**Journal of Nuclear Medicine, published on April 6, 2019 as doi:10.2967/jnumed.119.227967**

Original scientific article

# FAPI-PET/CT: Mean intensity of tracer-uptake (SUV) in 28 different kinds of cancer

Clemens Kratochwil[1 *], Paul Flechsig[1,2 *], Thomas Lindner[1], Labidi Abderrahim[1], Annette Altmann[1,3], Walter Mier[1], Sebastian Adeberg[4,5], Hendrik Rathke[1], Manuel Röhrich[1], Hauke Winter[2,6], Peter K. Plinkert[7], Frederik Marme[8,9], Matthias Lang[10], Hans-Ulrich Kauczor[2,11], Dirk Jäger[12,13], Jürgen Debus[4,5,14], Uwe Haberkorn[1,2,3], Frederik L. Giesel[1]

(1) Department of Nuclear Medicine, University Hospital Heidelberg, Germany.
(2) Translational Lung Research Center Heidelberg (TLRC), German Center for Lung Research (DZL), Heidelberg, Germany
(3) Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center (DKFZ), Heidelberg, Germany.
(4) Department of Radiation Oncology, University Hospital Heidelberg, Germany
(5) Heidelberg Institute for Radiation Oncology (HIRO), Heidelberg, Germany
(6) Department of Surgery, Thoraxklinik at University Hospital Heidelberg, Germany
(7) Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Heidelberg, Germany.
(8) Department Obstetrics and Gynecology, University Hospital Heidelberg, Germany
(9) Department Obstetrics and Gynecology, University Hospital Mannheim, Germany
(10) Department of Surgery, University Hospital Heidelberg, Germany.
(11) Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg, Germany
(12) Department of Medical Oncology and Internal Medicine VI, National Center for Tumor Diseases (NCT), University Hospital Heidelberg, Germany
(13) Clinical Cooperation Unit Applied Tumor Immunity, German Cancer Research Center (DKFZ), Heidelberg, Germany
(14) Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

*****Authors contributed equally.

Running title: FAPI-PET/CT - SUV of various tumors

Word count: 3400

**Corresponding author:**

Clemens Kratochwil, MD

Department of Nuclear Medicine, University Hospital Heidelberg

Im Neuenheimer Feld 400, 69120 Heidelberg

Tel: +49-6221-56-7731

Fax: +49-6221-56-5288

## ABSTRACT

The recent development of quinoline based positron-emission-tomography (PET)-tracers that act as fibroblast-activation-protein inhibitors (FAPIs) demonstrated promising preclinical and clinical results. FAP is overexpressed by cancer associated fibroblasts (CAFs) of several tumor entities. Here we quantify the tumor-uptake in FAPI-PET/CT of various primary and metastatic tumors to identify the most promising indications for future application.

**Methods:** FAPI-PET/CTs were requested by various referring physicians according to individual clinical indications which were considered insufficiently covered by FDG-PET/CT or other imaging modalities. All PET/CTs were performed 1h after injection of 122-312 MBq $^{68}$Ga-FAPI-04. We retrospectively identified 80 patients with histopathological proven primary tumors or metastases or radiologically unequivocal metastatic lesions of histological proven primary tumors. Tumor uptake was quantified by SUVmax and SUVmean (60% isocontour).

**Results:** 80 patients of 28 different tumor entities (54 primary tumors and 229 metastases) were evaluated. The highest average SUVmax (>12) was found in sarcoma, esophageal, breast, cholangiocarcinoma and lung cancer. The lowest FAPI uptake (average SUVmax <6) was observed in pheochromocytoma, renal cell, differentiated thyroid, adenoid-cystic and gastric cancer. The average SUVmax of hepatocellular, colorectal, head-neck, ovarian, pancreatic and prostate cancer was intermediate (SUV 6-12). SUV varies across and within all tumor entities. Due to low background in muscle and blood-pool (SUVmax < 2), the tumor-to-background contrast ratios are > 3-fold in the intermediate and > 6-fold in the high intensity uptake group.

**Conclusion:** Several highly prevalent cancers presented with remarkably high uptake and image contrast in FAPI-PET/CT. The high and rather selective tumor uptake may open up new applications for non-invasive tumor-characterization, staging exams or radio-ligand therapy.

