Advances in Diagnostic Imaging

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6.1 Introduction on Imaging in NET

The definition "neuroendocrine tumours" (NETs) collects a variety of uncommon malignancies, broadly distributed in the body, but sharing the origin from the neural crest. The clinical onset of these tumours is unconventional with nonspecific symptoms, which reflects their possibility to arise in different anatomical regions and tissues. Moreover, NETs can keep the secretive activity of the cells they originate from in 60–70% of cases (functioning forms) or present as biologically inactive (non-functioning forms). This classification in non-functioning tumours impacts on the investigations needed for the diagnosis as per chosen modality and technical protocols. Despite their original functional attitude, notably, in the majority of cases, NETs are diagnosed when already advanced and metastatic, thus, symptomatic.

Accurate detection and characterisation of the primary tumour and the identification of the extent of disease are required to define an appropriate approach to treatment. Moreover, treatment monitoring and the detection of recurrent disease are crucial clinical objectives in the management of these tumours.

Clinical presentation, laboratory tests can guide the choice of the subsequent diagnostic imaging investigations: both Radiology and Nuclear Medicine can answer a wide array of questions on this challenging topic.

Either conventional imaging, namely ultrasound (US), computed tomography (CT) and magnetic resonance (MRI) or functional imaging through scintigraphy and PET-CT, contribute to the characterization of NETs. However, no single imaging technique represents the gold standard, and the sequence of exams needed for each tumour type may vary [1, 2].

It is then remarkable to underline that even though we live in an era of standardisation, personalisation of treatment (within a consensus guideline frame-shift) is often required to maximise the outcome, particularly in NETs, thus implying the need to build up a "multidisciplinary culture" approach.

From the morphological point of view, features like hyper-vascularisation, specific growth patterns and imaging appearance can help

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discriminate these tumours from other solid malignancies.

From the functional point of view, we have to consider that these diseases, albeit heterogeneous, hold some features derivative from their neural cell precursors, such as the amine pathway metabolism and the cellular overexpression of the somatostatin receptors (SSTR).

With these regard, nuclear medicine offers either scintigraphic techniques or PET-CT investigation to image both biological characteristics.

The two main categories of radiopharmaceuticals available aim to:

- enter the adrenergic pathway, namely the meta-iodo-benzyl-guanidine (MIBG), a norepinephrine analogue for scintigraphy and the F-DOPA for PET-CT imaging and,
- bind somatostatin receptors (both gamma-emitting and positron-emitting radiolabelled analogues are available).

Metabolic assessment of NETs, using FDG PET-CT, is also possible in selected cases, to better investigate the aggressive tumour attitude.

According to topography, we will distinguish NETs that origin from the gastrointestinal tract, usually called GEP (gastro-entero-pancreatic), and non-GEP which generally includes lung NETs (L-NETs), medullary thyroid carcinoma, Merkel, pheochromocytoma/paraganglioma and neuroblastoma.

Pulmonary NETs usually present as well-differentiated tumours, including low- and intermediate-grade malignant tumours, historically divided into typical and atypical carcinoids, sharing clinical and pathological traits, as opposed to the poorly differentiated high-grade large-cell neuroendocrine carcinoma and small-cell lung carcinoma.

Contrast-enhanced CT is the diagnostic gold standard for lung NETs, while, in the well-differentiated forms, somatostatin receptor imaging may visualise nearly 80% of the primary tumours and appears to be most sensitive for metastatic disease. The poorly differentiated lung NETs commonly benefit more from FDG PET-CT imaging [3].

All GEP NETs are potentially malignant: proliferation, differentiation and biological characteristics influence the metastatic widespread of disease, and understanding the natural history of these lesions has profoundly changed the approach from diagnosis to treatment in the last decades.

Morphological imaging is widely applied for the initial staging of the patients affected by GEP NETs. The evolution of the diagnostic tools with the introduction of improved multi-detector CT and MR, innovative contrast media, has profoundly influenced sensitivity and specificity. In contrast, functional imaging investigations contribute not only in detecting the lesions but lead towards a better understanding of the tumour behaviour, gaining a role in the prognostic evaluation and change of treatment and follow up management [4].

We aim at outlining the primary diagnostic imaging tools available for NETs—lung, GEP and other non-GEP—and discuss the possible future options of imaging.

6.2 Technical and Technological Aspects

6.2.1 Imaging

Current conventional diagnostic methods to evaluate NETs include morphologic modalities such as endoscopic US (EUS), abdominal ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI).

The endoscopic US finds its primary importance in the investigation and histological diagnosis of GEPs. Only afterwards, when grading and histological diagnosis are confirmed, complete tumour staging with whole-body CT or MRI should be performed. This sequence of events is in line with the current guidelines for the management of neuroendocrine tumours [5], and it is essential to assess the extent of disease and to plan the most appropriate treatment approach.

