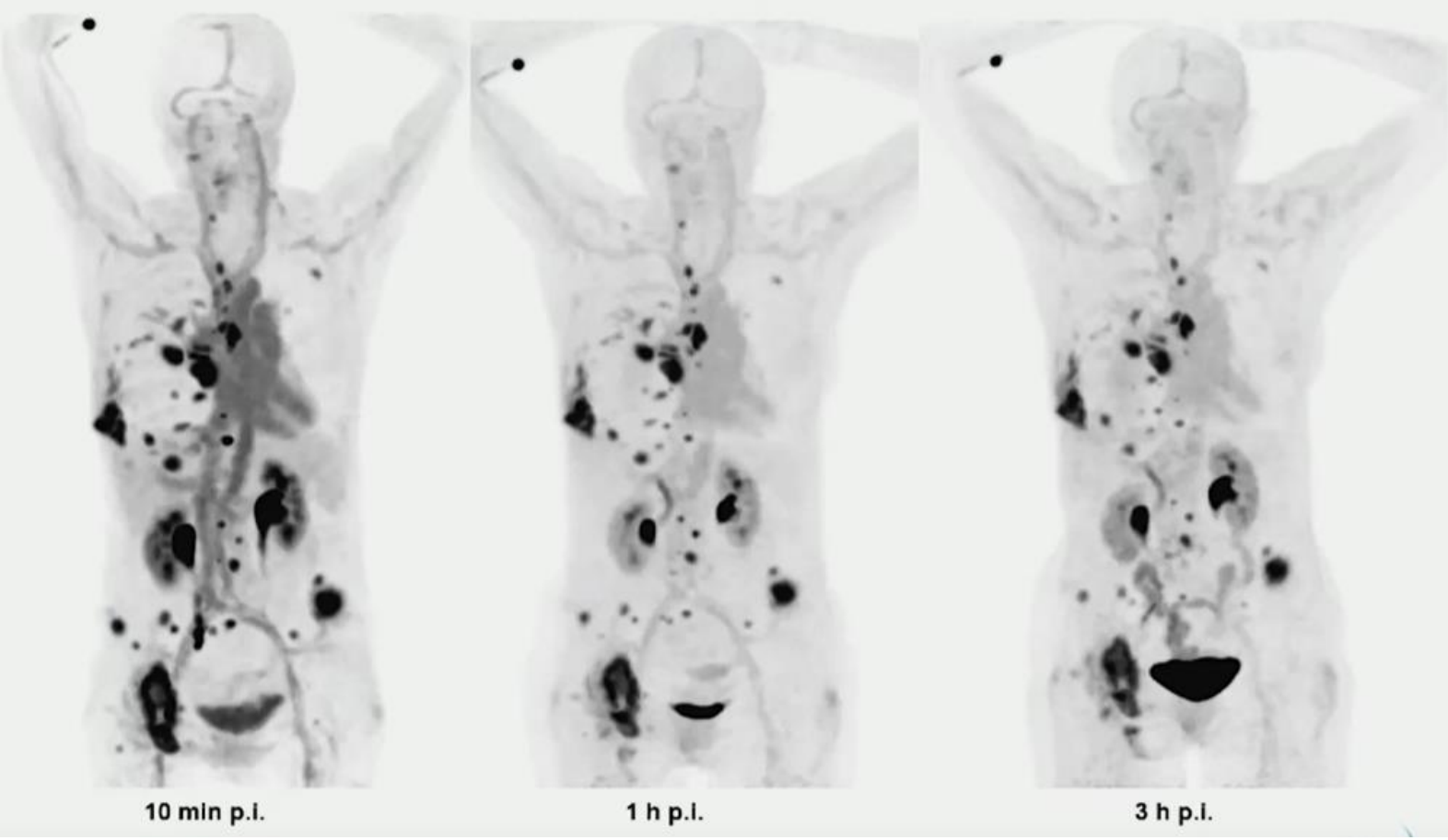
FIGURE 3. Tumor–to–normal-organ ratios of ^{68}Ga-labeled FAPI derivatives, calculated from AUCs 0–2 h after intravenous administration of radiotracers ($n = 1$).

Which FAPi

J Nucl Med 2019; 60:1421–1429 DOI: 10.2967/jnumed.118.224469

FAPi-46

- Of 15 FAPI variants, FAPI-46 showed:
- Improved tumor to blood, liver, muscle, and intestinal uptake.
- High uptake in different tumor entities as early as 10 min after tracer administration.
- FAPi-46 led to high-contrast images for improved diagnostic application
- May be used as a theranostic molecule also for therapy.



