Research in Imaging - Update

Considering the distribution of neuroendocrine cells throughout the body, it is important that the imaging covers the several sites where it is possible to observe them – central nervous system, respiratory tract, throat, gastrointestinal tract, thyroid, skin, breast and genitourinary system (Pan et al., 2022).

Imaging plays a vital role in the diagnosis, staging and therapeutic monitoring of NEN. The surgical planning is critically dependent on the detailed anatomical evaluation in order to have accurate information about the location of the primary tumour and local and distant metastases, provided by multiphase CT and MRI; but the selection and monitoring of systemic therapies are increasingly dependent on the use of molecular imaging (Iravani et al., 2022; Ma et al., 2022).

Most NENs correspond to well-differentiated NETs and express somatostatin receptors (SSTRs) that represents the cellular target for currently approved radiopharmaceuticals used for both diagnosis and therapy (Fortunati et al., 2022).

The diagnosis of bone metastases from neuroendocrine tumours is relatively complicated and requires a combination of multiple methods, such as (Pan et al., 2022):

- X-ray;
- Magnetic Resonance Imaging (MRI);
- Computed Tomography (CT);
- Bone scan;
- Somatostatin Receptor Imaging (Octreoscan®);
- PET-CT with ^{68}Ga-somatostatin analogues;
- PET-CT with ^{18}F-FDG.

It is also important to establish a correlation between the imaging and the histopathology analysis (Pan et al., 2022).

Nuclear Medicine plays an important role in the diagnostic and therapy (Fortunati et al., 2022).

The use of somatostatin receptor analogues in PET has superior diagnostic performance in comparison to SPECT with ^{111}In-Pentatreotide (Octreoscan®), with the former being the modality of choice for functional imaging of NETs (Iravani et al., 2022).

Most NETs are accurately studied with ^{68}Ga-DOTA-peptides while the forms with variable-to-low SSTR expression can be detected by using ^{18}F-FDOPA (such as neuroblastoma, medullary thyroid carcinoma, pheochromocytoma, abdominal paraganglioma) (Fortunati et al., 2022).

On the therapeutic side, ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE have been extensively used for target treatment of SSTR-positive NET (Fortunati et al., 2022).

PRRT efficacy has been demonstrated in many different studies with limited toxicity and tremendous impact on the patient's quality of life (Fortunati et al., 2022).

Radiopharmaceutical ^{18}F-FDOPA

The radiopharmaceutical ^{18}F-FDOPA is a structural analogue to dopamine and can reflect the metabolism of dopamine in NENs. However, considering the difficult synthesis and purification

procedure and early poor yield, it was not promoted in the clinical practice; but, in the recent years, progress has been made in these areas (Ma et al., 2022).

^{18}F-FDOPA has been widely explored in NENs, where the primary indication is tumours with low or ambiguous SSTR expression, and medullary thyroid cancer (Ma et al., 2022).

The 18F-FDOPA could be considered a first-line imaging modality for well-differentiated midgut tumours with low proliferation rate, but it seems of limited utility in adult with hyperinsulinism and pancreatic NETs due to physiological pancreatic uptake, but this might be drawback by the use of carbidopa premedication (Lussey-Lepoutre et al., 2016).

Radiopharmaceutical ^{18}F-AIF-NOTA-octreotide

When the comparison is performed between ^{18}F-AIF-NOTA-octreotide and ^{18}F-FDG, it is noted that ^{18}F-AIF-NOTA-octreotide at 90 minutes post-administration, the radiotracer's localisation augmented in kidneys and bladder, while the spleen demonstrated the highest uptake. Physiological uptake is also found in the pituitary, thyroid, adrenal glands, uncinate process of the pancreas, stomach and intestine level. A low background activity was noted in the brain, lung, muscle and bone (Fortunati et al., 2022).

The brain uptake of ^{18}F-AIF-NOTA-octreotide is low due to the intact blood-brain barrier, which is an important aspect for the detection of brain metastases.

The ^{18}F-AIF-NOTA-octreotide uptake was higher than in ^{18}F-FDG scans according to the differentiation grade - ^{18}F-AIF-NOTA-octreotide SUV_{max} was higher in well-differentiated than in poorly differentiated NETs (Fortunati et al., 2022).

Radiopharmaceutical ^{18}F-SiFAlin-TATE

The radiopharmaceutical ^{18}F-SiFAlin-TATE is a promising somatostatin analogue, which has the first-in-human scan in 2019 in a patients with metastatic NET with unknown primary, presenting liver metastases (Fortunati et al., 2022; Ilhan et al., 2019).

In the study performed by Ilhan et al., the patient had a scan with 68Ga-DOTATATE showing cardiac and bone metastases; the ^{18}F-SiFAlin-TATE was also performed and was comparable to 68Ga-DOTATATE. In the study performed by Ilhan et al., a retrospective study with 13 patients; the ^{18}F-SiFAlin-TATE the tumour uptake was higher- which led to a favourable tumour-to-liver and tumour-to-spleen ration. The studies realised support the potential utility of ^{18}F-SiFAlin-TATE (Fortunati et al., 2022; Ilhan et al., 2019, 2020).

Radiopharmaceutical ^{64}Cu-DOTATATE/DOTATOC

The radiopharmaceutical ^{64}Ga-DOTATATE is the latest SSTR agonist approved by the FDA for localisation of SSTR-positive NENs; it was designed to overcomes the challenges from ^{68}Ga-labeled somatostatin analogues. This radiopharmaceutical presents a longer half-life, better image resolution and more sensitive in diagnosing SSTR-positive GEP-NENs (Ma et al., 2022).

The authors Loft et al. compared different 64Cu-DOTATATE PET-CT scans for tumour lesion detection in patients with NENs scanned at 1- and 3-hours post-administration – concluding that

the radiopharmaceutical has an excellent performance from 1- to 3-hours post-administration, with no significant differences in the number of lesions detected, which is also associated to a high-contrast image between those two time points (Pfeifer et al., 2015).

