Chapter 4: Medical Imaging

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PRACTICE POINTS

1. Radiological and molecular PET/CT imaging are clinically used for neuroendocrine neoplasm (NEN) management. The indication, choice, and frequency of imaging are dependent on the disease and clinical setting given the heterogeneity of NEN.

2. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most widely available radiological modalities for detecting and monitoring sites of disease. Some limitations of CT include inadequate characterisation or identification of small primary NEN lesions, lymph nodes or bone metastases. MRI is superior for brain and bone marrow assessment.

3. Targeted endoscopic ultrasound (EUS) is used for detection and to guide tissue sampling of small primary pancreatic and duodenal NEN lesions. Contrast-enhanced ultrasound (CE-US) has shown good diagnostic detection and re-staging capabilities of liver metastases.

4. Molecular imaging with [^{G8}Ga]Ga-DOTA-octreotate (^{G8}Ga-DOTATATE) PET/CT is a well-established modality for detecting somatostatin receptor expressing well-differentiated NEN with high sensitivity, specificity and management impact, and also provides theranostic assessment to determine suitability for radionuclide therapy.

5. Molecular imaging with 2-[18F]fluoro-2-deoxy-D-glucose (FDG) PET/CT provides characterisation of NEN, where lesions with high FDG avidity are typically associated with higher tumour grade, poor differentiation and worse prognosis.

6. Dual tracer imaging using ^{G8}Ga-DOTATATE and FDG PET/CT is a strong biomarker and can provide non-invasive whole-body assessment of disease phenotype, biology, prognosis, guiding biopsy site and therapeutic management for selected patients.

7. Other available but less commonly used molecular imaging PET tracers for NEN include: [^{68}Ga]Ga-NOTA-exendin 4, [^{18}F]FDOPA, and Metaiodobenzylguanidine (MIBG).

8. Potential new advances for NEN imaging include development of novel molecular imaging tracers, and dual energy CT (DECT) shows promising potential to increase sensitivity and specificity of lesion detection.

9. Given the complexity and heterogeneity of NEN, the frequency and choice of imaging modality for follow-up/response assessment should be considered in the context of the initial disease imaging phenotype, tumor kinetics/grade, specific indication for treatment, patient's general health condition and integrated with clinical, biochemical and QOL parameters.

INTRODUCTION

Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) arise from cells involved in neurohormonal regulation of the gastrointestinal tract and vary in clinical presentation, pathology and behaviour. Approximately 14% of GEPNENs present with symptoms related to hormonal secretion(1), ranging from small pancreatic NENs secreting specific hormones such as insulin or gastrin, to those with carcinoid syndrome from small bowel NEN with hepatic or ovarian metastases. Approximately 40-50% of patients with GEPNEN present with metastatic disease(2), emphasising the importance of accurate staging to guide local or systemic treatment. Approximately one quarter of patients are diagnosed incidentally during screening procedures or procedures performed for other reasons, and the remainder present with symptoms attributable to their disease, including abdominal or bone pain(1).

The purpose, choice and frequency of imaging depends upon the clinical scenario. Based upon imaging guidelines from European Neuroendocrine Tumor Society (ENETS)(3), European Association of Nuclear Medicine (EANM)(4), Society of Nuclear Medicine & Multi-society Workgroup for Molecular Imaging Appropriate Use Criteria(5) and EANM Focus 3 consensus(6), indications for imaging for GEPNEN include:

1. Diagnosis:

    - Evaluation of suggestive symptoms and/or biochemical abnormalities.
    - Evaluation of a mass suggestive of NEN not amenable to endoscopic or percutaneous biopsy (e.g. ileal lesion, hypervascular pancreatic mass, mesenteric mass), particularly with somatostatin receptor molecular imaging.

2. Localisation:

    - Detection of a primary GEP NEN in the appropriate clinical context (e.g. hormonal syndrome or metastatic disease).

3. Initial Staging after histologic diagnosis:

    - Evaluation of the presence, location and extent of metastatic disease to allow selection and planning of appropriate treatment.

4. Indirect assessment of the tumoral grade, disease behaviour and prognosis: based on the expression of tumoral somatostatin receptors [SSR] (by SSR imaging) or glucose metabolism (by FDG PET/CT).

5. Treatment selection:

    - Patients for somatostatin analogues (SSA)
    - Patients for SSR-targeted Peptide Receptor Radionuclide Therapy (PRRT) based on tumour somatostatin receptor [SSR] expression for theranostics
    - Molecular targeted therapies and chemotherapy
    - Surgery or liver-directed therapy

6. Treatment monitoring:

   - Restaging of the efficacy after a defined course of treatment (e.g. after PRRT or systemic treatment)

7. Surveillance / Detection of recurrent disease:

   - Restaging at time of clinical or laboratory progression

Both radiological and molecular imaging may be required at one or more points during the course of the disease. Patients with carcinoid tumours may also require periodic (typically yearly) echocardiography to detect possible cardiac complications of carcinoid syndrome.

RADIOLOGICAL DIAGNOSTIC IMAGING

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most widely available radiological imaging modalities for detecting and monitoring sites of disease. Radiologists with sub-specialty expertise and the use of special scanning protocols enable maximum sensitivity and specificity for NEN imaging (7).

Computed Tomography (CT)

CT is widely available and used for the diagnosis and staging of NENs. Contemporary CT scanners enable a fast acquisition, and thin slice reformatting resulting in high spatial and temporal image resolution which can be crucial in the detection of small lesions(8).

The scanned field-of-view should include the lower neck (to identify supraclavicular lymphadenopathy, which is a relatively common manifestation of upper abdominal primaries), chest, abdomen and pelvis. Routine imaging should encompass a multiphase CT protocol with IV contrast and if possible, negative oral contrast such as water, except when there are recognised contraindications. Chest CT is performed in inspirational breath hold and with IV contrast at a pulmonary venous contrast phase(9) whereas importantly, abdominal CT examinations should include two contrast phases: An arterial phase through the liver and pancreas, and a portal venous phase to cover the abdomen and pelvis. With evolution of CT scanners, a non-contrast CT phase is no longer part of the routine scanning technique since it usually does not add any valuable information but it can be useful in the detection and follow-up of liver metastases(3).

Contrast phase imaging should be tailored to the CT scanner since protocols and image acquisition can differ between vendors and CT models. Images should be reconstructed and reformatted on a dedicated workstation. Within the upper abdomen, the arterial phase is different between the pancreas and the remaining abdomen. Following high-flow IV contrast injection (4-5 ml/sec) the arterial phase is adapted according to the region of interest, with the pancreas usually imaged with a 35 sec delay whereas the stomach/ duodenum is usually performed with a 45 sec delay(10). Recent studies demonstrate a high sensitivity and specificity for detection of highly vascular primary lesions and liver metastases when using a multiphasic protocol including an arterial phase(3, 10, 11). Administration of oral positive

contrast is not recommended to avoid obscuring small vascularized tumours in the stomach wall or small bowel(3).