**Key words:** FAPI, breast cancer, colorectal cancer, lung cancer, PET/CT

## INTRODUCTION

Several tumor entities, e.g. breast, colon and pancreatic carcinomas, are characterized by a strong desmoplastic reaction (*1*). Cancer associated fibroblasts (CAFs) and extra-cellular fibrosis can contribute up to 90% of the gross tumor-mass, leaving original tumor cells in minority (*2,3*). Many CAFs differ from normal fibroblasts by their relative specific expression of FAP. Therefore, FAP-specific inhibitors have first been developed as anti-cancer drugs and consecutively advanced into tumor-targeting radiopharmaceuticals (*4,5*).

A biodistribution and initial dosimetry study of FAPI-PET/CT with two DOTA-containing ligands suggested that these tracers may expand and enrich the diagnostic cancer portfolio currently covered by FDG (*6*). Moreover, the biodistribution suggested that FAPI may be suitable for radio-ligand therapy (*7*). Based on the favorable initial results, FAPI-PET/CTs were requested by various referring physicians based on individual clinical indications. Often scans were ordered to improve tumor-delineation for planned surgery or radiotherapy. Thus, even lesions that were already unequivocally identified radiologically or by histopathology could be additionally characterized with FAPI-PET/CT.

Aim of this retrospective analysis was to quantify FAPI-uptake in a variety of primary, metastatic or recurring cancers.

## MATERIALS AND METHODS

### Patients

All patients were referred to the experimental diagnostics by their treating oncologist, who were facing an unmet diagnostic challenge, that could not be solved sufficiently with standard diagnostic means. While location and nature of tumor lesions was frequently known the intent was to improve tumor delineation e.g. for planning of radiotherapy. All patients gave written informed consent to receive FAPI-PET/CT on an individual patient basis. The data were analyzed retrospectively with approval of the local ethics committee (No. S016/2018).

### Radiopharmaceuticals

Synthesis and labeling of $^{68}$Ga-FAPI-04 has already been described previously (*4,5*). Following the regulations of the German Pharmaceuticals Act §13(2b) indication and labeling of the FAPI-tracers were conducted under the direct responsibility of the applying physician. Injected activities were dependent on labeling yields. According to a previous dosimetry estimate - effective dose 1.6 mSv / 100 MBq (*6*) - an upper limit of 370 MBq regarding radiation exposure and a lower limit of 100 MBq per exam to achieve sufficient count rate have been considered.

### PET/CT-Imaging

All imaging was performed on a Biograph mCT Flow scanner (Siemens, Erlangen, Germany). Following non-contrast-enhanced low-dose CT (130keV, 30mAs, CareDose; reconstructed with a soft-tissue kernel to a slice thickness of 5mm), PET was acquired in 3-D mode (matrix 200 × 200) using FlowMotion (Siemens). The emission data were corrected for randoms, scatter and decay. Reconstruction was performed with an ordered subset expectation maximization (OSEM) algorithm with 2 iterations / 21 subsets and Gauss-filtered to a transaxial resolution of 5 mm at full-width at half-maximum; Attenuation correction was performed using the non-enhanced low-dose CT data. The injected activity for the FAPI exams ranged 122-312 MBq and the PET scans were started 1h post injection. 500ml saline with 20mg Lasix was infused from 15 min before to 30 min after tracer application. The patients were asked to self-report any abnormalities 30 min after finishing the examination.

**Imaging Evaluation**

Tumor tracer uptake was quantified by SUVmean and SUVmax at 1 h post injection, respectively. For calculation of the standardized uptake value (SUV), circular regions of interest were drawn around the tumor lesions with focally increased uptake in transaxial slices and automatically adapted to a three-dimensional volume-of-interest with e.soft software (Siemens) at a 60 % isocontour. The unspecific background in blood-pool (aortic vessel content) and muscle was quantified with a circular 2 cm diameter sphere.

## RESULTS

### Adverse Events

All patients tolerated the examination well. No drug-related pharmacological effects or physiologic responses occurred. During injection and the 1.5 h of follow-up no patient reported any new symptoms.

### Quantifying FAPI-Uptake in Primary Tumors and Metastatic Disease

Patient numbers were not sufficient to compare SUVs of primary tumors vs. metastases for individual cancers. The overall mean (11.5±5.5 vs 10.0±6.3), median (10.7 vs 8.5) and SUV range (2.9-21.6 vs 2.0-44.8) of FAPI in primary tumors (n=54) and metastatic lesions (n=229) did not differ (Fig. 1). Subsequently we analyzed primary and metastatic lesions of individual tumor entities in a pooled fashion.