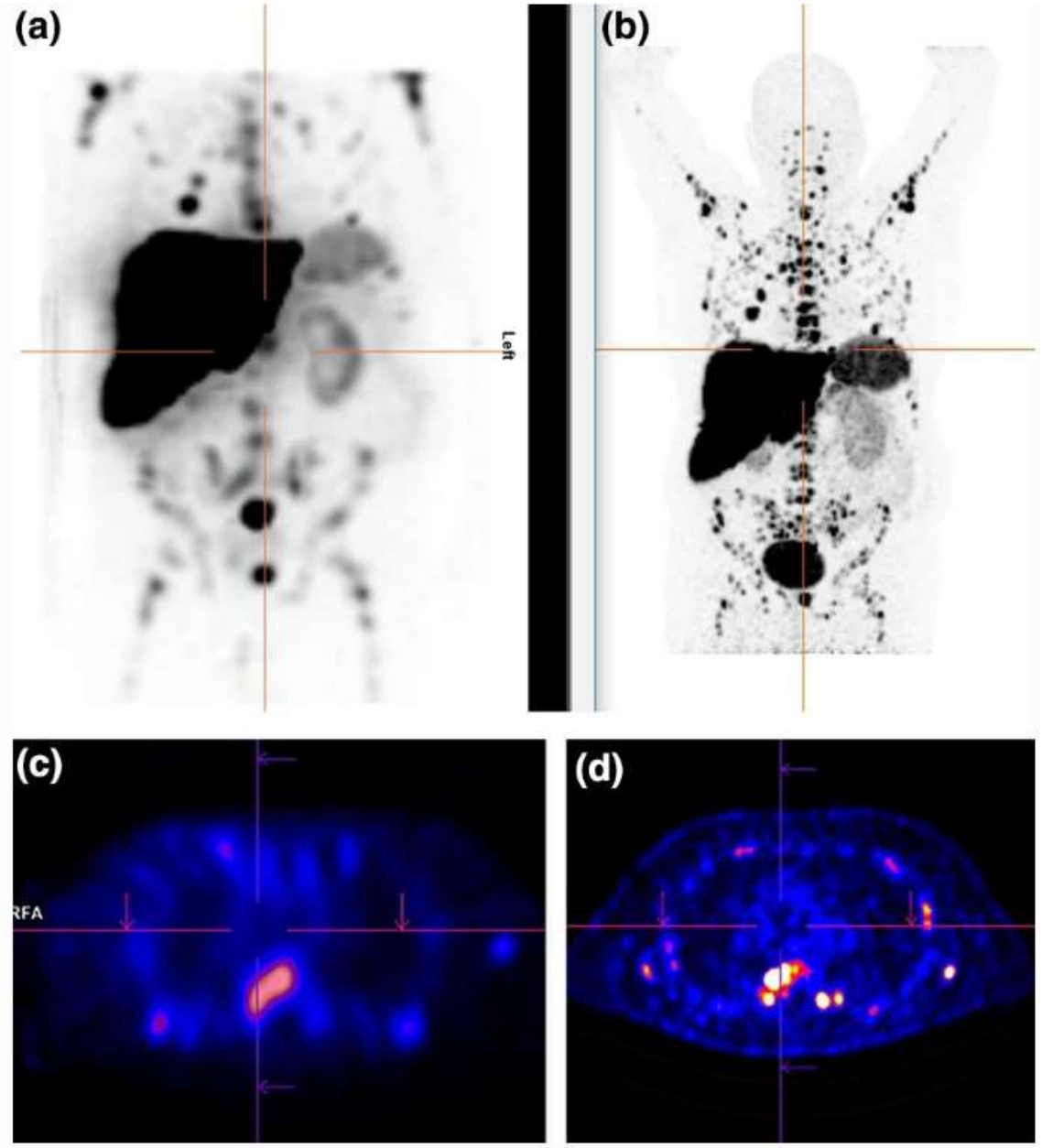

Figure 1 – (a) ^{177}Lu-somatostatin analogue – maximum intensity projection (MIP) image of a 61-year-old male patient and (b) 3 months later follow-up with ^{64}Cu-DOTATOC PET-CT MIP images showing metastasized NET (grade 1) Transaxial images with ^{177}Lu-somatostatin analogue (c) and 3 months later follow-up with ^{64}Cu-DOTATOC PET.CT (d) (Mirzaei et al., 2020).

The high detection rate of possible lesions with high target-to-background contrast means the possibility of the safe application of 64Cu-DOTATOC in patients with NETs; there is also a good correlation of multiple metastases with lesions detected in a post-therapeutic scan with 177Lu-somatostatin analogue. This means that the radiopharmaceutical 64Cu-DOTATOC could be used in treatment planning and follow-up in metastatic NETs (Mirzaei et al., 2020).

Radiopharmaceutical ^{64}Cu-SARTATE

The radiopharmaceutical ^{64}Cu-MeCOSar-Tyr^{3}-octreotate (^{64}Cu-SARTATE) was studied by Hicks et al. and provides an opportunity to assess the clearance kinetics out to, and potentially beyond, 24-hour after administration - Figure 2 (Hicks et al., 2019).

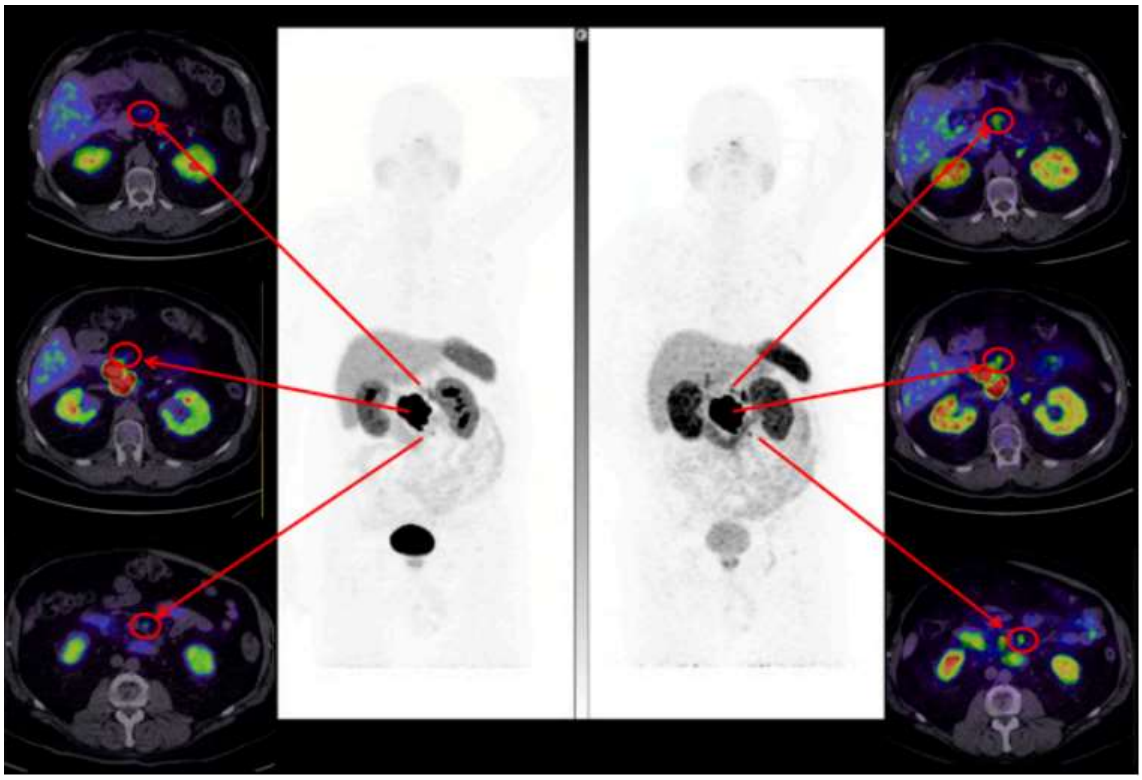

Figure 2 – Superior lesion detection at 4-hour. High lesion contrast on ^{64}Cu-SARTATE at 4-hours (right) better defines regional nodal disease than ^{68}Ga-DOTATATE images at 1-hour (left) in patients with large pancreatic primary tumour but slightly greater small-bowel activity, indicating some hepatobiliary excretion (Hicks et al., 2019).

The high uptake and retention of ^{64}Cu-SARTATE in tumour and accompanying clearance of activity from the liver provides high-contrast diagnostic images until at least 24-hours after administration, which increased the flexibility of time for the Nuclear Medicine department and the potential use of multiple time-point dosimetry before the ^{67}Ga-SARTATE PRRT. It is also important to mention that the radionuclide ^{64}Cu makes commercial good-manufacturing-practice production and distribution to remote sites (Hicks et al., 2019).

The ^{64}Cu-SARTATE/67Cu-SARTATE could be a good theranostic pair (Hicks et al., 2019).

Radiopharmaceutical SSTR antagonists

SSTR antagonists have the chance to improve SSTR-PET-CT imaging because it recognises a higher number of SSTR-binding sites, are not internalised and have lower dissociation rate (Fortunati et al., 2022).

The research group Nicolas et al. chose to explore the radiopharmaceutical ^{68}Ga-OPS202 biodistribution – the tumour and renal uptake persist over time, whereas organs such as spleen,

lungs and liver, along with urinary excretion, are progressively washed out. Tumour contrast was highest at 1-hour post-administration whereas 4-hour images suffer poor count statistics. Remarkably low accumulation of ^{68}Ga-OPS202 is seen in sst_2 receptor-positive organs, such as pituitary, spleen, adrenals and uncinate process of the pancreas. It was demonstrated a rapid clearance from the blood, resulting in low background activity, especially in the liver and gastrointestinal tract (Nicolas et al., 2018).

The team Hou et al. compared the sensitivity of ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTA-TATE PET/CT for detecting the responsible of tumour-induced osteomalacia - Figure 3 (Hou et al., 2022).