18F-FAPi-74 in Lung Cancer

- Fast uptake – 10 minutes
- Stable uptake

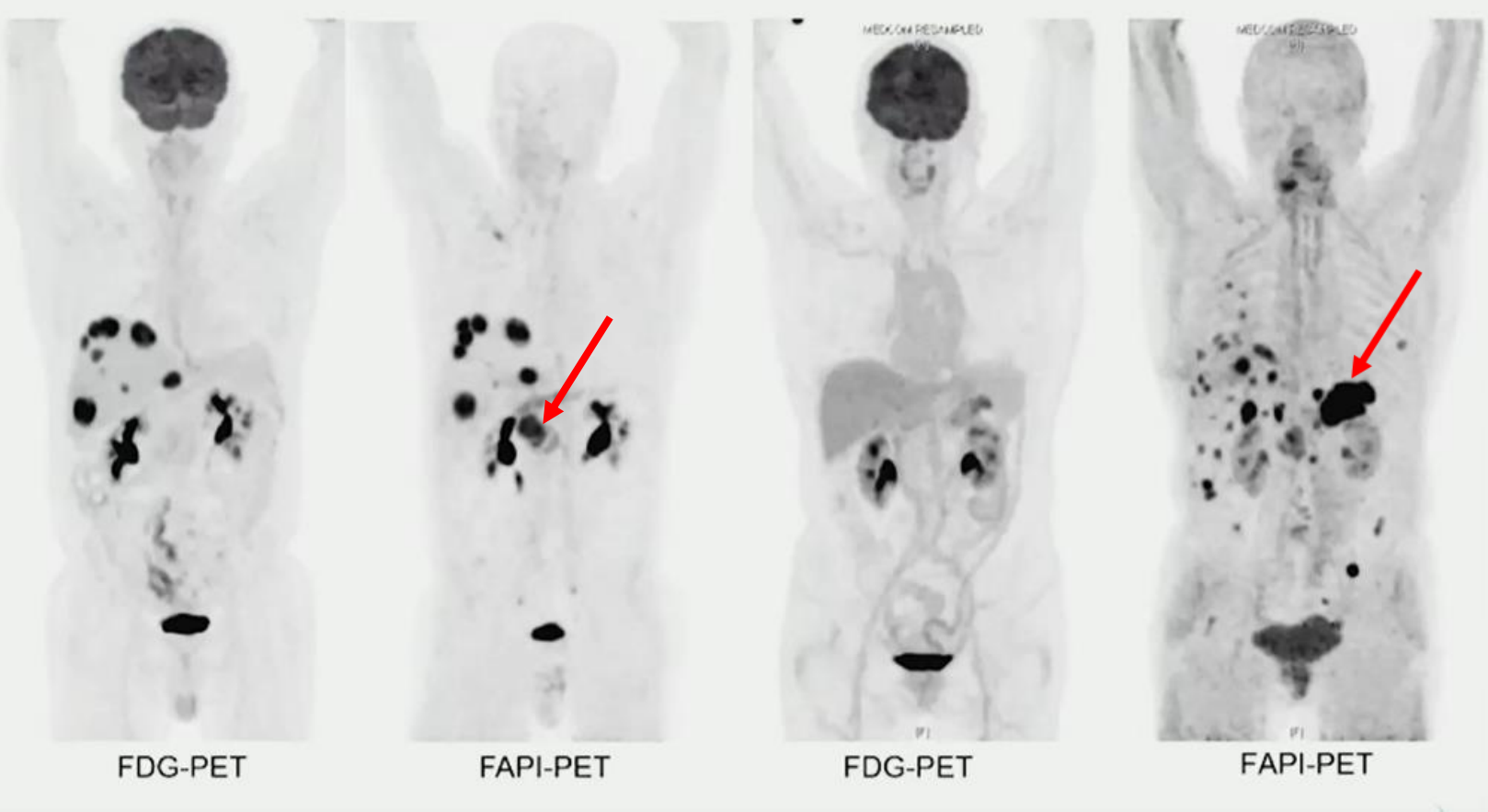
PET-Tracer	Effective Dose (mSv / MBq)	Reference
^{18}F-FAPI-74	0.014	this work
^{68}Ga-FAPI-74	0.016	this work
^{68}Ga-FAPI-2/4/46	0.008-0.015	(*5,33*)
^{68}Ga-PSMA-11	0.023	(*34*)
^{68}Ga-DOTATOC/-TATE	0.021	(*35*)
^{18}F-FDG	0.020	(*36*)
^{18}F-FLT	0.028	(*37*)
^{18}F-FET	0.016	(*38*)
^{18}F-FSPG	0.032	(*39*)
^{18}F-PSMA-1007	0.022	(*40*)
^{18}F-Flurbetaben	0.015	(*41*)
^{18}F-Flurpiridaz	0.019	(*42*)
^{18}F-Fluorocholine	0.031	(*43*)
^{18}F-MISO	0.013	(*44*)