The highest average SUVmax (>12) was found in sarcoma, esophageal, breast, cholangiocarcinoma and lung cancer. The lowest FAPI uptake (average SUVmax <6) was observed in renal cell, differentiated thyroid, adenoid-cystic, gastric carcinoma and pheochromocytoma. The average SUVmax of hepatocellular carcinoma, colorectal carcinoma, head-neck-cancer, ovarial carcinoma, pancreatic and prostate cancer was intermediate (SUV 6-12). All tumor entities exhibited a high inter-individual SUV variation (Fig. 2). Due to the low background activity (average SUVmean of blood-pool, muscle 1.2, 1.0; SUVmax 1.6 and 1.4), the tumor-to-background ratios are >3 in the intermediate and >6 in the high intensity uptake group (Fig. 2). These high ratios resulted in high image contrast and excellent tumor delineation in most of the evaluated patients (Fig. 3).

## DISCUSSION

The aim of this retrospective analysis was to quantify the uptake of FAPI-ligand in different types of cancer.

The highest uptake (average SUVmax >12) was found in lung, breast and esophageal cancer, cholangiocellular carcinoma and sarcoma. This may open indications for FAPI-PET/CT for cases where FDG-PET/CT faces its limitations. Due to low uptake of FDG in low-grade sarcomas there is a wide overlap between benign and malignant lesions and even dual-time point imaging could not eliminate this well-known limitation of FDG-PET/CT (*8,9*). The main limitation of FDG-PET/CT in staging of esophageal cancer is its low to moderate sensitivity for lymph node staging (*10*) and delineation between viable tumor and regional esophagitis. In breast cancer FDG-PET/CT is commonly used in recurrence but not generally recommended for initial staging (*11*). Cholangiocarcinoma exhibits considerable variability in FDG-uptake, which was correlated with a weak expression of hexokinase-2 (*12*). FDG-PET/CT performs well in lung cancer; however high cerebral background requires brain-MRI for complete staging (*13*). Thus, these tumors may benefit FAPI-PET/CT imaging. However, the limited number of patients examined per FAPI-PET/CT until now does not allow subgroup analysis of histological variants or differentiation grades.

Surprisingly colon and pancreatic cancers, i.e. the ones with the highest desmoplastic reaction by histopathology (*3*), demonstrated only intermediate FAPI-uptake (SUV 6-12). The liver is the first target organ for metastases of colorectal cancer. We already reported a significantly lower hepatic background for FAPI (SUV 1.7) than for FDG (SUV 2.8). This may be advantageous for liver metastasis detection (*6*). Within the patients reported here, we identified liver metastases as small as 1cm in diameter (Fig. 4). Due to its limited sensitivity of 30% for detecting lymph node metastasis (*14*) and false-positive findings in acute pancreatitis, FDG-PET is of limited usefulness for surgical planning in pancreatic cancer (*15*). Thus, even intermediate uptake in FAPI-PET/CT presents a reasonable perspective to improve clinical diagnostic performance. In ovarian cancer, another tumor in the intermediate-intensity group, FDG can overcome some limits of conventional imaging but due to peristaltic activity often suffers from heterogeneous uptake in the intestinal wall (*16,17*). In contrast FAPI demonstrates very low unspecific intestinal/peritoneal uptake and might be superior to identify peritoneal carcinomatosis, the main clinical

challenge of advanced stage ovarian cancer. Head and neck tumors often go along with local inflammation. Unfortunately, a recent review reported that most original work found that FDG-PET/CT is not useful in discriminating benign from malignant tumors because of the overlap of uptake in both conditions (*18-20*). In this setting FAPI-PET/CT may offer an advantage regarding tumor-delineation e.g. for planning of radiotherapy (Fig. 5). Differentiation between residual/recurrent disease and post-chemoradiation fibrosis was reported to be a diagnostic challenge for FDG (*21*). It should be mentioned that unspecific fibrosis may also cause issues for FAPI-PET; however, due to the inherent difference of normal activated fibroblasts and CAFs (*4,5*) this still needs to be proven. Intermediate-high FAPI-uptake was also observed in prostate cancer. However, only patients with PSMA-negative tumors, which are the minority of prostate cancers, were selected to receive additional FAPI-PET/CT and due to this selection bias our cohort does not reflect typical patients.

FDG-PET often performs poor in renal cell carcinoma, pheochromocytoma and neuroendocrine tumors including medullary thyreoid cancer and insulinomas. This limitation is unlikely to be overcome as SUVs for these tumors are also low for FAPI (average SUVmax <6). This likely not a significant problem as several special PET tracers such as $^{18}$F-DOPA for neuroblastoma/pheochromocytoma (*22*), $^{68}$Ga-labeled somatostatin analogs for neuroendocrine tumors (*23*), $^{89}$Zr-girentuximab for renal cell carcinoma (*24*) and $^{68}$Ga-Exendin targeting glucagon-like peptide-1 receptor on insulinoma (*25*) recently closed this gap.