CT is commonly used for disease monitoring, and response assessment using RECIST 1.1 criteria is the most commonly used measure for clinical trials (12).

CT constitutes the basic radiological modality for the diagnosis, staging, restaging and surveillance due to its wide availability and detailed contrast-enhanced imaging characteristics of NEN lesions ***(Appendix, Figure 1)***. However, there are recognised limitations of its ability to characterise or identify small malignant primary NEN lesions, lymph nodes or bone metastases(3). Dual energy CT (DECT) is a fairly new technology that shows promising capabilities to benefit oncology patients due to creating energy-dependent attenuation profiles for specific materials (e.g. iodine and calcium) which has the potential to increase sensitivity as well as specificity of lesions (13, 14).

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is now more frequently used in staging and restaging due to its increasing availability. It is in general superior for brain and bone marrow assessment and has similar, if not higher sensitivity and specificity of abdominal metastatic disease detection compared to CT. Thus, equivocal or difficult-to-detect liver lesions on CT are usually further evaluated with contrast enhanced MRI especially in the setting of preoperative imaging workup for liver resection. MRI imaging usually utilizes intravenous, extracellular Gadolinium as contrast material agent but there are also liver specific contrast agents available as part of a dedicated liver MRI protocol. These hepatobiliary specific contrast agents show varying uptake by functioning hepatocytes and are excreted into the bile on a delayed hepatobiliary phase. When utilizing liver specific contrast agents, the detection rate of liver metastatic disease is superior to CT (3, 10, 15) ***(Appendix, Figure 2)***. Current MRI protocols should include a diffusion restriction sequence that adds to the sensitivity of lesion detection. In general, MRI protocols are less standardized than CT protocols. When ordering an MRI, detailed information and specific indication should be provided so that the optimal MRI protocol and contrast agent is applied(16-18). It is also often helpful to pair MRI and SSR specific PET/CT information.

PET/MRI scanners have become more widely available in recent years and some studies have shown PET/MRI to be superior to PET/CT alone(19). Nevertheless, PET/MRI is more expensive and depending on the vendor might have inferior technical specifications compared to a standalone MRI or PET/CT. In addition, MRI cannot be performed for some patients, for example due to non-MR-compatible metallic foreign bodies or claustrophobia. Furthermore, CT spatial image resolution can be superior in obese patients and/ or when motion and breathing artefact reduce overall image quality, so PET/CT is still considered advantageous in these settings. PET/MRI could be considered in patients with better prognosis and/ or younger patients given the reduced ionizing radiation (20), but further studies are required to establish its use in NEN.

Ultrasound (US)

Targeted endoscopic ultrasound (EUS) is frequently used for detection, further work-up and to guide tissue sampling of small primary lesions, especially of pancreatic and duodenal NEN. It has a high primary detection rate(21) and in addition enables evaluation of locoregional lymphadenopathy.

Diagnostic ultrasound (US) as well as contrast-enhanced ultrasound (CE-US) can play a role in work-up of liver metastases in rare cases when CT and MRI findings are equivocal or not feasible. US is, however, highly operator, patient and machine dependent and this needs to be taken into consideration when ordering and interpreting the results. It is therefore also less useful in monitoring lesions.

CE-US has shown good diagnostic detection and re-staging capabilities of liver metastases(22, 23) and should be considered as an alternative modality in pregnant patients(24).

MOLECULAR IMAGING

SSR imaging

Somatostatin receptors (particularly subtype 2) are commonly overexpressed on NEN and represent a useful molecular imaging target(25). [^{111}In]In-DTPA-octreotide was the first approved radiopharmaceutical for NEN imaging using single-photon emission computed tomography (SPECT)/CT. More recent development of three ^{68}Ga-labelled octreotide derivates DOTATOC, DOTATATE and DOTANOC (26-28) using positron emission tomography (PET)/CT has led to significant improvement in imaging resolution and quantitation. Despite differences in receptor affinity, definite superiority of one compound over others has not been demonstrated.

The most widely used tracer is [^{G8}Ga]Ga-DOTA-octreotate (^{G8}Ga-DOTATATE), recently approved by the US Food and Drug Administration (FDA) for localisation of SSR-positive NEN and is reimbursed in Australia for limited indications. The recommended activity is 2MBq/kg of body weight between 100-200MBq (4). Numerous studies demonstrate superiority over [^{111}In]In-DTPA-octreotide SPECT/CT and conventional imaging, with estimated sensitivity of 90-94% and specificity 90-92%(29-31). ^{G8}Ga-DOTATATE PET/CT also demonstrates high management impact (44%) even when performed after [^{111}In]In-DTPA-octreotide scan (32) and the majority of management change was classified as intermodality (30, 33). Existing guidelines recommend the replacement of [^{111}In]In-DTPA-octreotide imaging with SSR PET/CT (5). Imaging indications include assessment of disease extent (staging / restaging), for pre-surgical staging, detection of unknown primary site (particularly localisation in context of endocrine syndrome), evaluation of patients with suspected biochemical evidence and symptoms of NET without disease identified on conventional imaging, theranostic assessment to determine suitability for radionuclide therapy, treatment monitoring and follow-up of disease identified predominantly on SSR PET/CT. More recently, PET tracer [^{64}Cu]Cu-DOTA-octreotate (^{64}Cu-DOTATATE) has also been approved by the FDA in 2020 for imaging of well differentiated SSR-positive NEN.

A high incidence and density of SSR are found in well-differentiated Grade 1 and 2 GEP-NENs (functioning and non-functioning). Whilst more prospective studies are needed, SSR positive disease has been observed in a high proportion (>80%) of Grade 3 NET cases, and approximately 40% in NEC

(neuroendocrine carcinoma) (34). SSR positive disease is also observed in pulmonary NENs, phaeochromocytoma and paraganglioma (PPGL), neuroblastoma and a proportion of medullary thyroid carcinoma(35, 36). Other malignancies may also demonstrate avidity, including meningioma, lymphoma, breast cancer, renal cell carcinoma, head and neck cancer, hepatocellular carcinoma and gastric carcinoma (37). Lesion uptake on ^{G8}Ga-DOTATATE PET/CT is reported according to the modified Krenning Scoring system for semi-quantitative grading of pathologic uptake, ranging from 0 (no uptake), 1 (very low), 2 (SUVmax ≤ liver background), 3 (SUVmax > liver), 4 (SUVmax > spleen) (38), and an uptake threshold of Krenning score ≥3 is usually required for suitability for PRRT. Several pitfalls to ^{G8}Ga-DOTATATE PET/CT reporting include sites of physiologic activity (prominent pancreatic uncinate process, splenunculus), focal osseous activity (vertebral haemangioma, fracture and degenerative bone disease), inflammatory uptake (reactive nodes, prostatitis and post-radiotherapy change) and incidental meningioma (39).

Reporter awareness of apparent 'pseudo-progression' following commencement of Somatostatin Analogue (SSA) therapy is critical for accurate ^{G8}Ga-DOTATATE PET reporting. Lesions may appear more intense after commencement of SSA, due to altered distribution of radiotracer in the body, typically seen with a decrease in physiologic uptake (thyroid, liver, spleen) and increased tumour uptake (40, 41). Careful review of co-registered CT and use of consistent PET window thresholds are important to recognise this phenomenon, rather than misinterpretation as progression.