The abdominal US is an advantageous technique for the study of NETs mainly because of its immediateness and non-invasiveness,

especially in the case of pancreatic NETs and in the evaluation of liver metastasis. Also, it is suitable for the guidance of core needle biopsy and fine-needle aspiration cytology for histopathologic analysis. Nevertheless, it has low sensitivity, and it is operator-dependent, lacking reproducibility and it is then inadequate as a primary tool for diagnosis and follow-up of the disease [6].

For all of these reasons, a CT scan is often the initial imaging study in patients with signs and symptoms suggestive of NET. This technique, together with MRI, provides excellent anatomic detail of the tumours and of its relationship with nearby organs being essential for disease staging and surgical planning.

Nowadays, multi-detector CT scanners are used and characterised by high spatial resolution (even <1 mm). Moreover, CT allows for multiplanarity (axial, coronal, sagittal reconstructions) and volume rendering techniques which may help delineate the tumour itself, the organ involved and nearby structures. These details further improve accuracy and imaging interpretation [7] for a correct staging and therapeutic planning. Differently from the US, CT scan is reproducible, allowing to perform the exam with the same protocols and parameters. Moreover, it is a suitable and reliable imaging technique to compare baseline and follow-up images.

The characteristic behaviour of primary functioning NETs (mainly gastrointestinal and lung NETs) and of their metastases is the arterial phase hyper-enhancing after intravenous contrast media administration, describing highly vascularized lesions. On the contrary, non-functioning NETs appear as large masses with heterogeneous enhancement due to necrotic and haemorrhagic changes [8].

For example, in the case of gastrointestinal NETs, another option could be to perform contrast-enhanced CT scan with oral contrast material earlier than usual (i.e. before the portal venous phase). This technique may help detect small enhancing neuroendocrine tumours in the small intestine. Besides, CT protocols with similar modifications can help depict small enhancing neuroendocrine tumours in the stomach and rectum.

Significant limitations of CT are as follows:

- To date, no standardised parameters exist on the exact scanning delay of the contrast-enhancement phase and on the amount of contrast medium to administer, the latter is generally calculated based on the patients' weight.
- Small lesions and peritoneal lesions are challenging to identify; the identification of metastatic lymph nodes is especially challenging as size criteria, including RECIST criteria, still are of limited value.
- Iodinated contrast media makes this technique of limited use in patients at risk for allergic reactions and those with impaired renal function.

MRI is especially suitable for staging and restaging of liver metastases; it is not as useful as CT at detecting small intestine NETs, but it is very advantageous for the detection and localisation of primary pancreatic NETs, instead.

MRI has the advantage of a high spatial resolution (2–4 mm), which is amplified by examination at a higher field strength in a 3T scanner [9]. Currently, guidelines suggest the use of a magnetic field of at least 1.5T, which also allows the applicability of specific sequences. As for CT, the 3D acquisition allows for multiple anatomical planes viewing and reconstruction; thus, for a more accurate interpretation of the lesions.

Even MRI requires administration of intravenous contrast medium to increase tissue contrast and facilitate its characterisation, and the ability to contrast soft tissues is higher when compared to CT, which is one of the reasons why, as previously said, it is the most sensitive technique for the detection of liver metastases. The use of liver-specific contrast media can increase tissue contrast (Gadoxetate disodium—Primovist). Moreover, NETs are typically hyper-vascularised tumours and enhance after contrast injection in the late arterial phase. This characteristic also works for NET liver metastases even if, occasionally, some patients may show both

hyper-vascular and hypo-vascular liver secondary lesions.

Diffusion-weighted MRI (DWI) is an essential tool of this imaging technique, especially in the oncologic field. It is based on the restricted diffusion of water molecules in highly cellular tissue such as tumours Literature shows evidence that it has the potential for distinguishing high-grade from low-grade tumours by quantifying the tumour's apparent diffusion coefficient (ADC) in the images (ADC map). Also, evidence exists showing that DWI and ADC map analysis is even more sensitive than the commonly used T2-weighted fast spin-echo or dynamic gadolinium-enhanced sequences. Therefore, DWI is currently the most promising technique for investigating NETs [10, 11].

MR cholangiopancreatography is another important MRI tool and consists of specific cholangio-pancreatic sequences performed with the previous administration of oral negative contrast (e.g. pure blueberry juice). These specific sequences enable the radiologist to study the intra and extrahepatic biliary tree and pancreatic ducts. They, therefore, allow providing essential information to the surgeon for surgical planning. MRI with the administration of oral negative contrast should always be performed before surgical resection of a pancreatic NET [12].

Guidelines on MRI protocols exist for pancreatic NETs, but no validated protocols are available for the other GEPs and neuroendocrine tumours of different origin. As for pancreatic NETs, MRI should include T1- and T2-weighted MR sequences, dynamic three-dimensional (3D) sequence before and after intravenous administration of contrast medium (Gadolinium) with multiarterial, venous and delayed (>5 min) acquisition and diffusion-weighted (DWI) sequences. Fat suppression on T1- and T2-weighted images is useful to maximise the signal intensity differences between the pancreatic tumour and the adjacent normal pancreatic tissue.