The current imaging findings are largely consistent with histopathology reports. FAP-expression on activated fibroblasts in tumor stroma was quantified already in 1990 using the antibody F19 (*3*). Well in line with our results, a weak desmoblastic reaction was observed in renal cell cancer and neuroblastoma/pheocromocytoma; intermediate staining in pancreatic, gastric, endometrial/cervix cancer; and high expression in breast cancer (*3*). In contrast to this historical paper, we found a higher FAPI-uptake in neuroendocrine tumors (intermediate group in FAPI-PET, weak in histology) and lung cancer (high uptake in FAPI-PET, intermediate in histology). For colorectal cancer, which was the most commonly high-expressing tumor in the work of Garin-Chesa et al. (*3*), we only measured intermediate values. Low case numbers, heterogeneity of expression, random effects in tissue sampling and high inter-individual variability appear the most appropriate explanations for these differences between histological *in-vitro* and

imaging *in-vivo* results. Another explanation and also a possible reason for the high inter-individual variability can be patient selection. Immunohistochemical work-up has primarily been performed in early stage non-metastatic, thus rather indolent tumors. In contrast, the patients evaluated per FAPI-PET/CT are a more heterogeneous group. Most they presented with recurrent and metastatic disease and sometimes (most frequently in colorectal cancer patients) even after several lines of systemic therapy. We also want to emphasize, that the aim of this work was only to characterize true-positive lesions (proven by histopathology or unequivocal radiological findings of histopathological proven primary tumors) as no acceptable gold-standard to rule out false-negative findings was available. Thus sensitivity and overall diagnostic accuracy cannot be determined.

FAP was considered a promising target for nuclear-labeled tumor probes in 1994. Due to tumor-to-liver ratios of up to 21:1 the antibody $^{131}$I-mAbF19 could delineate liver metastases of colorectal cancer as small as 1 cm in diameter (*26*). This was confirmed by our observations (Fig. 4) and is supported by earlier data that CAFs are already found in lesions above 1-2 mm in diameter (*27*). However, well in line with typical antibody kinetics the optimal time for tumor imaging with $^{131}$I-mAbF19 was 3 to 5 days after administration (*26*). In contrast, FAPI-PET/CT can be performed 10 min to 1 h after administration and in contrast to FDG studies can be done without fasting and resting time (*6*). This is a potential operational advantage as observed between PSMA-targeting with the antibody J591 and an optimal imaging after 6-8 days (*28*) vs. low-molecular weight PSMA-ligands that can be imaged 1h p.i. (*29*).

## CONCLUSION

Several epidemiologically important tumor entities, in particular breast, esophagus, lung, pancreatic, head and neck and colorectal cancer, present with a remarkably high uptake in FAPI-PET/CT. This may open new applications for non-invasive tumor-characterization and staging exams. As the FAPI-tracers contain the universal DOTA-chelator also a theragnostic approach - after labeling the ligand with an appropriate therapeutic radionuclide - seems feasible. Other known FDG-limitations, e.g. in differentiated thyroid and renal cell carcinoma, can probably not be overcome with FAPI. The limitations of this report, such as retrospective evaluation, a heterogeneous patient collective and low case number for some kinds of tumor, require further studies.

**DISCLOSURES:** Patent application for quinoline based FAP-targeting agents for imaging and therapy in nuclear medicine presents a potential financial conflict of interest for authors CK, TL, WM, UH, FLG. No other potential conflicts of interest relevant to this article exist.

### Key Points

QUESTION: To quantify the FAP-expression in different kind of tumors.

PERTINENT FINDINGS: According to this retrospective evaluation, several epidemiologically important tumor entities present with a remarkably high uptake in FAPI-PET/CT.

IMPLICATIONS FOR PATIENT CARE: $^{68}$Ga-FAPI PET/CT has a high potential to overcome some limitations of $^{18}$F-FDG in the field of non-invasive tumor characterization and staging exams and thus warrants further evaluation.