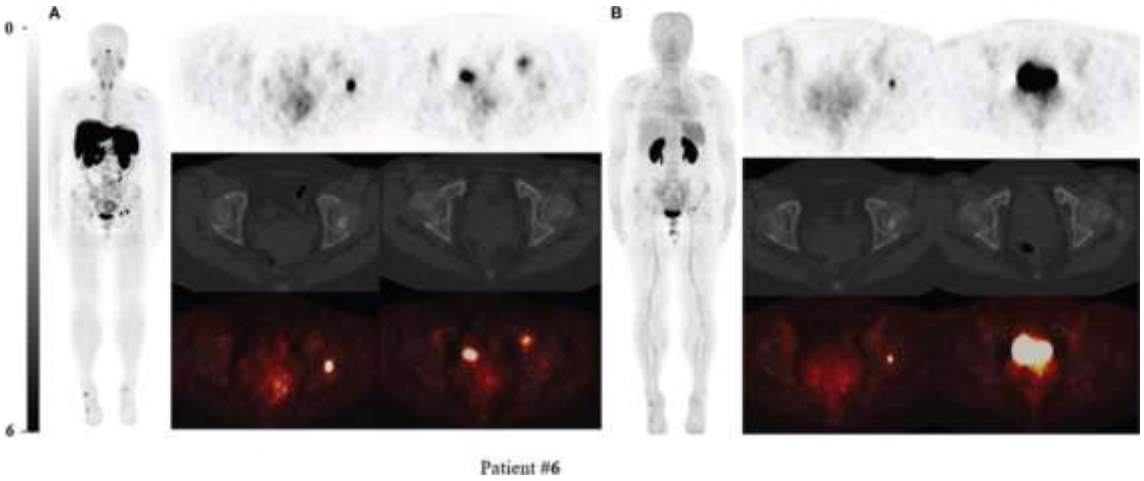

Figure 3 – ^{68}Ga-DOTA-TATE PET/CT compared with ^{68}Ga-DOTA-JR11 PET/CT in patient with multiple lesions. Two intensive uptake lesions in the left femoral head and left public bone revealed a ^{68}Ga-DOTA-TATE PET/CT (A), which suggested that they might be culprit tumours. The lesion of the left femoral head showed osteogenic change. However, the lesion in the left public bone only showed slightly increased uptake and the focus in the left femoral head still showed high uptake on ^{68}Ga-DOTA-JR11 PET/CT (B). The lesion of the left femoral head was confirmed as the responsible tumour of tumour-induced osteomalacia by postsurgical pathological results (Hou et al., 2022).

The data available in the literature suggest higher tumour uptake of JR11 than of DOTATOC – higher tumour radiation doses may be delivered by antagonists (Bodei & Weber, 2018).

Radiopharmaceutical Exendin

Insulinomas is one of the most common types of functional pancreatic NETs, which arises from β-cells (Fortunati et al., 2022).

Surgery is the gold standard of the treatment of insulinoma, but, for this, the location of the neoplastic mass is of primary importance. However, this detection can be challenging because insulinomas are often small sized and multifocal; and conventional imaging (such as, CT and MRI) often show low sensitivity. Also, only a minority of insulinomas express SSTR and can be detected by DOTA-peptide tracers. On the other hand, emerging evidence supports the use of radiotracers binding Glucagon-like peptide-1 receptor (GLP-1R), a G-protein-coupled receptor expressed on pancreatic β cells and overexpressed in insulinomas (Fortunati et al., 2022).

The instability of GLP-1 makes it unsuitable for radiolabelling; therefore, Exendin-4, an agonist with strong bidding affinity for GLP-1R is used. ^{68}Ga is used radiolabel NOTA-MAL-Cys39-

exendin-4, which demonstrates high accuracy for insulinoma localisation with a high tumour-to-pancreas ratio (Fortunati et al., 2022).

There is also the chance of radiolabelling Exendin-4 in order to use in the SPECT-CT technology, such as ^{111}In-DOTA-exendin-4, which was studied by Christ et al. by injecting the radiopharmaceutical in six patients with endogenous hyperinsulinaemic hypoglycaemia - Figure 4 (Christ et al., 2013).

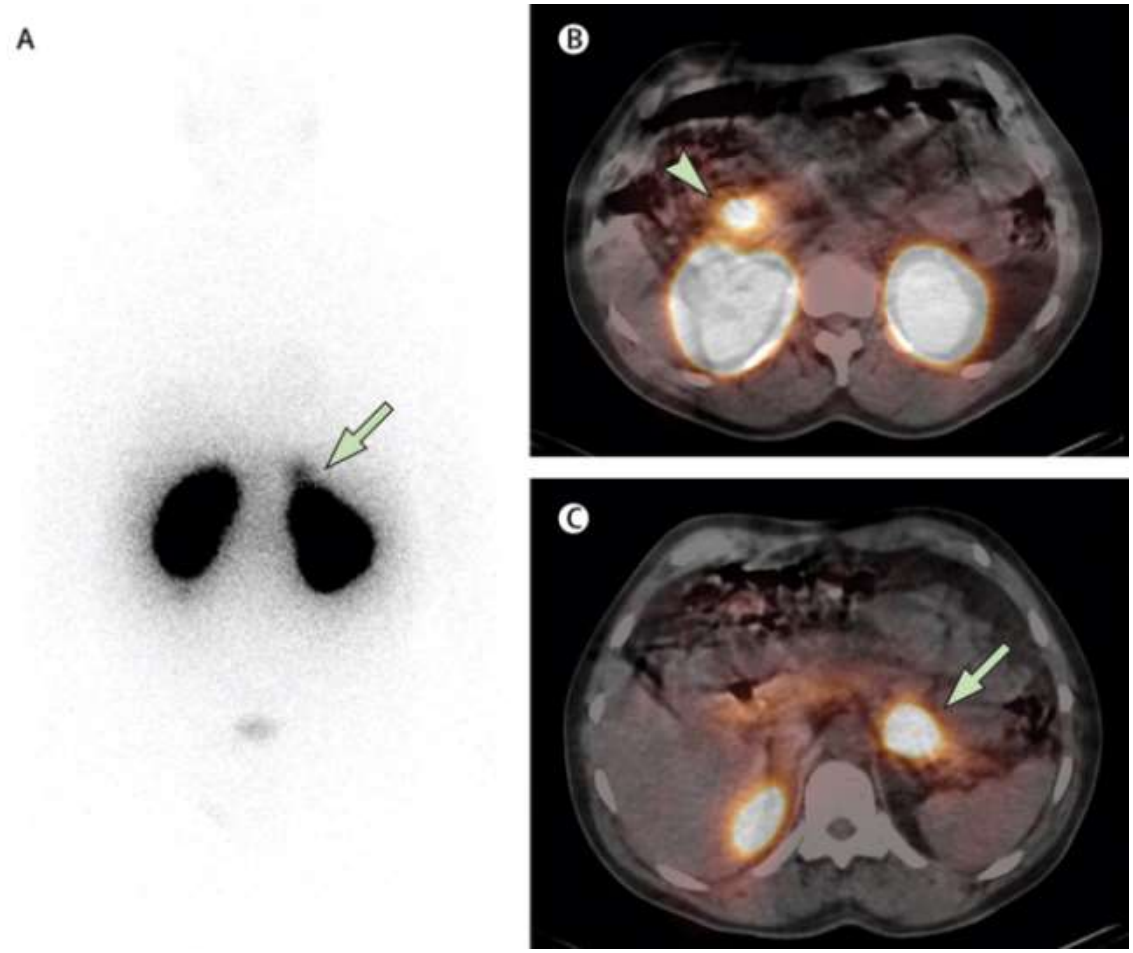

Figure 4 – Whole-body planar images (A) and SPECT-CT images (B and C) at 4 hours post-injection of 108 MBq of ^{111}In-DTPA-exendin-4 (Christ et al., 2013).

During this study was detected in the region of the pancreatic head, Brunner's gland of the duodenum, which homogeneously expresses GLP-1R at high density, but it can lead to false-positive results (Christ et al., 2013).

Radiopharmaceutical ^{18}F-MFBG

The radiopharmaceutical ^{18}F-fluorobenzylguanidine (MFBG) is an analogue of ^{123}I-MIBG, which is accumulated in cells through the same norepinephrine transporter uptake mechanism of ^{123}I-MIBG (Fortunati et al., 2022).

The use of ^{123}I-MIBG means that the patient needs to perform a preparation for the scan (such as, many drugs interfere with uptake and retention of MIBG, like tricyclic antidepressants,

antihypertensives; a thyroid blockage should be used in order to prevent the uptake of free iodine by the thyroid), has a poor image resolution, low quantitative accuracy and the scan acquisition is long. In order to overcome these issues, ^{18}F-MFBG could be a successful alternative (Fortunati et al., 2022).