FAPI-74 PET/CT Using Either 18F-AlF or Cold-kit 68Ga-labeling: Biodistribution, Radiation Dosimetry and Tumor Delineation in Lung Cancer Patients

Journal of Nuclear Medicine, published on June 26, 2020 as doi:10.2967/jnumed.120.245084

FAPi vs FDG

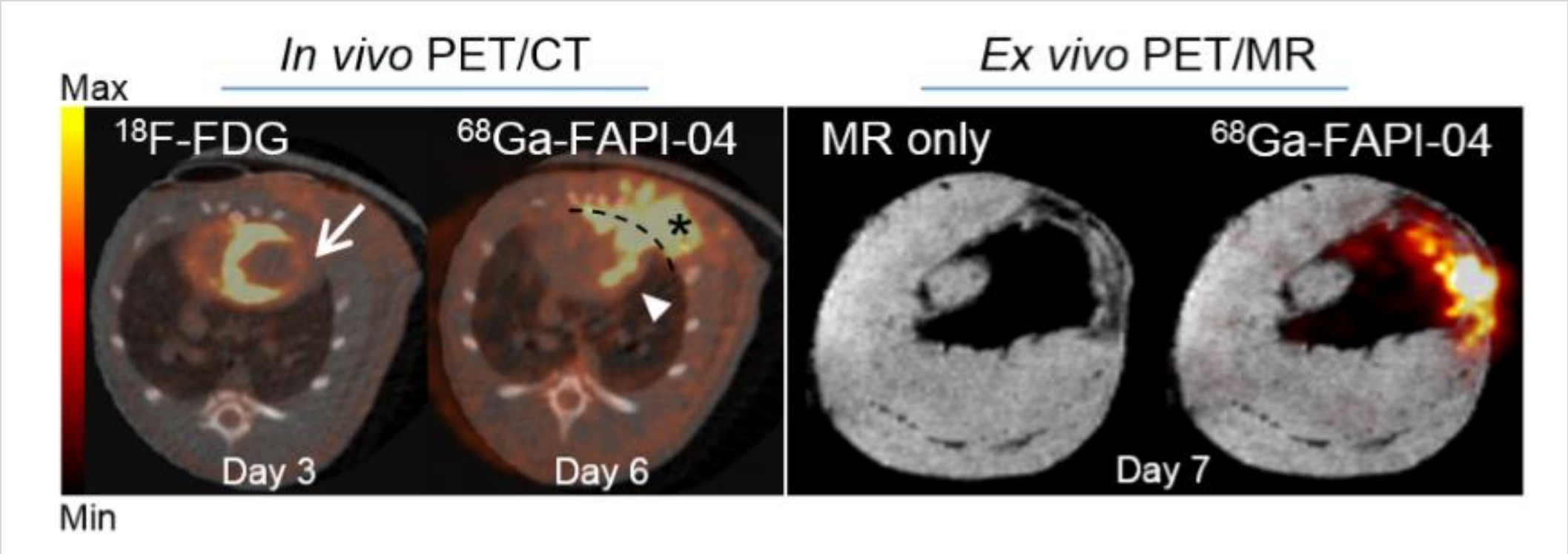
	FDG	FAPi-74
Imaging Modality	PET	PET
Uptake Mechanism	Glucose metabolism	CAF
Cancer specific	NO	YES
Tumor Specific	NO	NO
Fasting	YES	NO
Injection Dose (MBq/kg body weight)	2.5	1.8–2.2
Injection to Imaging Time (Minutes)	60	10 - 60
Effective Radiation Dose (mSv/MBq)	0.02	0.014 – 0.016
Brain Uptake	YES	NO



FAPi vs FDG in Pancreatic Cancer

- Better visualization of the primary tumor
- Better metastasis detection
- FAPi is better than FDG in Pancreatic Cancer

Non-Oncological FAPi Imaging



Journal of Nuclear Medicine, August 12, 2019 doi:10.2967/jnumed.119.226993

FAPi LABELING KIT

FAPi KIT

- The NOTA-chelator ligand FAPI-74 can be labeled with both ^{18}F-AlF (Aluminum-Fluoride) and ^{68}Ga.
- 18F-FAPI-74 enables centralized large-scale production
- 68Ga-FAPI-74 allows decentralized cold-kit labeling for flexible routine use.

פילוח שוק ופוטנציאל עסקי

גודל השוק

- <u>גודל השוק</u>:
- בארה"ב כ- 2 מיליון נבדקים בשנה באמצעות PET
- באירופה כ- 2.5 מיליון נבדקים
- בישראל כ- 60 אלף נבדקים.

Thank you for your attention.