**REFERENCES**


1. Siveke JT. Fibroblast-Activating Protein: Targeting the roots of the tumor microenvironment. *J Nucl Med.* 2018;59:1412-1414.
2. Hamson EJ, Keane FM, Tholen S, Schilling O, Gorrell MD. Understanding fibroblast activation protein (FAP): substrates, activities, expression and targeting for cancer therapy. *Proteomics Clin Appl.* 2014;8:454-63.
3. Garin-Chesa P, Old LJ, Rettig WJ. Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. *Proc Natl Acad Sci USA*. 1990;87:7235-9.
4. Loktev A, Lindner T, Mier W, et al. A new method for tumor imaging by targeting cancer associated fibroblasts. *J Nucl Med*. 2018 Apr 6. pii: jnumed.118.210435. [Epub ahead of print]
5. Lindner T, Loktev A, Altmann A, et al. Development of quinoline based theranostic ligands for the targeting of fibroblast activation protein. *J Nucl Med.* 2018 Apr 6. pii: jnumed.118.210443. [Epub ahead of print]
6. Giesel F, Kratochwil C, Lindner T, et al. FAPI-PET/CT: biodistribution and preliminary dosimetry estimate of two DOTA-containing FAP-targeting agents in patients with various cancers. *J Nucl Med.* 2018 Aug 2. pii: jnumed.118.215913. [Epub ahead of print]
7. Loktev A, Lindner T, Burger EM, et al. Development of novel FAP-targeted radiotracers with improved tumor retention. *J Nucl Med.* 2019 Mar 8. pii: jnumed.118.224469.
8. Parghane RV, Basu S. Dual-time point 18F-FDG-PET and PET/CT for Differentiating Benign From Malignant Musculoskeletal Lesions: Opportunities and Limitations. *Semin Nucl Med.* 2017;47:373-391.
9. Tagliabue L, Del Sole A. Appropriate use of positron emission tomography with [(18)F]fluorodeoxyglucose for staging of oncology patients. *Eur J Intern Med.* 2014;25:6-11.
10. Jiang C, Chen Y, Zhu Y, Xu Y. Systematic review and meta-analysis of the accuracy of 18F-FDG PET/CT for detection of regional lymph node metastasis in esophageal squamous cell carcinoma. *J Thorac Dis.* 2018;10:6066-6076.
11. Caresia Aroztegui AP, García Vicente AM, Alvarez Ruiz S, et al. 18F-FDG PET/CT in breast cancer: Evidence-based recommendations in initial staging. *Tumour Biol.* 2017;39:1010428317728285.

12. Paudyal B, Oriuchi N, Paudyal P, et al. Clinicopathological presentation of varying 18F-FDG uptake and expression of glucose transporter 1 and hexokinase II in cases of hepatocellular carcinoma and cholangiocellular carcinoma. *Ann Nucl Med.* 2008;22:83-6.
13. Flechsig P, Mehndiratta A, Haberkorn U, Kratochwil C, Giesel FL. PET/MRI and PET/CT in Lung Lesions and Thoracic Malignancies. *Semin Nucl Med.* 2015;45:268-81.
14. Kauhanen SP, Komar G, Seppänen MP, et al. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. *Ann Surg.* 2009;250:957-63.
15. Strobel O, Büchler MW. Pancreatic cancer: FDG-PET is not useful in early pancreatic cancer diagnosis. Nat Rev Gastroenterol Hepatol. 2013;10:203-5.
16. Marzola MC, Chondrogiannis S, Rubello D. Fludeoxyglucose F 18 PET/CT Assessment of Ovarian Cancer. *PET Clin.* 2018;13:179-202.
17. Kitajima K, Murakami K, Sakamoto S, Kaji Y, Sugimura K. Present and future of FDG-PET/CT in ovarian cancer. *Ann Nucl Med.* 2011;25:155-64.
18. Bertagna F, Nicolai P, Maroldi R, et al. Diagnostic role of (18)F-FDG-PET or PET/CT in salivary gland tumors: A systematic review. *Rev Esp Med Nucl Imagen Mol.* 2015;34:295-302.
19. Zafereo ME. Evaluation and staging of squamous cell carcinoma of the oral cavity and oropharynx: limitations despite technological breakthroughs. *Otolaryngol Clin North Am.* 2013;46:599-613.
20. Plaxton NA, Brandon DC, Corey AS, et al. Characteristics and limitations of FDG PET/CT for imaging of squamous cell carcinoma of the head and neck: A comprehensive review of anatomy, metastatic pathways, and image findings. *AJR Am J Roentgenol.* 2015;205:W519-31.
21. Lai V, Khong PL. Updates on MR imaging and $^{18}$F-FDG PET/CT imaging in nasopharyngeal carcinoma. *Oral Oncol.* 2014;50:539-48.
22. Amodru V, Guerin C, Delcourt S, et al. Quantitative $^{18}$F-DOPA PET/CT in pheochromocytoma: the relationship between tumor secretion and its biochemical phenotype. *Eur J Nucl Med Mol Imaging.* 2018;45:278-282.