A study conducted by Pandit-Taskar et al., the first-in-human study with ^{18}F-MFBG analysing 10 patients with metastatic neuroblastoma and paraganglioma/pheochromocytoma indicated the biodistribution, pharmacokinetics and organ dosimetry of the radiopharmaceutical.

The overall distribution of ^{18}F-FMBG appeared to be similar to ^{123}I-MIBG; although prominent uptake was seen in normal liver, the activity decreased with time and lesions were detectable at 1-hour post-administration with high contrast, though later images showed more contrast and a higher number of lesion are seen in some patients (Pandit-Taskar et al., 2018).

The kidneys are the primary source of excretion, and, consequently, the bladder is the critical organ, because the urine accumulates in the bladder – similar to what happens in ^{123}I-MIBG (Pandit-Taskar et al., 2018).

Regarding the biodistribution, similar myocardial uptake, prominent in the initial scans and activity decreases with time; GI uptake was also seen, but it is not prominent and it does not interfere with the detection of lesions in the region (Pandit-Taskar et al., 2018).

A comparison between ^{123}I-MIBG and ^{18}F-FMBG can be found in Figure 5 (Samim et al., 2021).

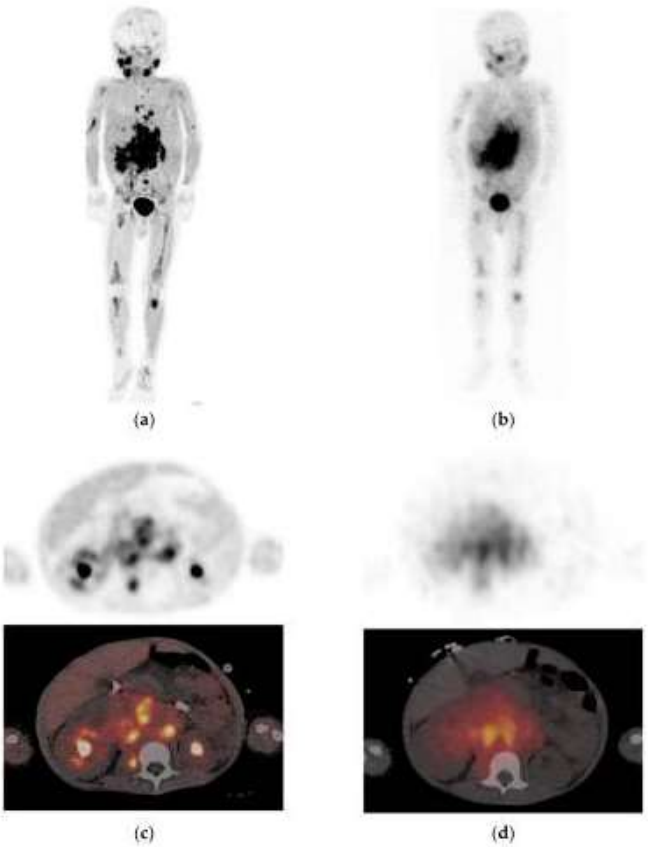

Figure 5 – Example of a neuroblastoma patient with extensive metastases who underwent ^{123}-MIBG and ^{18}F-MFBG imaging within 1 day. These figure illustrate the superior image quality and tumour delineation of (a) ^{18}F-MFBG PET maximum intensity projection and (c) axial PET-CT cue to higher spatial resolution, higher tumour-to-background contrast,

and improved counting statistics compared to (b) ^{123}I-MIBG planar scintigraphy and (d) axial view in SPECT-CT (Samim et al., 2021).

Radiopharmaceutical ^{68}Ga-CXCR4

The drug C-X-C motif chemokine receptor 4 (CXCR4) is overexpressed in more aggressive and dedifferentiated NEN (Fortunati et al., 2022).

The author Weich et al., describe that the use of CXCR4 in imaging through the radiopharmaceutical ^{68}Ga-Pentixafor as an alternative to ^{18}F-FDG in poorly differentiated NEC (Fortunati et al., 2022).

The ^{68}Ga-Pentixafor positivity is associated with adverse prognosis, early progression and shortened overall survival (Fortunati et al., 2022).

Authors discovered that CXCR4 can be considered as a “tumour driver” which regulates the microenvironment and dissemination of metastasis – for example, ^{68}Ga-Pentixafor spleen uptake in solid tumour patient correlates with the suppression of antitumour immune responses. On the other hand, high spleen uptake in NEN is correlated with elevated leukocyte count and thrombocytosis possibly attributed to high tumour metabolism (Fortunati et al., 2022).

One of the images released in a comparison between ^{68}Ga-Pentixafor and ^{18}F-FDG – Figure 6.

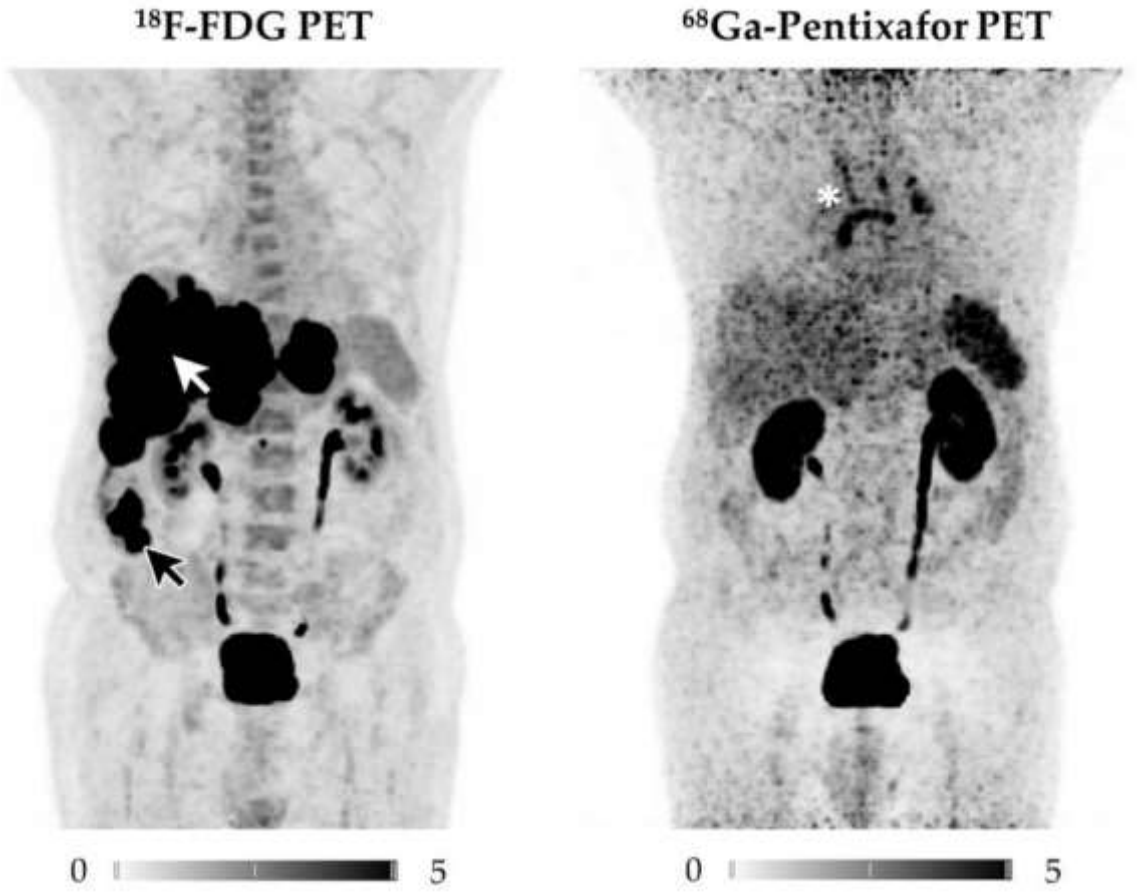

Figure 6 – Maximum Intensity Projections (MIP) of the ^{18}F-FDG (left) and ^{68}Ga-Pentixafor. Whereas ^{18}F-FDG depicts the ileal primary (black arrow) as well as multiple liver metastases (white arrow), none of the tumour manifestations are

revealed by CXCR4-directed PET imaging. Incidental finding: the mediastinal tracer uptake in ^{68}Ga-Penxtixafor (white star) was traceable to enlarged mediastinal lymph nodes, most likely due to chronic lung fibrosis and not related to NEC, as follow-up imaging confirmed (Weich et al., 2021).