^{G8}Ga-DOTATATE PET/CT demonstrates incremental value over CT for identification of bone metastases, localisation of primary small bowel NENs and enables visualisation of small lymph node metastases that may not be able to be characterised on CT or MRI (3-5).

FDG PET/CT and Dual Tracer Imaging

2-[18F]fluoro-2-deoxy-D-glucose [^{18}F]FDG – FDG is widely used in clinical oncology and is the most used PET tracer in Australia due to its availability and clinical utility. This is a radiolabelled-glucose analog, with uptake by tissues being closely correlated with tissue metabolism. Uptake is typically high in rapidly growing active tumours.

As previously outlined, ^{G8}Ga-DOTATATE uptake (detecting SSR expression) is characteristic of well differentiated NEN, whereas the opposite applies for FDG uptake. For NEN, FDG positivity is correlated with higher tumour grade, poor differentiation, and worse prognosis (42-45). Therefore, molecular imaging using GaTate and FDG tracers provide useful complementary information for NEN imaging. This is particularly relevant for characterizing NEN given it is not a homogenous entity. It is well recognized that significant lesional disease heterogeneity can exist within an individual patient, such that well differentiated lesions can co-exist with higher grade components (46, 47). Hence, tumour grading based on biopsy of a single most accessible lesion alone may not be representative of the true highest-grade disease for a patient.

Dual Tracer Imaging – There is increasing evidence that a dual tracer imaging approach – using ^{G8}Ga-DOTATATE PET/CT imaging to detect SSR expression as marker of tumour differentiation, and FDG to assess glucose metabolism/metabolic activity – can provide non-invasive whole-body assessment of

disease phenotype, biology, prognosis with clinical management impacts for patients with NEN. ***(Appendix, Figures 3,4,5,6).***

1) Recent studies have shown promise with this combined approach as a prognostic imaging biomarker in NEN (48, 49). Patients with FDG positive/SSR negative disease have poor prognosis and shorter overall survival compared to patients with FDG positive/SSR positive, or solely SSR positive disease (latter with best prognosis).
2) Information obtained from dual tracer imaging could guide appropriate biopsy site for grading of disease, the most FDG-avid lesion likely representative of highest proliferative activity (50).
3) Importantly, the combined imaging phenotype is useful to guide patient management including assessing suitability for peptide receptor radionuclide therapy (PRRT). For PRRT to be effective, all lesions must have high SSR expression to enable adequate therapeutic targeting. PRRT can be effective for patients with FDG-avid disease provided that high SSR-expression is retained at all disease sites to allow targeting of lesions (51). However, if there is evidence of spatially discordant (FDG positive/SSR negative) disease, PRRT alone will be of limited benefit and other systemic or combination options should be considered (48, 52).

Link to Chapter 10 PRRT

Dual tracer whole body imaging provides valuable information for selected patients. However, due to differences in resources and regulatory limitations, this dual tracer strategy is yet to be universally applied but is becoming increasingly recognised as an important approach for patients with NEN. In Australia, many centres have adopted such imaging approaches in selected cases. Based on current information, dual tracer imaging indications may include:

1) patients with higher grade disease including Grade 2 and Grade 3 NEN;
2) patients with Grade 1 disease with non-^{G8}Ga-DOTATATE avid suspicious lesions on radiological imaging, or
3) more rapid progression than expected (e.g. progression within 6 months, which may indicate disease heterogeneity or initial sampling error);
4) at the time of significant disease progression after prolonged stable disease (which may indicate change of grade or potential grade transformation, to characterise tumour biology);
5) to guide site of (re-)biopsy site of the most FDG avid lesion which should yield highest grade disease; and
6) for therapeutic/theranostic selection for patients with higher grade disease (Grade 2 and 3).

Further prospective data is needed to establish its clinical use and role in this evolving landscape, to allow optimal disease characterisation, guide therapeutic management and follow-up of patients with NEN.

Other Available PET Tracers

[^{68}Ga]Ga-NOTA-exendin 4

High expression of glucagon-like peptide-1 (GLP-1) receptors on nearly all insulinomas has led to the development of [^{68}Ga]Ga-NOTA-exendin 4, a GLP-1 analogue, for localisation of insulinoma(53). In a

prospective study of 52 patients with endogenous hyperinsulinaemic hypoglycaemia, [^{68}Ga]Ga-NOTA-exendin 4 identified 42/43 patients with insulinoma, although 9 patients did not undergo surgical intervention(54). The only non-avid insulinoma was a grade 2 tumour subsequently identified with SSR imaging: a 'flip-flop' relationship with GLP-1R -ve / SSR +ve expression also observed by other researchers in metastatic insulinoma (55).

Induction of hypoglycaemia following tracer injection requires monitoring of blood glucose level and intravenous dextrose infusion(56). Intense renal uptake is a pitfall that may obscure lesions in the pancreatic tail, with delayed imaging at 2-3 hours proposed in negative cases to allow renal washout and better visibility of the pancreatic tail region (56, 57).

[^{18}F]FDOPA

This is an L-DOPA analogue with a mechanism of uptake by L-type amino acid transporter type 1 (LAT1) in neuroendocrine cells, where it is decarboxylated to dopamine and stored in secretory granules. Primary clinical roles for NEN include localisation and staging of phaeochromocytoma and paraganglioma (PPGL; refer to recent EANM/SNM guidelines for specific details (58)), medullary thyroid carcinoma (initial staging and evaluation of biochemical recurrence defined as calcitonin > 150 pg/ml(59)) and assessment of congenital hyperinsulinism. It also has a potential role in localisation of endocrine syndromes, including insulinoma.

Although useful for assessment of well-differentiated midgut NEN(36), it is much less widely available than ^{68}Ga-DOTATATE and the absence of a theranostic 'pair' limits its utility in this setting.

The decarboxylase inhibitor carbidopa is administered prior to tracer injection to reduce background physiologic pancreatic uptake and increase avidity of phaeochromocytoma(60). However, carbidopa is not used for congenital hyperinsulinism investigation due to potential suppression of pancreatic focal lesions, and there is controversy regarding its use for localisation of pancreatic lesions, particularly insulinoma(61, 62). False positive pitfalls include biliary excretion into gallbladder and small bowel and uncinate process physiologic uptake(36).

Metaiodobenzylguanidine (MIBG) was developed in the early 1980s to visualise tumours of the adrenal medulla. MIBG actively enters NEN cells via the epinephrine transporter and is stored in neurosecretory granules. In Australia it is used predominantly for staging/localisation of PPGL(58) and neuroblastoma(63), and a theranostic role to determine suitability for treatment with [^{131}I]I-MIBG(64). Although previously used for imaging and therapy of GEP- and pulmonary-NEN(65), radiolabelled MIBG has been superseded by the more convenient imaging, effective therapy, and the more favourable radiation safety profile of the ^{68}Ga/^{177}Lu-DOTA-octreotate theranostic pair. Imaging is typically performed on SPECT/CT using the gamma-emitter [^{123}I]I-MIBG, however the PET emitter [^{124}I]I-MIBG provides higher resolution images and may enable prospective dosimetry for radionuclide therapy(66).