23. Barrio M, Czernin J, Fanti S, et al. The Impact of Somatostatin Receptor-Directed PET/CT on the Management of Patients with Neuroendocrine Tumor: A Systematic Review and Meta-Analysis. *J Nucl Med.* 2017;58:756-761.
24. Hekman MCH, Rijpkema M, Aarntzen EH, et al. Positron Emission Tomography/Computed Tomography with 89Zr-girentuximab Can Aid in Diagnostic Dilemmas of Clear Cell Renal Cell Carcinoma Suspicion. *Eur Urol.* 2018;74:257-260.
25. Antwi K, Fani M, Heye T, et al. Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: evaluation of diagnostic accuracy in a prospective crossover imaging study. *Eur J Nucl Med Mol Imaging.* 2018;45:2318-2327.
26. Welt S, Divgi CR, Scott AM, et al. Antibody targeting in metastatic colon cancer: a phase I study of monoclonal antibody F19 against a cell-surface protein of reactive tumor stromal fibroblasts. *J Clin Oncol.* 1994;12:1193-203.
27. Davidson B, Goldberg I, Kopolovic J. Inflammatory response in cervical intraepithelial neoplasia and squamous cell carcinoma of the uterine cervix. *Pathol Res Pract*. 1997;193:491-495.
28. Pandit-Taskar N, O'Donoghue JA, Beylergil V, et al. $^{89}$Zr-huJ591 immuno-PET imaging in patients with advanced metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2014;41:2093-105.
29. Afshar-Oromieh A, Hetzheim H, Kübler W, et al. Radiation dosimetry of (68)Ga-PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing. *Eur J Nucl Med Mol Imaging.* 2016;43:1611-20.

## Figure legends

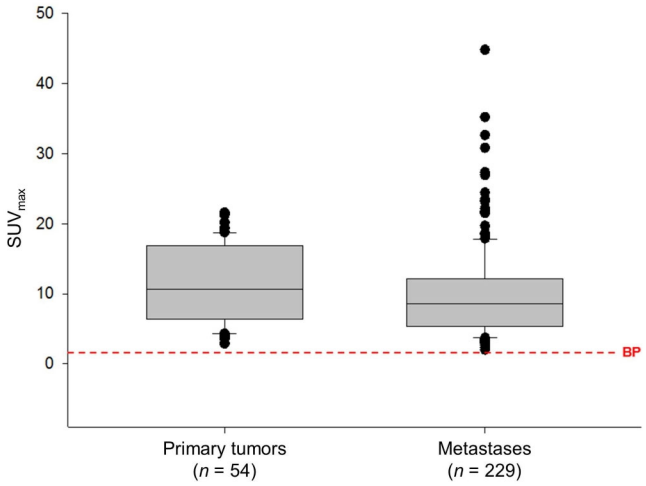


**Figure 1:** Neither mean, median nor range of SUVmax of $^{68}$Ga-FAPI-04 PET differs significantly between primary tumors and metastases.