Other characteristics of the ^{68}Ga-Pentixafor images is that the spleen always has high uptake – this characteristic was explored by Lewis et al..

The suppression of anti-tumour immunity is majorly regulated through immunosuppressive myeloid-derived suppressor cells (MDSCs), which originate in the spleen. Tumour infiltrating MDSCs cells are known to express high levels of CXCR4 and to migrate towards the SDF-1 gradient. Unfortunately, the role of CXCR4 in the spleen for MDSCs differentiation and release to peripheral sites remains unclear. This way, there is strong evidence that underlines the pivotal roles of the spleen and CXCR4 in the immune response to tumours (Lewis et al., 2021).

Lewis et al. investigated the possibility of elevated ^{68}Ga-Pentixafor uptake of spleen could be associated with an activated state of spleen and/or immune activity and clinical outcome; it was found that platelet count was positively associated with splenic drug uptake, regardless of tumour entity (Lewis et al., 2021).

A possible explanation could possibly be a marker for spleen CXCR4 expression and tumours with a higher inflammatory component and tumours that rely more heavily on a functional tumour microenvironment that recruits platelets and leukocytes (Lewis et al., 2021).

No differences were found in the survival outcomes when investigation the drug uptake in the spleen, indicating that the ^{68}Ga-Pentixafor uptake is not suitable to predict patient's outcomes, as it could be seen from the Figure 7 (Lewis et al., 2021).

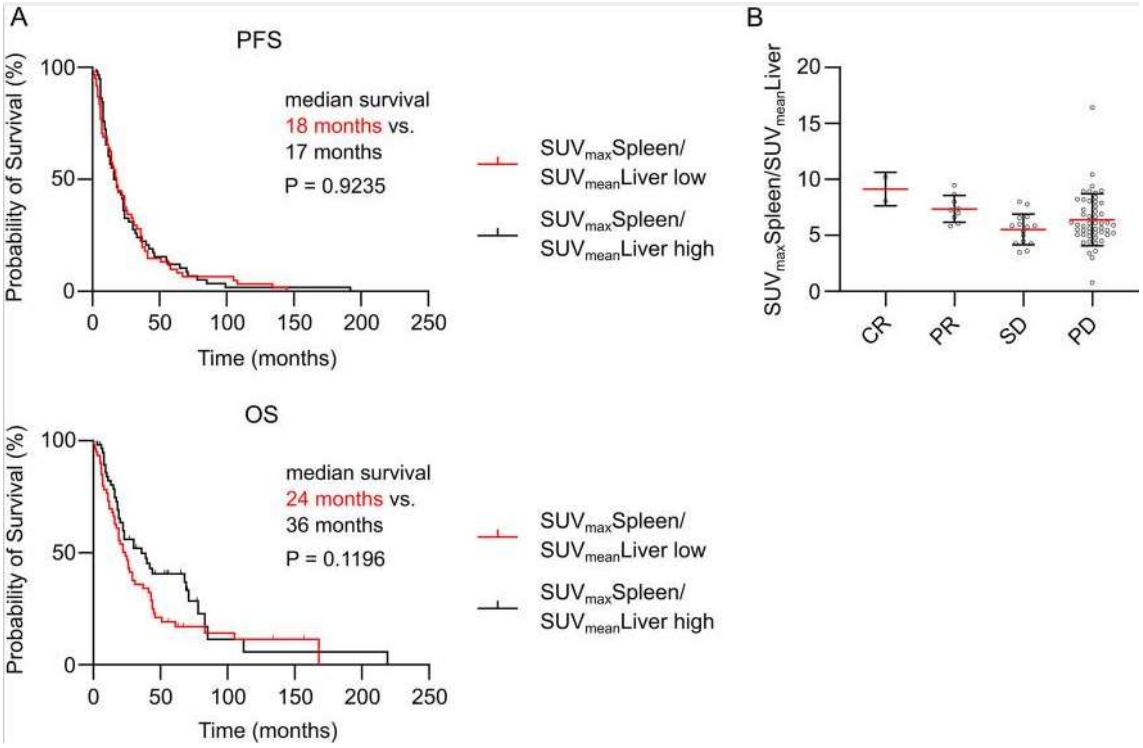

Figure 7 – Spleen ^{68}Ga-Pentaxifor uptake does not correlate with clinical outcomes in solid tumour patients. (A) Kaplan-Meier survival curves of progression-free survival (PFS) and overall survival (OS) of all solid tumour patients in the study

separated by the median into two groups of low and high spleen-to-liver ratios ($SUV_{max\text{-}spleen}/SUV_{mean\text{-}liver}$), PFD: low, n=61, high, n=58; OS: low, n=61, high, n=54. (B) Comparison of $SUV_{max\text{-}spleen}/SUV_{mean\text{-}liver}$ with remission statis of all patients, complete remission (CR), n=2; partial remission (PR), n=9; stable disease (SD), n=15; progressive disease (PD), n=51 (Lewis et al., 2021).

The statement that the use of ^{68}Ga-Pentixafor could lead to a new therapeutic approach with ^{177}Lu-Pentixather is not supported by Weich et al., especially because it leads to bone marrow ablation and it would require autologous stem cell support.

Radiopharmaceutical ^{68}Ga-PSMA

Immunochemistry investigations showed that the prostate-specific membrane antigen (PSMA) can also be overexpressed on the endothelial cells of the neo-vasculature of several types of solid tumours, such as, well-differentiated thyroid carcinoma, lung adenocarcinoma, gastric and colon adenocarcinoma and renal carcinoma. This way, there is emerging evidence of its potential capacity to accidentally identify non-prostatic tumours (Fortunati et al., 2022).

A clinical case of a 68-year-old man with medullary thyroid cancer, who earlier underwent total thyroidectomy and left neck dissection as primary surgery and left modified radical neck dissection and radiotherapy for nodal recurrence. The patient has persistently rising calcitonin (raising from to 107 ng/mL) and carcinoembryonic antigen level (27 ng/mL) (Arora et al., 2018).

When the second recurrence happened, the options of surgery and radiotherapy were already exhausted and the patient had negative results in the MIBG and somatostatin receptors in PET-CT, which means that ^{131}I-MIBG and ^{177}Lu-DOTATATE (Arora et al., 2018).

In order to explore the option of ^{177}Lu-DKFZ-PSMA 617, he underwent ^{68}Ga-PSMA PET-CT scan, which showed soft-tissue density lesion in the left paratracheal region – this lesion also tested positive for ^{18}F-FDG. The images of this clinical case can be found in Figure 8 (Arora et al., 2018).