POTENTIAL NEW DEVELOPMENTS OF NOVEL TRACERS FOR NEN IMAGING

Cholecyctokinin-2 (CCK2) receptors - In vitro studies have shown that other peptide receptors such as glucose-dependent insulinotropic polypeptide (GlP) receptor are overexpressed in NENs(67). In particular, CCK-2 receptors are over-expressed in medullary thyroid cancer (68-70), insulinoma (71), and may represent an important molecular target for NEN with low or absent SSR expression. It has been observed that 55% of NEN patients with negative SSR-2 imaging have positive uptake on CCK-2 PET imaging(72). Further advances in the development of radiolabelled CCK-2 PET imaging with potential theranostic application for patients with low SSR-expressing NEN are promising and expected.

SSR2 antagonists - There is evidence that radiolabeled antagonist have higher tumour uptake than agonists (73). [^{177}Lu]Lu-DOTA-JR11 ([^{177}Lu]Lu-OPS201) is currently being evaluated in a phase 1-2 multicenter theranostic study (ClinicalTrials.gov identifier: NCT02592707), and in a theranostic study of the associated ^{68}Ga-diagnostic agent (ClinicalTrials.gov identifier: NCT02609737).

Other potential radionuclide diagnostic / theranostic pairs of interest include ^{64}Cu/^{67}Cu and ^{44}Sc/^{47}Sc offering the potential for prospective dosimetry and more personalized therapy.

FOLLOW-UP / RESPONSE ASSESSMENT

The heterogeneity and complexity of NEN limits the development of a generalized follow-up or response assessment regimen. Current expert consensus guidelines recommend and support different types and frequency of follow up according to disease and the clinical setting (74-79). Practices may also differ depending on local expertise, availability of resources, regulation and infrastructure.

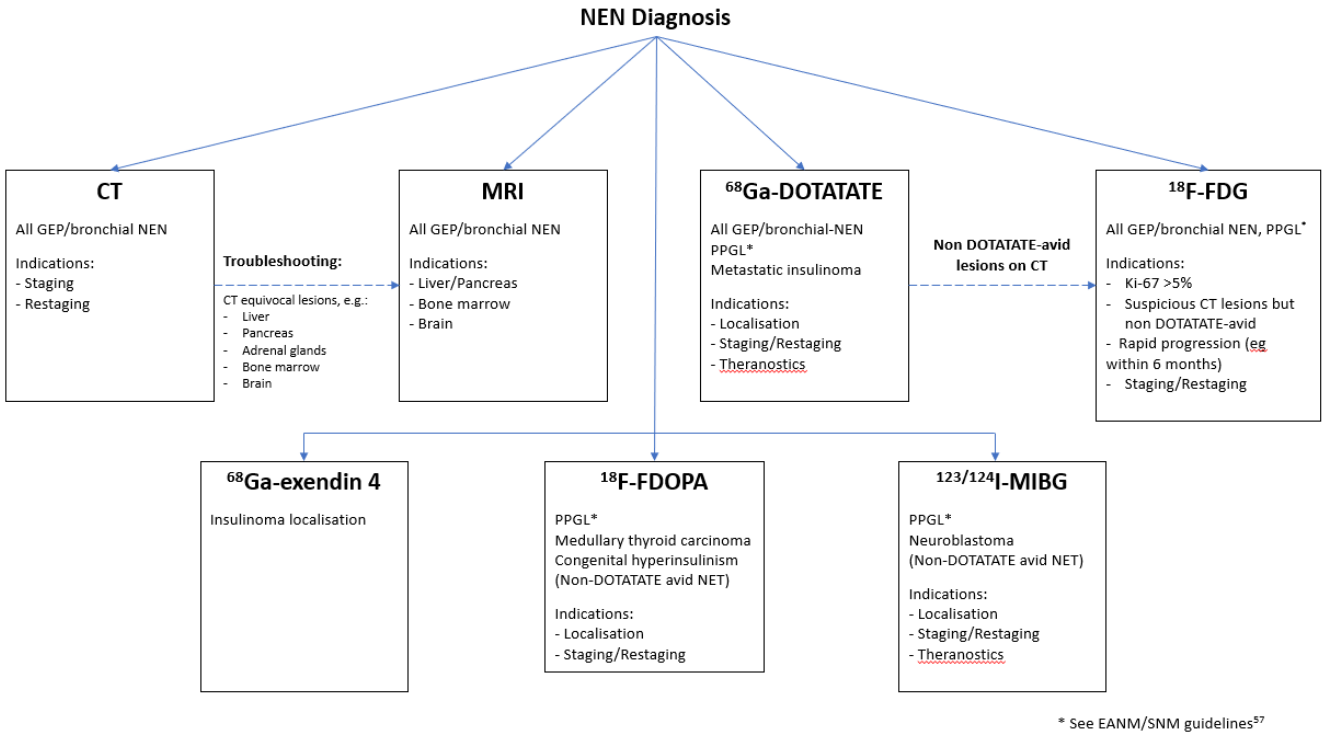
Overall, response assessment should consist of a composite of clinical, quality of life parameters, biochemical markers and imaging, with the strategy being tailored for the individual patient. From the imaging perspective, the use of radiological and molecular PET/CT imaging should be regarded as complementary. The frequency and choice of modality are dependent on the initial disease imaging phenotype, tumour kinetics/grade, the expected mechanism of response and the patient's general health condition. In general, less frequent imaging is required for limited stage or low grade tumours, and more frequent imaging may be warranted for patients with higher grade NEN, metastatic FDG-avid disease, large tumour burden, aggressive tumour behaviour, severe endocrinopathy or high CgA levels (74).

RECIST 1.1 is still considered the standard modality for anatomical response assessment, particularly for trial purposes. Whilst CT is widely available, some limitations need to be recognized, including re-assessment of small (sub-cm) primary, nodal or bony lesions; inferiority of assessing liver, bone and brain lesions compared to MRI; and the need to have comparable three-phase liver CT protocol. 'Pseudoprogression' perceived by an increase in tumour size (usually associated with a necrotic process) may lead to misinterpretation of progressive disease and premature cessation of treatment regimen(78). If suspected, follow-up imaging or correlating with molecular PET imaging will provide further clarification. Given the high diagnostic sensitivity of ^{G8}Ga-DOTATATE PET/CT in detecting NEN

lesions compared to CT (particularly for small primary lesions, nodal or osseous disease), if positive at baseline, incorporation during restaging should be considered, and at the time of suspected recurrence(80). FDG PET/CT is often useful for restaging if disease is avid at baseline, if rapid progression or disease transformation is suspected. However, the frequency of ^{G8}Ga-DOTATATE and FDG PET/CT restaging would depend on baseline imaging phenotype, tumour grade and kinetics, cost and availability, and further data is required. Annual molecular imaging is probably sufficient to determine the need for further treatment for low grade NEN phenotype.