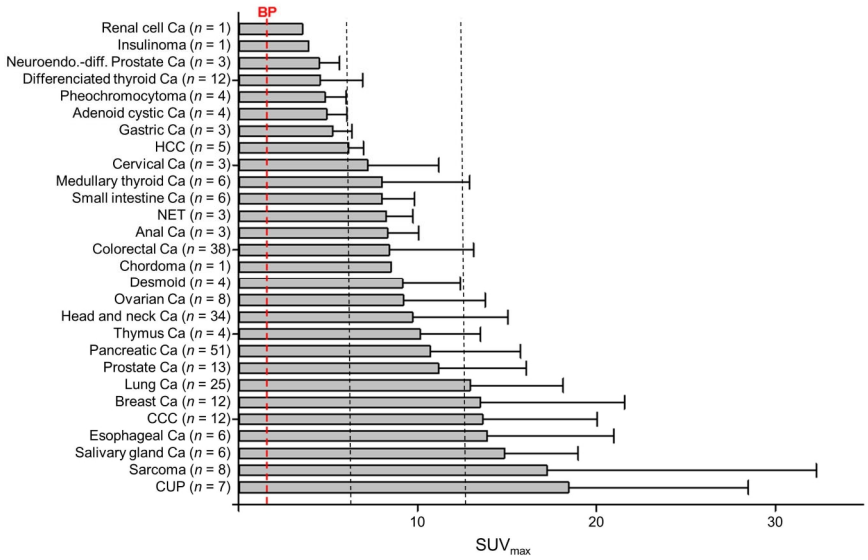


**Figure 2:** Average SUVmax of FAPI-PET/CT in various tumor entities. Low, intermediate and high uptake was defined by cut-off at SUVs 6 and 12. In comparison the average background (blood-pool) was found SUV 1.4. *(Ca = cancer; CCC = cholangiocellular carcinoma; CUP = carcinoma of unknown primary; HCC = hepatocellular carcinoma; NET = neuroendocrine tumor)*

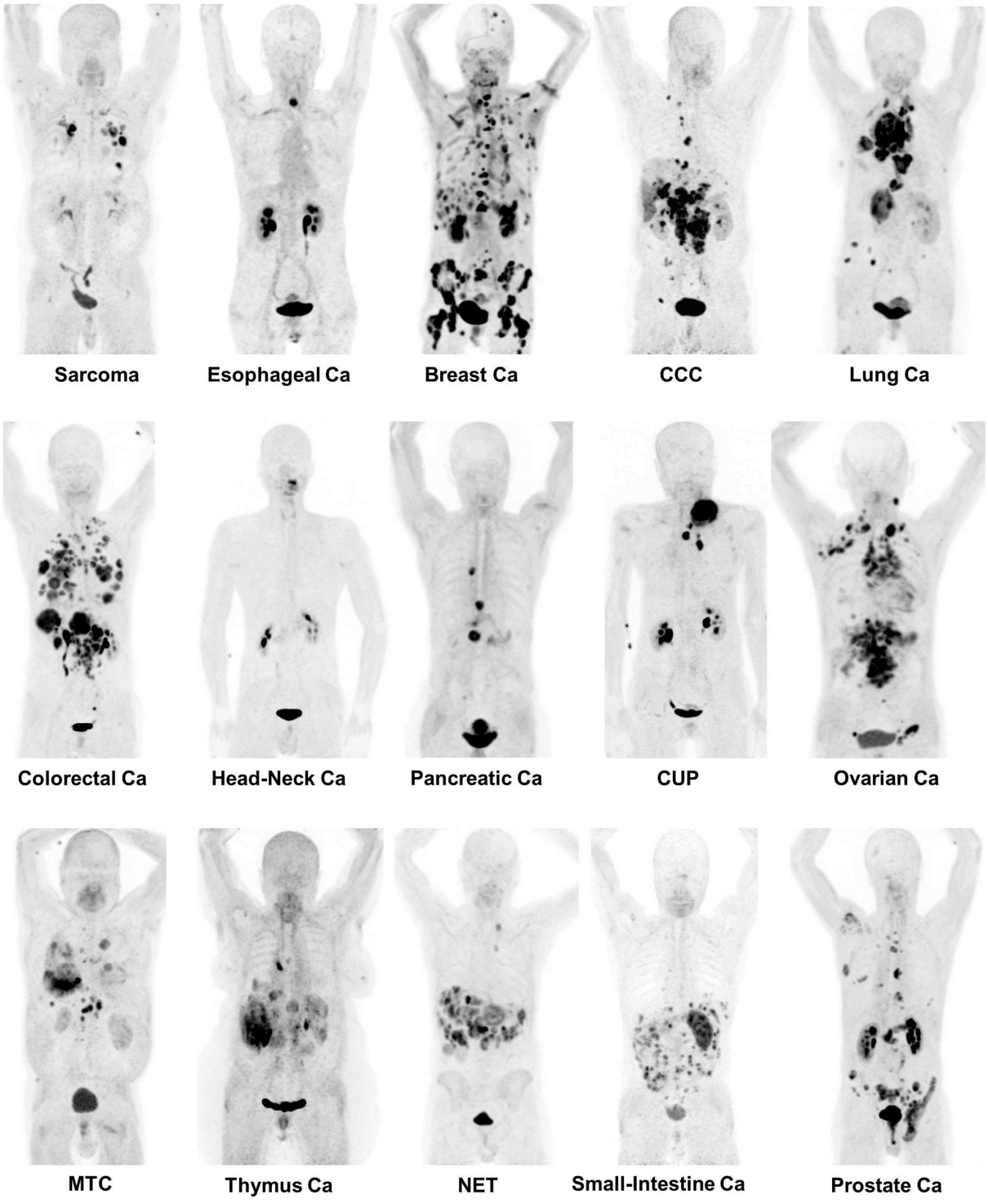


**Figure 3:** Maximum intensity projections of FAPI-PET/CT in patients reflecting 15 different, histologically proven tumor entities (sorted by uptake in descending order). *(CCC = cholangiocellular carcinoma; CUP = carcinoma of unknown primary; MTC = medullary thyroid cancer; Ca = carcinoma; NET = neuroendocrine tumor)*