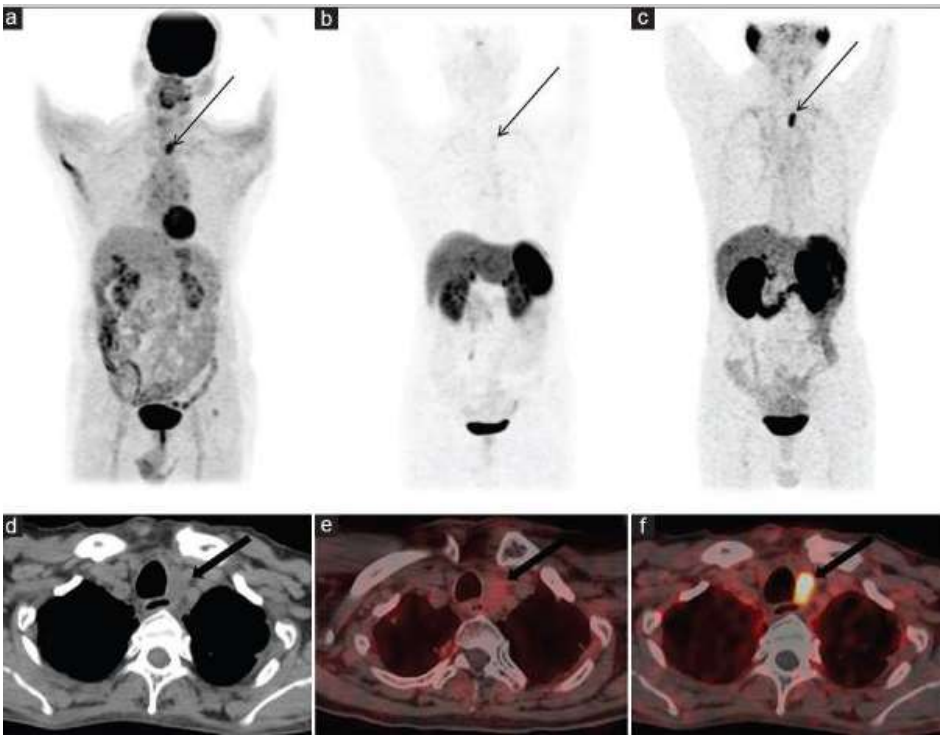

Figure 8 – Maximum intensity projection (MIP) images of ^{18}F-FDG (a), ^{68}Ga-DOTANOC (b) and ^{68}Ga-PSMA (c), revealing increased uptake in the ^{18}F-FDG and ^{68}Ga-PSMA in the left paratracheal recurrent soft-tissue lesion, but no significant uptake on the scan and somatostatin receptor scan (thin black arrow). Axial CT (d), fused ^{68}Ga-DOTANOC and ^{68}Ga-PSMA (f) images reveal soft-tissue density lesion in the left paratracheal region, extending into tracheoesophageal groove (d) with increased PSMA uptake (black arrow, SUV_{max}=19.7 and $SUV_{max\text{-}liver}$=8.0) (Arora et al., 2018).

In a clinical case published by Prabhu et al., a 47-year-old female with metastatic pancreatic neuroendocrine tumour. The patient was treated with long-acting octreotide, but this one failed to halt disease progression (Prabhu et al., 2018).

Initially, a ^{68}Ga-DOTANOC scan was acquired, which showed good uptake in the primary and metastatic lesions, but considering that these tumours are highly vascular and PSMA in known in the endothelium of tumour neovasculature. The ^{68}Ga-PSMA-HBED-CC was performed, which also showed uptake in the primary and metastatic liver lesions (Prabhu et al., 2018).

However, the intensity of the uptake was low when compared to ^{68}Ga-DOTANOC, but it remains to be seen how much uptake will be seen in high-grade NETs which are known to be poorly DOTANOC avid (Prabhu et al., 2018).

The images of this clinical case can be found in Figure 9 (Prabhu et al., 2018).

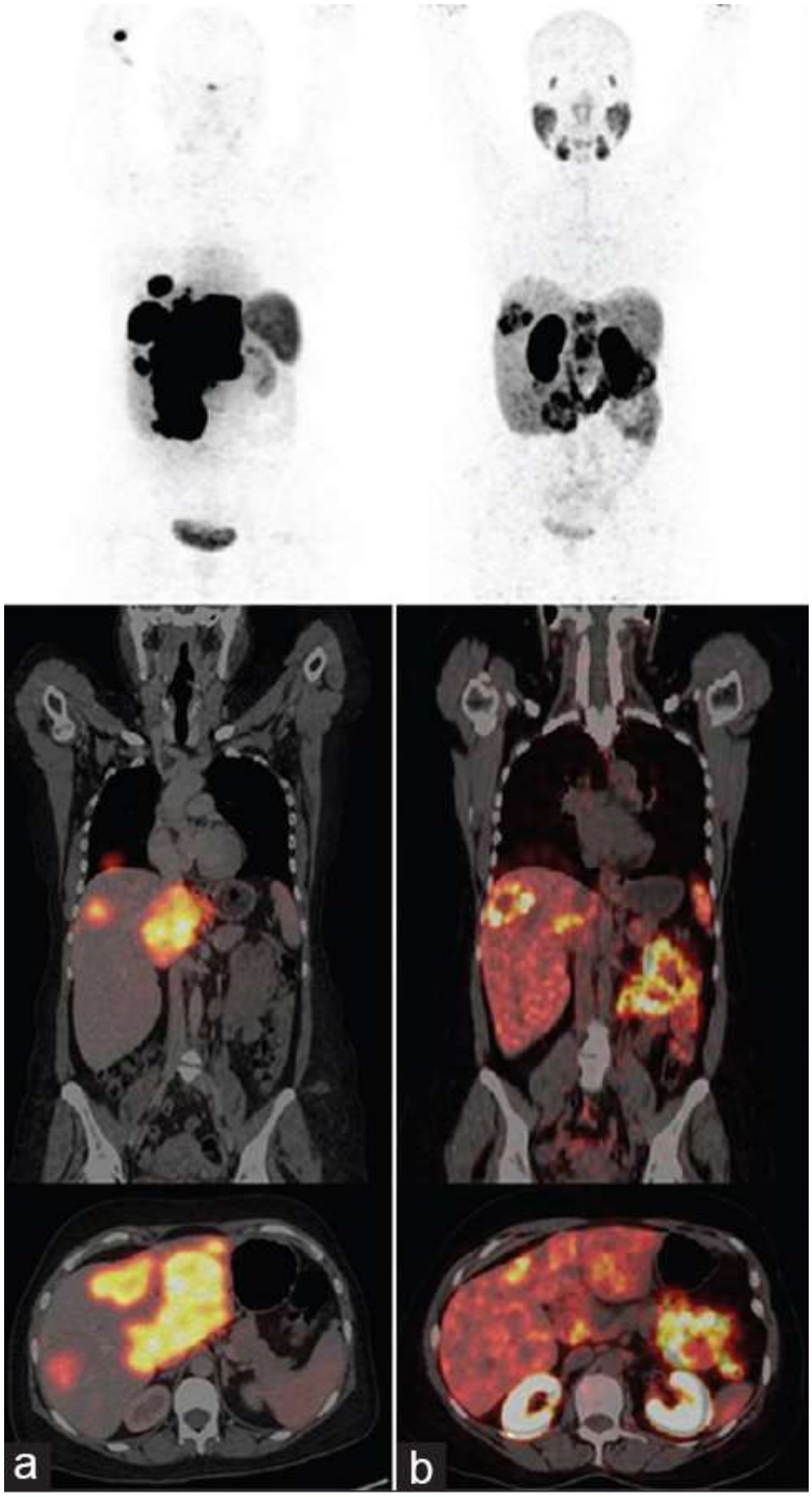
a
b

Figure 9 – ^{68}Ga-DOTANOC (a) and ^{68}-PSMA-11 (b) in case of metastatic pancreatic neuroendocrine tumour; showing increased uptake tracer uptake in multiple liver lesions. However, the intensity of uptake was less in ^{68}Ga-PSMA when compared to ^{68}Ga-DOTANOC images (Prabhu et al., 2018).

Radiopharmaceutical ^{68}Ga-FAPI

^{68}Ga-FAPI is a promising radiopharmaceutical in PET-CT where FAPI corresponds to a fibroblasts activation protein (FAP) inhibitor overexpressed in fibroblasts – this is associated with malignancy and poor prognosis, tumour growth and metastatic spread in several tumour entities (Fortunati et al., 2022; Yordanova et al., 2020).

Different types of tumours express strongly FAP, especially epithelial carcinomas (Fortunati et al., 2022).

The biodistribution of 68Ga-FAPI is quite low when compared to other radiopharmaceuticals, such as 18F-FDG, which allows an improvement in the detection of metastases in the brain, head and neck, liver, peritoneum, mesentery, omentum and axial skeleton (Fortunati et al., 2022).

Among all the FAPI tracers, FAPI-04 showed improved FAP binding and pharmacokinetics (Fortunati et al., 2022).

In a study developed by Kratochwil et al., where 28 different types of tumours were evaluated with ^{68}Ga-FAPI, showing an intermediate tracer uptake with tumour-to-background ratio being higher than 3. This way, in NETs with disseminated metastatic disease, FAPI can give a contribute to non-invasive tumour characterisation and help making decisions about treatment planning. The same conclusion was achieved by Chen et al. when comparing ^{68}Ge-FAPI-04 with ^{18}F-FDG, especially when identifying liver metastases, peritoneal carcinomatosis and brain tumours.