NEN is a complex disease, and the modality and how to measure treatment success would need to be tailored to the specific indication for the patient: whether treatment is administered solely for uncontrolled hormone-secretory symptoms (usually in indolent functional disease), for oncologic progression, or both. Overall, imaging should be integrated with regular clinical and laboratory assessment when assessing for response and planning ongoing management.

DIAGNOSTIC FLOW CHART



* See EANM/SNM guidelines[57]

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APPENDIX: FIGURE 1 TO FIGURE 6

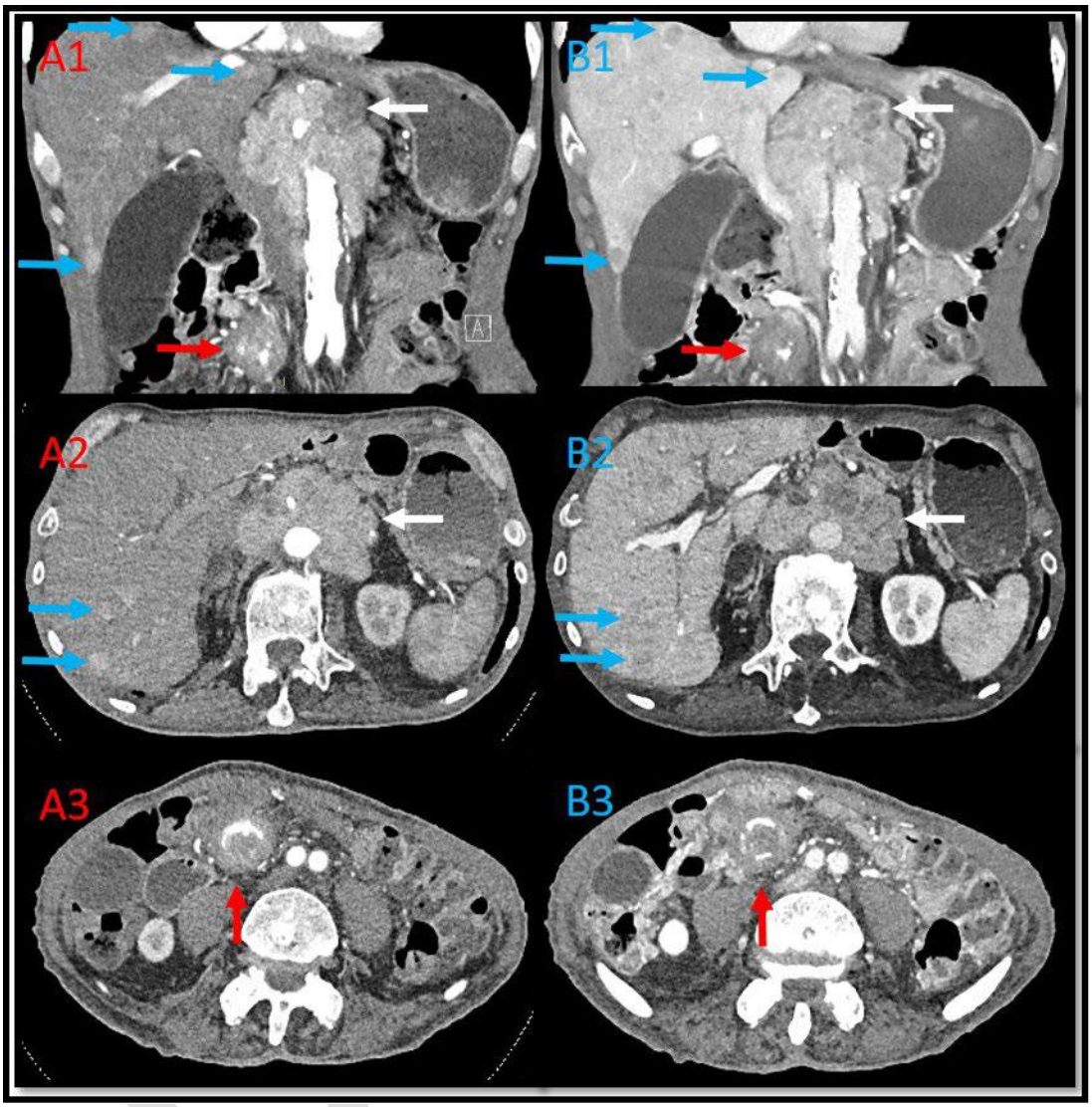

Figure 1. Example of a diagnostic CT of a well differentiated small bowel grade 1 primary NEN (Ki-67 of <1%).

80-year-old male presented with diarrhoea and weight loss.

CT was performed in arterial (A) and portal venous (B) phase with coronal (1) and axial reformats (2). The different contrast phases and reformats help in detection and visualisation of the different vascularised aspects of the partially calcified small bowel primary (red arrows), retroperitoneal lymph node (white arrows) and liver metastases (blue arrows).

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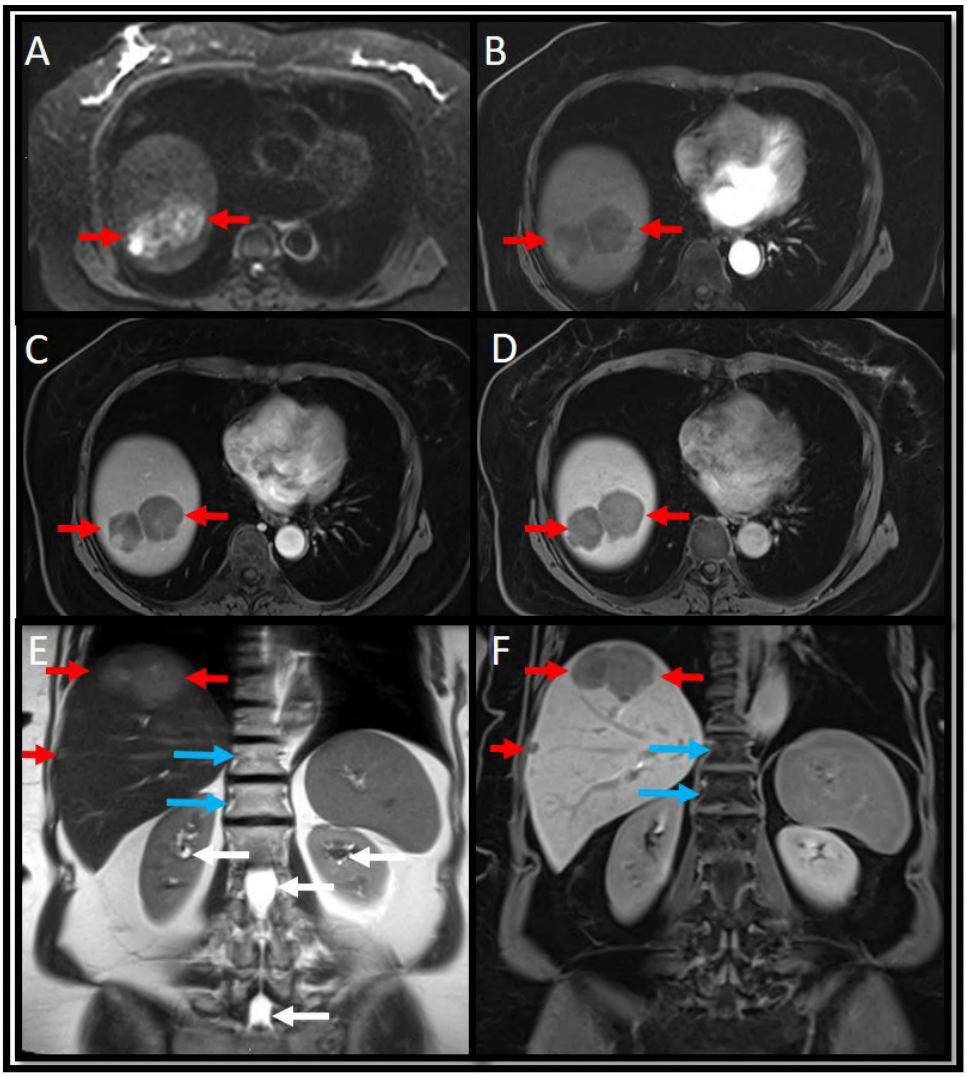