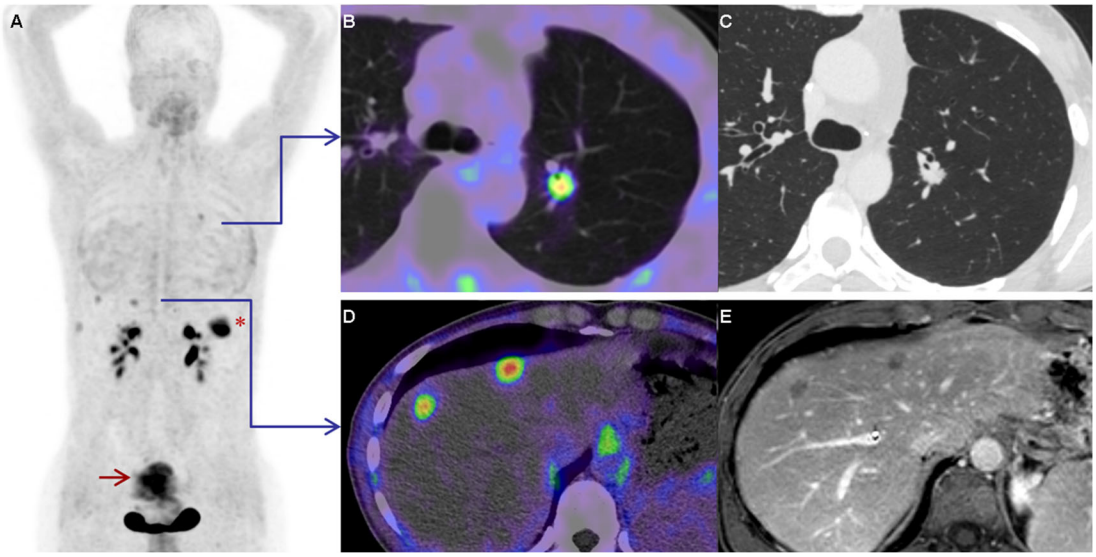


**Figure 4:** Maximum intensity projection (A) of a patient with colorectal carcinoma. Due to low physiological background uptake, tiny lesions in lung (B) and liver (D) were detected by $^{68}$Ga-FAPI-04 PET/CT and measured in dedicated computed tomography of the lung (C) and hepatic magnetic resonance imaging (E) with long axis diameters of 1 cm. *(red arrow = unspecific uptake in uterus; * = primary tumor in left colon flexure)*

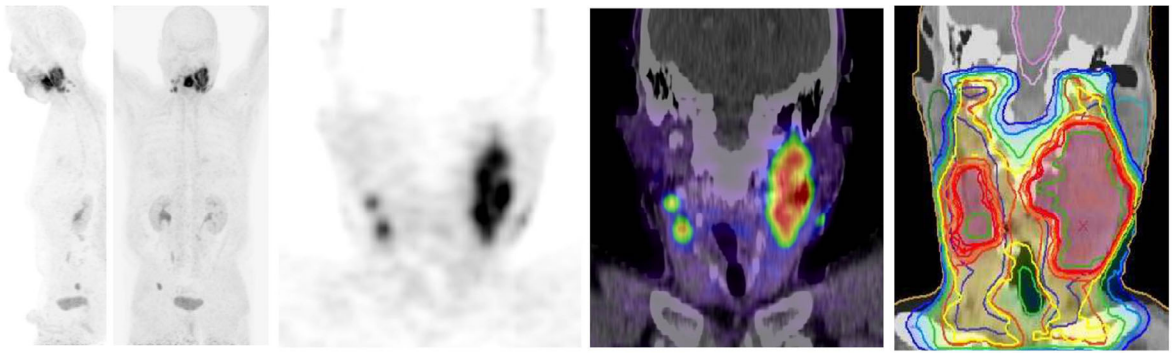

**Figure-5:** Amongst others, one clinical application for FAPI-PET/CT can be to improve gross tumor volume delineation in the preparation of external-beam radiotherapy – in this case a squamous cell carcinoma of the neck with local lymph-node metastases.