One of the examples of detecting liver metastases was published by Chen et al. – Figure 10.

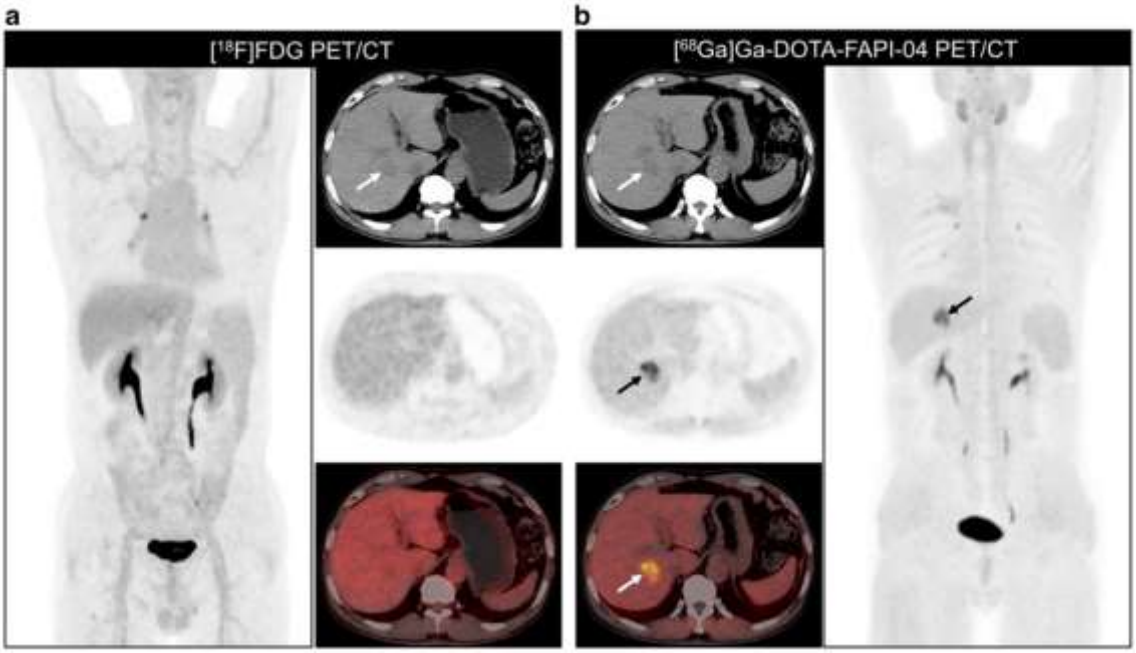

Figure 10 – A 69-year-old man who presented with a 3-history of abdominal discomfort and previous ultrasound revealed suspicious liver nodule in the right lobe. This patient underwent PET-CT scan with ^{18}F-FDG for differentiation of the underlying malignancy. However, no abnormal activity was observed on the maximum intensity projection (MIP) and axial

images (a); although, the corresponding CT scan showed an ill-defined nodule in the liver (arrow). This patient was referred to ^{68}Ga-DOTA-FAPI-04 PET-CT imaging for further discrimination of the liver nodule, which revealed a strong FAPI-avid nodule (arrow) in MIP and axial images (b). The liver biopsy identified hepatocellular carcinoma (HCC) (Chen et al., 2021).

In the study performed by Chen et al., it was also possible to verify that the primary and metastatic lesions demonstrated higher uptake of ^{68}Ga-DOTA-FAPI-04 than ^{18}F-FDG, which means that the former may be able to determinate doubtful lesion observed in the conventional imaging, locate the primary site of unknown malignancies and the site of recurrence.

Although preliminary data indicate that FAPI is a tracer with favourable biodistribution in NEN, but further studies are needed to provide additional value in the clinical management of NEN with elevated content of activated fibroblasts (Fortunati et al., 2022).

Nowadays, in clinical practice, SSTR agonists are used for the diagnosis and therapy of well-differentiated NENs (Fortunati et al., 2022).

For high-grade grades 2 and 3 and NEC, ^{18}F-FDG is currently used. On the other hand, ^{18}F-FDOPA is used for medullary thyroid cancer, pheochromocytoma and abdominal paraganglioma (Fortunati et al., 2022).

The radiopharmaceuticals ^{18}F-FDG and ^{68}Ga-SSTR agonists have complementary effects. When performed together, it leads to a better localisation and diagnostic value of GEP-NENs (Ma et al., 2022).

In the recent years, there has been emerging evidence about the potential promising role of new radiopharmaceuticals that exploit different targets in the NET cells (Fortunati et al., 2022).

However, the clinical impact of these new radiopharmaceuticals is still not completely known due to the limited number and very heterogenous cohort of studied patients. This way, more studies are needed to better ascertain the clinical settings in which these tracers will provide an added value and definitive clinical impact (Fortunati et al., 2022).

It is important to stress that the role of Nuclear Medicine in NENs has grown over the last two decades and its practice can confirm that it can offer many alternative valid solutions (Ma et al., 2022).

Clara Ferreira

References

Arora, S., Prabhu, M., Damle, N. A., Bal, C., Kumar, P., Nalla, H., & Arun Raj, S. T. (2018). Prostate-specific Membrane Antigen Imaging in Recurrent Medullary Thyroid Cancer: A New Theranostic Tracer in the Offing? *Indian Journal of Nuclear Medicine : IJNM : The Official Journal of the Society of Nuclear Medicine, India*, *33*(3), 261–263. https://doi.org/10.4103/ijnm.IJNM_10_18

Bodei, L., & Weber, W. A. (2018). Somatostatin Receptor Imaging of Neuroendocrine Tumors: From Agonists to Antagonists. *Journal of Nuclear Medicine*, *59*(6), 907–908. https://doi.org/10.2967/jnumed.117.205161

Chen, H., Pang, Y., Wu, J., Zhao, L., Hao, B., Wu, J., Wei, J., Wu, S., Zhao, L., Luo, Z., Lin, X., Xie, C., Sun, L., Lin, Q., & Wu, H. (2020). Comparison of [68Ga]Ga-DOTA-FAPI-04 and [18F] FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer. *European Journal of Nuclear Medicine and Molecular Imaging*, *47*(8), 1820–1832. https://doi.org/10.1007/s00259-020-04769-z

Chen, H., Zhao, L., Ruan, D., Pang, Y., Hao, B., Dai, Y., Wu, X., Guo, W., Fan, C., Wu, J., Huang, W., Lin, Q., Sun, L., & Wu, H. (2021). Usefulness of [68Ga]Ga-DOTA-FAPI-04 PET/CT in patients presenting with inconclusive [18F]FDG PET/CT findings. *European Journal of Nuclear Medicine and Molecular Imaging*, *48*(1), 73–86. https://doi.org/10.1007/s00259-020-04940-6

Christ, E., Wild, D., Ederer, S., Béhé, M., Nicolas, G., Caplin, M. E., Brändle, M., Clerici, T., Fischli, S., Stettler, C., Ell, P. J., Seufert, J., Gloor, B., Perren, A., Reubi, J. C., & Forrer, F. (2013). Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: a prospective multicentre imaging study. *The Lancet Diabetes & Endocrinology*, *1*(2), 115–122. https://doi.org/10.1016/S2213-8587(13)70049-4

Fortunati, E., Argalia, G., Zanoni, L., Fanti, S., & Ambrosini, V. (2022). New PET Radiotracers for the Imaging of Neuroendocrine Neoplasms. *Current Treatment Options in Oncology*, *23*(5), 703–720. https://doi.org/10.1007/s11864-022-00967-z

Hicks, R. J., Jackson, P., Kong, G., Ware, R. E., Hofman, M. S., Pattison, D. A., Akhurst, T. A., Drummond, E., Roselt, P., Callahan, J., Price, R., Jeffery, C. M., Hong, E., Noonan, W., Herschtal, A., Hicks, L. J., Hedt, A., Harris, M., Paterson, B. M., & Donnelly, P. S. (2019). 64 Cu-SARTATE PET Imaging of Patients with Neuroendocrine Tumors Demonstrates High Tumor Uptake and Retention, Potentially Allowing Prospective Dosimetry for Peptide Receptor Radionuclide Therapy. *Journal of Nuclear Medicine*, *60*(6), 777–785. https://doi.org/10.2967/jnumed.118.217745