Figure 2. Example of MRI liver with i.v. hepatobiliary specific contrast material of liver metastasis of a well differentiated grade 2 primary rectal NEN.

74-year-old female presented with positive faecal occult blood test and no other symptoms.

Different MRI liver sequences in axial and coronal planes show multiple heterogeneous liver metastases (red arrows). MRI enables detailed bone marrow assessment (blue arrows) and high sensitivity and specificity with regards to fluid which often is superior compared to diagnostic CT. This example nicely shows CSF liquor and urine within the non-obstructed renal collecting system (white arrows).

A: axial diffusion weighted imaging (DWI)
B-D: axial T1 fat saturated sequence in arterial, portal venous and delayed hepatobiliary phase
E: coronal T2 HASTE sequence
F: coronal T1 fat saturated sequence in delayed hepatobiliary phase

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Grade 1 NEN, ^{G8}Ga-DOTATATE +ve / FDG -ve imaging phenotype

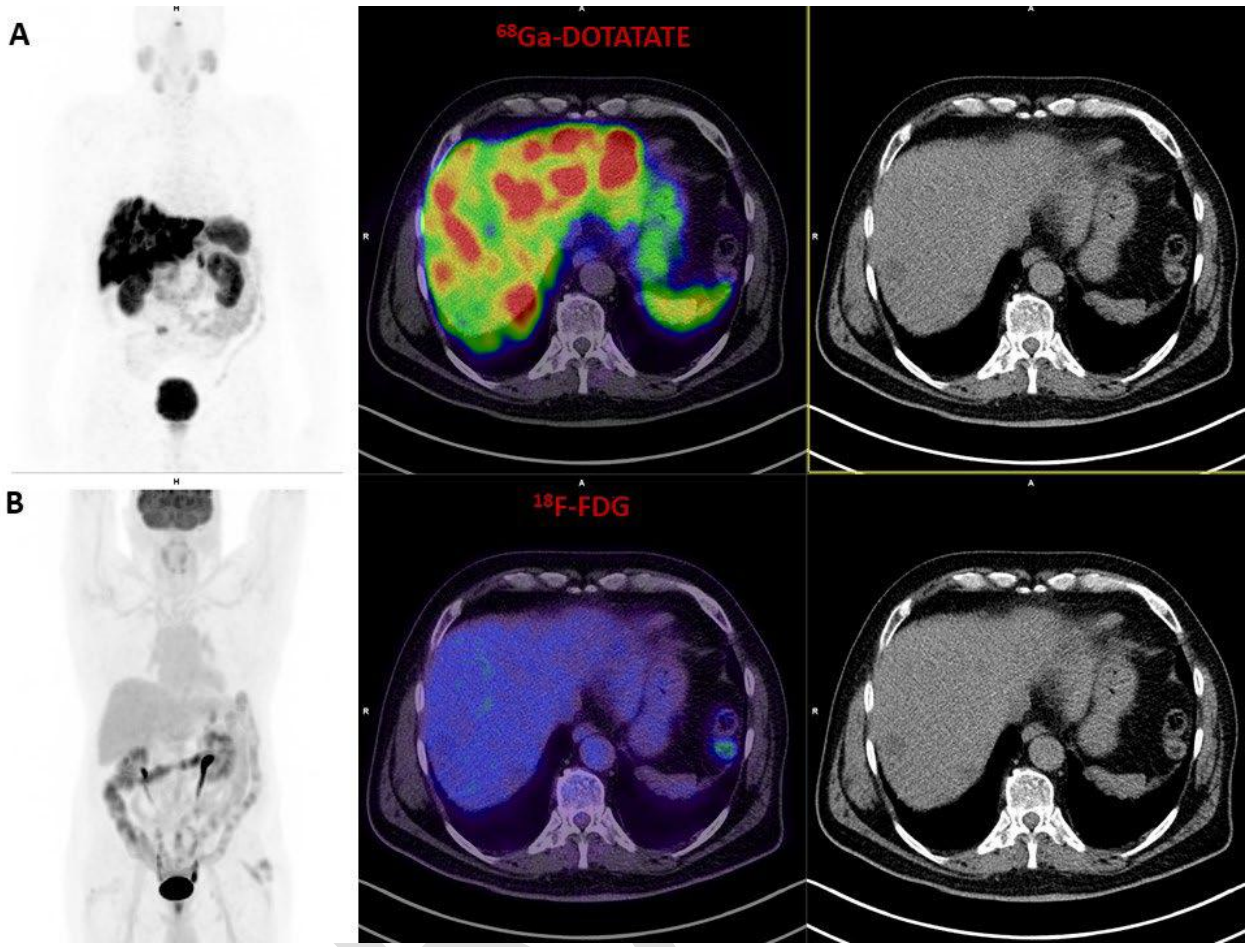

Figure 3. 74-year-old man presented with longstanding symptoms of carcinoid syndrome and liver biopsy confirmed features of a metastatic small bowel NEN (Grade 1, Ki-67 <1%).

Each row (left to right) comprises maximum intensity projection, fused PET/CT and non-contrast CT images. Row A (68Ga-DOTATATE) demonstrates very intensely DOTATATE avid (Krenning score 4, uptake > spleen) small bowel primary lesion and extensive diffuse hepatic metastatic disease. Row B (18F-FDG) demonstrates no appreciable FDG avidity at sites of disease, consistent with a low grade NEN. This molecular imaging phenotype is amenable to treatment with PRRT because all measurable sites of disease demonstrate DOTATATE avidity > liver.

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Grade 2 NEN, ^{G8}Ga-DOTATATE +ve / FDG +ve concordant imaging phenotype

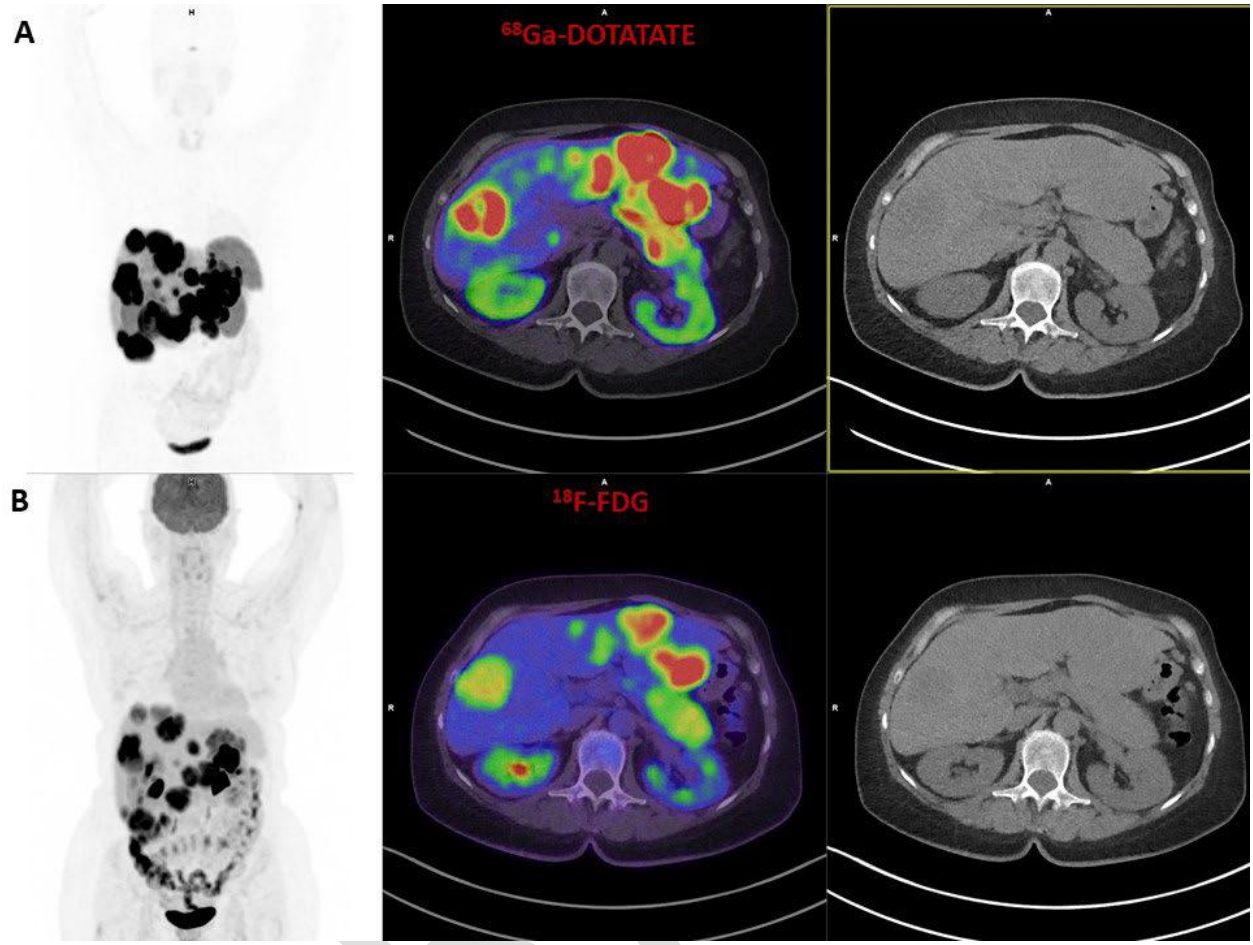

Figure 4. 65-year-old woman presented with hypercalcaemia and was subsequently diagnosed with a metastatic pancreatic NEN (Grade 2, Ki-67 10%).

Each row (left to right) comprises maximum intensity projection, fused PET/CT and non-contrast CT images. Row A (68Ga-DOTATATE) demonstrates very intensely DOTATATE avid (Krenning score 4, uptake > spleen) pancreatic tail primary lesion and multifocal bilobar hepatic metastatic disease. Row B (18F-FDG) demonstrates variable moderate-intense concordant FDG avidity at all sites of disease, consistent with an intermediate grade NEN. This molecular imaging phenotype is amenable to treatment with PRRT because all measurable sites of disease demonstrate DOTATATE avidity > liver and there is no discordant FDG avid disease.

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Grade 3 NEN, concordant imaging phenotype