Hou, G., Zhang, Y., Liu, Y., Wang, P., Xia, W., Xing, X., Huo, L., Li, F., & Jing, H. (2022). Head-to-Head Comparison of 68Ga-DOTA-TATE and 68Ga-DOTA-JR11 PET/CT in Patients With Tumor-Induced Osteomalacia: A Prospective Study. *Frontiers in Oncology*, *12*. https://doi.org/10.3389/fonc.2022.811209

Ilhan, H., Lindner, S., Todica, A., Cyran, C. C., Tiling, R., Auernhammer, C. J., Spitzweg, C., Boeck, S., Unterrainer, M., Gildehaus, F. J., Böning, G., Jurkschat, K., Wängler, C., Wängler, B., Schirrmacher, R., & Bartenstein, P. (2020). Biodistribution and first clinical results of 18F-SiFAlin-TATE PET: a novel 18F-labeled somatostatin analog for imaging of neuroendocrine tumors. *European Journal of Nuclear Medicine and Molecular Imaging*, *47*(4), 870–880. https://doi.org/10.1007/s00259-019-04501-6

Ilhan, H., Todica, A., Lindner, S., Boening, G., Gosewisch, A., Wängler, C., Wängler, B., Schirrmacher, R., & Bartenstein, P. (2019). First-in-human 18F-SiFAlin-TATE PET/CT for

NET imaging and theranostics. *European Journal of Nuclear Medicine and Molecular Imaging*, *46*(11), 2400–2401. https://doi.org/10.1007/s00259-019-04448-8

Iravani, A., Parihar, A. S., Akhurst, T., & Hicks, R. J. (2022). Molecular imaging phenotyping for selecting and monitoring radioligand therapy of neuroendocrine neoplasms. *Cancer Imaging*, *22*(1), 25. https://doi.org/10.1186/s40644-022-00465-3

Kratochwil, C., Flechsig, P., Lindner, T., Abderrahim, L., Altmann, A., Mier, W., Adeberg, S., Rathke, H., Röhrich, M., Winter, H., Plinkert, P. K., Marme, F., Lang, M., Kauczor, H.-U., Jäger, D., Debus, J., Haberkorn, U., & Giesel, F. L. (2019). 68 Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. *Journal of Nuclear Medicine*, *60*(6), 801–805. https://doi.org/10.2967/jnumed.119.227967

Lewis, R., Habringer, S., Kircher, M., Hefter, M., Peuker, C. A., Werner, R., Ademaj-Kospiri, V., Gäble, A., Weber, W., Wester, H.-J., Buck, A., Herhaus, P., Lapa, C., & Keller, U. (2021). Investigation of spleen CXCR4 expression by [68Ga]Pentixafor PET in a cohort of 145 solid cancer patients. *EJNMMI Research*, *11*(1), 77. https://doi.org/10.1186/s13550-021-00822-6

Loft, M., Carlsen, E. A., Johnbeck, C. B., Johannesen, H. H., Binderup, T., Pfeifer, A., Mortensen, J., Oturai, P., Loft, A., Berthelsen, A. K., Langer, S. W., Knigge, U., & Kjaer, A. (2021). 64 Cu-DOTATATE PET in Patients with Neuroendocrine Neoplasms: Prospective, Head-to-Head Comparison of Imaging at 1 Hour and 3 Hours After Injection. *Journal of Nuclear Medicine*, *62*(1), 73–80. https://doi.org/10.2967/jnumed.120.244509

Lussey-Lepoutre, C., Hindié, E., Montravers, F., Detour, J., Ribeiro, M.-J. S., Taïeb, D., & Imperiale, A. (2016). The current role of 18F-FDOPA PET for neuroendocrine tumor imaging. *Médecine Nucléaire*, *40*(1), 20–30. https://doi.org/10.1016/j.mednuc.2016.01.003

Ma, X., Ding, Y., Li, W., Li, Q., & Yang, H. (2022). Diagnosis and management of gastroenteropancreatic neuroendocrine neoplasms by nuclear medicine: Update and future perspective. *Frontiers in Oncology*, *12*. https://doi.org/10.3389/fonc.2022.1061065

Mirzaei, S., Revheim, M.-E., Raynor, W., Zehetner, W., Knoll, P., Zandieh, S., & Alavi, A. (2020). 64Cu-DOTATOC PET-CT in Patients with Neuroendocrine Tumors. *Oncology and Therapy*, *8*(1), 125–131. https://doi.org/10.1007/s40487-019-00104-1

Nicolas, G. P., Beykan, S., Bouterfa, H., Kaufmann, J., Bauman, A., Lassmann, M., Reubi, J. C., Rivier, J. E. F., Maecke, H. R., Fani, M., & Wild, D. (2018). Safety, Biodistribution, and Radiation Dosimetry of 68 Ga-OPS202 in Patients with Gastroenteropancreatic Neuroendocrine Tumors: A Prospective Phase I Imaging Study. *Journal of Nuclear Medicine*, *59*(6), 909–914. https://doi.org/10.2967/jnumed.117.199737

Pan, Q., Yang, W., Zhang, Z., & Shao, Z. (2022). Rare Bone Metastasis of Neuroendocrine Tumors of Unknown Origin: A Case Report and Literature Review. *Orthopaedic Surgery*, *14*(10), 2766–2775. https://doi.org/10.1111/os.13384

Pandit-Taskar, N., Zanzonico, P., Staton, K. D., Carrasquillo, J. A., Reidy-Lagunes, D., Lyashchenko, S., Burnazi, E., Zhang, H., Lewis, J. S., Blasberg, R., Larson, S. M., Weber, W. A., & Modak, S. (2018). Biodistribution and Dosimetry of 18 F-Meta-

Fluorobenzylguanidine: A First-in-Human PET/CT Imaging Study of Patients with Neuroendocrine Malignancies. *Journal of Nuclear Medicine*, *59*(1), 147–153. https://doi.org/10.2967/jnumed.117.193169

Pfeifer, A., Knigge, U., Binderup, T., Mortensen, J., Oturai, P., Loft, A., Berthelsen, A. K., Langer, S. W., Rasmussen, P., Elema, D., von Benzon, E., Højgaard, L., & Kjaer, A. (2015). 64 Cu-DOTATATE PET for Neuroendocrine Tumors: A Prospective Head-to-Head Comparison with 111 In-DTPA-Octreotide in 112 Patients. *Journal of Nuclear Medicine*, *56*(6), 847–854. https://doi.org/10.2967/jnumed.115.156539

Prabhu, M., Damle, N. A., Gupta, R., Arora, S., Arunraj, S. T., & Bal, C. (2018). Demonstration of 68Ga-prostate-specific Membrane Antigen Uptake in Metastatic Pancreatic Neuroendocrine Tumor. *Indian Journal of Nuclear Medicine : IJNM : The Official Journal of the Society of Nuclear Medicine, India*, *33*(3), 257–258. https://doi.org/10.4103/ijnm.IJNM_6_18

Samim, A., Tytgat, G. A. M., Bleeker, G., Wenker, S. T. M., Chatalic, K. L. S., Poot, A. J., Tolboom, N., van Noesel, M. M., Lam, M. G. E. H., & de Keizer, B. (2021). Nuclear Medicine Imaging in Neuroblastoma: Current Status and New Developments. *Journal of Personalized Medicine*, *11*(4), 270. https://doi.org/10.3390/jpm11040270

Weich, A., Werner, R. A., Buck, A. K., Hartrampf, P. E., Serfling, S. E., Scheurlen, M., Wester, H.-J., Meining, A., Kircher, S., Higuchi, T., Pomper, M. G., Rowe, S. P., Lapa, C., & Kircher, M. (2021). CXCR4-Directed PET/CT in Patients with Newly Diagnosed Neuroendocrine Carcinomas. *Diagnostics*, *11*(4), 605. https://doi.org/10.3390/diagnostics11040605

Yordanova, A., Biersack, H.-J., & Ahmadzadehfar, H. (2020). Advances in Molecular Imaging and Radionuclide Therapy of Neuroendocrine Tumors. *Journal of Clinical Medicine*, *9*(11), 3679. https://doi.org/10.3390/jcm9113679