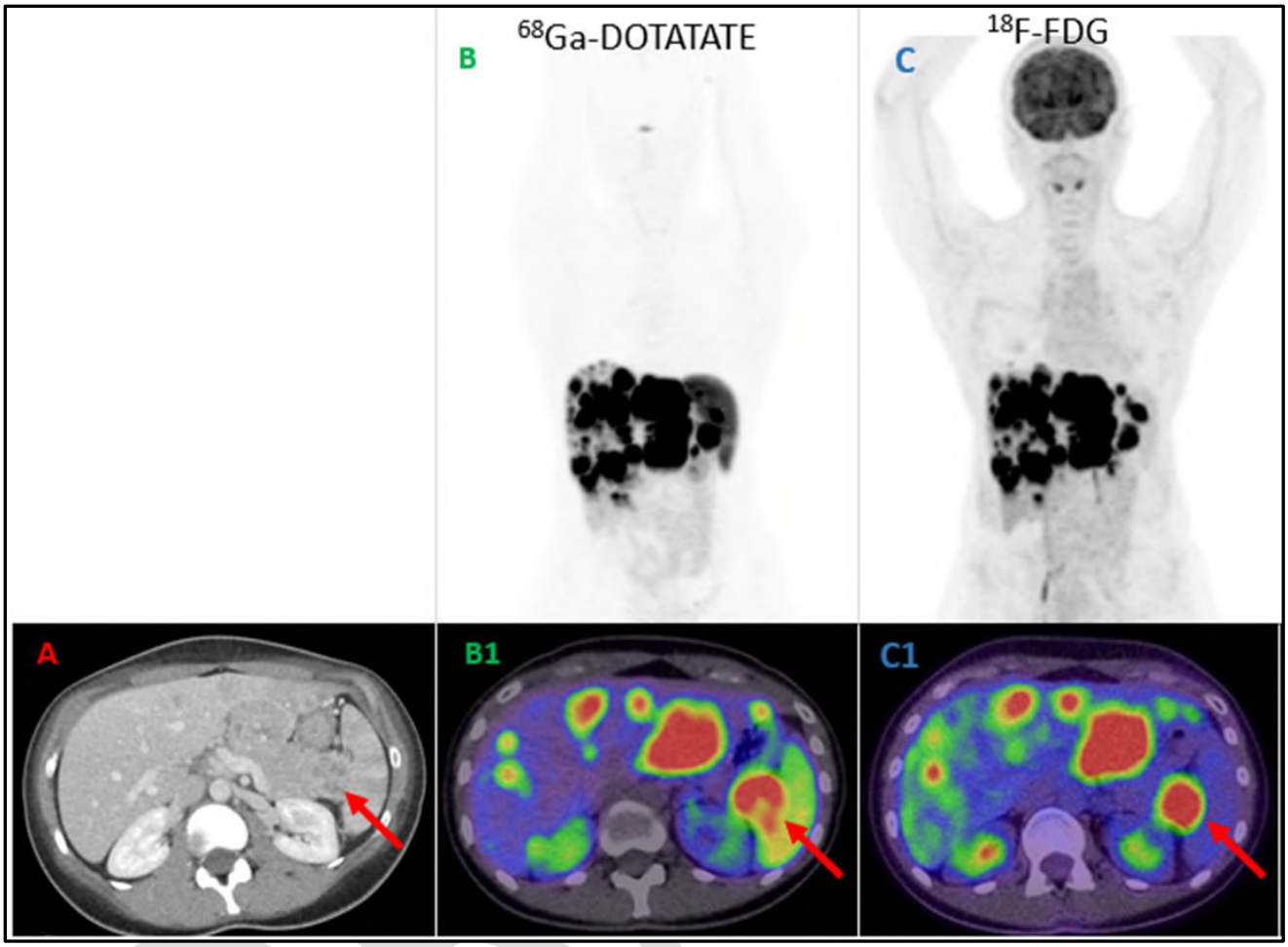

Figure 5. Case example of concordant imaging phenotype in Grade 3 NEN.

24-year-old female presented with abdominal pain and weight loss.

A diagnostic CT (A) showed a pancreatic lesion (red arrow) with multiple liver metastases suspicious of NEN. A ^{68}Ga-DOTATATE PET/CT (B: Maximum Intensity Projection MIP; B1: Trans-axial fused images) showed high uptake in the pancreatic primary and multiple liver metastases consistent with high SSR expressing NEN. An ^{18}F-FDG PET/CT (C: MIP; C1: Trans-axial fused images) showed high metabolic activity at all disease sites, spatially concordant with ^{68}Ga-DOTATATE PET/CT. Biopsy of a liver lesion confirmed well-differentiated Grade 3 NEN with Ki-67 of 50%. The high degree of FDG avidity is indicative of higher-grade disease.

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Grade 3 NEN, discordant imaging phenotype

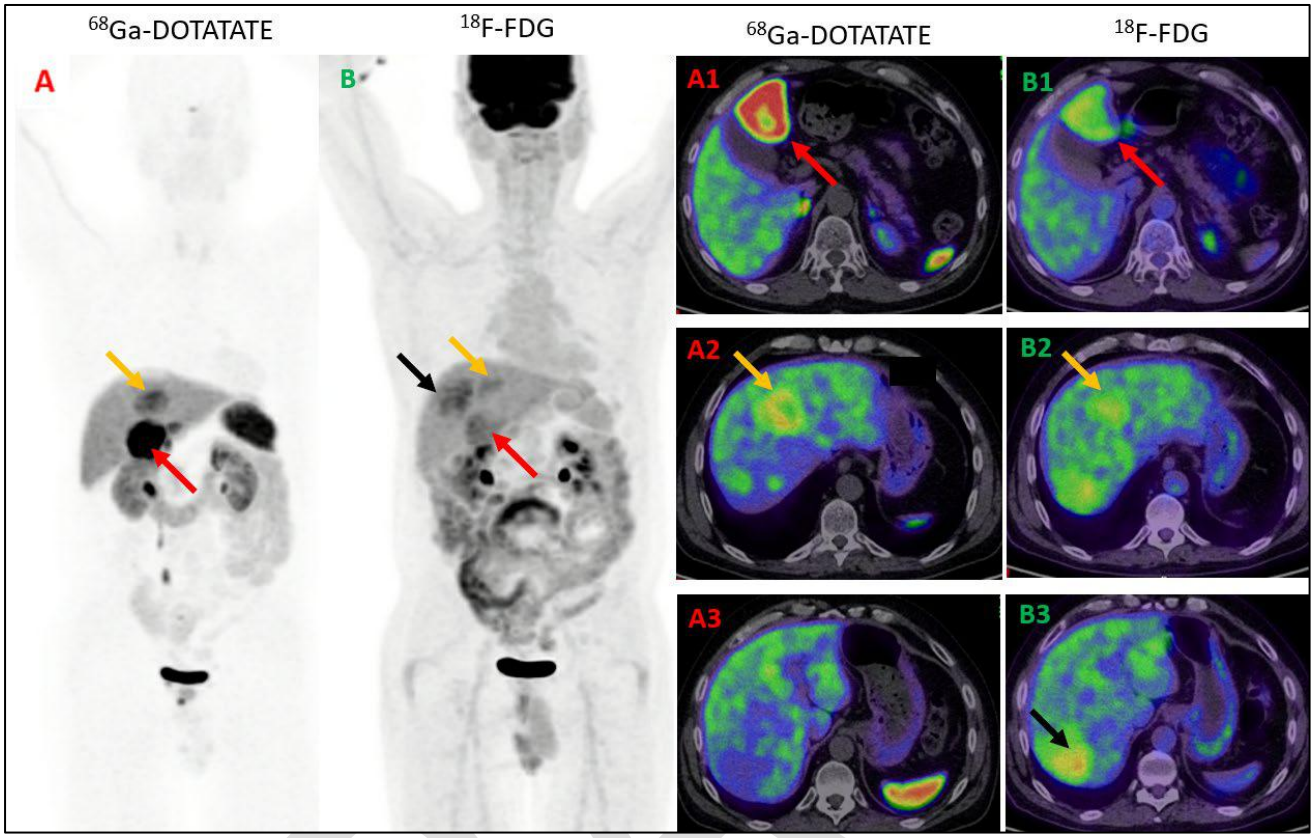

Figure 6. Case example of discordant imaging phenotype in high grade disease.

45-year-old male with previously resected pancreatic primary lesion, Ki-67 of 5%. Patient now presented with hepatic metastases.

A ^{68}Ga-DOTATATE PET/CT (A: MIP image) showed two SSR expressing liver lesions (lesion 1 red arrow; lesion 2 yellow arrow). An ^{18}F-FDG PET/CT (B: MIP image) showed FDG-avid uptake at these two lesions (corresponding yellow and red arrows). However, ^{18}F-FDG PET/CT showed a third lesion (black arrow), without SSR uptake. On trans-axial images, this lesion clearly shows FDG avidity (B3), but with no ^{68}Ga-DOTATATE avidity (A3). Subsequent biopsy of this lesion showed Grade 3 NET, with Ki-67 of 35%, suggestive of an area of high-grade disease.

Dual tracer imaging in this case guided the site of biopsy representative of the highest-grade disease, and type of therapy (systemic treatment, and not suitable for PRRT).

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