To conclude, one of the most important advantages of MRI is the absence of radiation exposure, which confirms its vital role as a technique of choice, in young patients or in those with the long-standing disease who require repeated follow-up imaging studies. Nevertheless, the costs and the requirement for extensive patient compliance still make it, in general, an optional imaging modality to CT.

Regarding the evaluation of response to therapy, MRI shares with CT the same limitations. Additionally, MRI is unsuitable for the study of small thoracic lesions because of the motion artefacts due to cardiac and respiratory activity, the low signal-to-noise ratio in the lung and the lower spatial resolution as compared to CT [13].

To date, an emerging field of investigation is represented by Radiomics especially in the case of pancreatic neuroendocrine tumours; in many patients, they present as small volume tumours at diagnosis, thus volume definition is one of the most critical characterisations. Radiomics may support and aid at a more straightforward identification and volume definition. Nevertheless, the "gold standard" is still represented by manual delineation by an expert radiologist, notwithstanding inter-observer variability. Further studies are needed to confirm and implement Radiomics and, consequently, stable radiomic features in this field.

6.2.2 Molecular Imaging

As previously mentioned, molecular imaging investigates two main features of NETs: the amine precursors pathway and the expression of somatostatin receptors on the cell surface. From the technological point of view, scintigraphy, SPECT(CT) and PET-CT are available for both functional features.

Guidelines for nuclear medicine imaging of NETs, with (iodine-131 or iodine-123) MIBG [14], with 111In-pentetreotide (somatostatin receptor scintigraphy, SRS) or with 68Ga-DOTA-peptide and 18F-DOPA, have been published in the past years [15–18].

Further reading of these guidelines is recommended for more details. However, we will here give an outline of the leading nuclear medicine techniques available to study NETs.

Radiolabelled MIBG (the isotopes used are iodine-131 or iodine-123) can well be considered

a metabolic probe for the study of NET; it is an analogue of the norepinephrine that can be taken up via the vesicular monoamine transporters ($VMAT_1$ and $VMAT_2$) and then stored in the secretory granules of the neuroendocrine cells without being further metabolised in a significant way [19]. The result is a specific concentration in these cells, allowing their visualisation in contrast to non-adrenergic tissues. Clinical indications are the detection, staging and restaging of NETs, particularly in case of pheochromocytomas, ganglioblastomas or neuroblastomas, paragangliomas, MEN2 syndrome, with an overall sensitivity of 85% and specificity of 89%, as reported in the literature [20]. Other clinical applications are medullary thyroid carcinoma and Merkel cell carcinoma.

This imaging technique is also used to select patients for therapy with ^{131}I-MIBG, to evaluate treatment response and in follow-up. Being MIBG radiolabelled with radioactive, thyroid blockade, using Lugol solution of potassium iodide, is essential to avoid thyroid irradiation from iodine (a minimum amount of free iodine is often present in the solution of the radiopharmaceutical, consequently to prevent collateral thyroid irradiation, thyroid blockage ought to be ensured).

131I-MIBG should nowadays exclusively be used for therapy, but in some centres, it is still applied also for diagnosis. Planar and SPECT images are acquired with different timing: at 24 h for 123I-MIBG and at 24 h, 48 h and even later for 131I-MIBG. Dedicated spot images may be useful in order to investigate some areas of interest further.

18F-FDOPA could be considered the PET radiopharmaceutical "counterpart" of MIBG for the study of the NET, as the enhanced intracellular transport and decarboxylation of the amino acid DOPA is the diagnostic target of 18F-FDOPA PET imaging. It is mainly used in the diagnosis and staging of pheochromocytoma and paraganglioma and for staging and restaging of medullary thyroid cancer with elevated serum levels of calcitonin. Well-differentiated NETs of the digestive tract and another endocrine, digestive tumours can also be evaluated using 18F-FDOPA PET, especially when somatostatin receptor scintigraphy is negative [21].

On the other side of NET imaging, there is a significant chapter of somatostatin analogues and receptor imaging.

The first tracer being commercially available and registered in Europe for somatostatin-receptor (SR) imaging was 111In-DTPA-D-Phe1-octreotide also named 111In-pentetreotide (OctreoScan, Mallinckrodt Medical), showing a high affinity for the sstr2 and lower affinity for the sstr3, 5 and 4 respectively, with high accuracy in the diagnosis and localisation of primary NETs and secondary lesions. Sensitivity reported for somatostatin receptor scintigraphy ranges between 70% and 95% according to the type of NET, especially in GEP NETs, with a reduction to 20–60% in insulinomas [22].

Other impressive scintigraphic results have been reported for the 99mTc-EDDA/HYNIC-Tyr3-octreotide (99mTc-EDDA/HYNIC-TOC), available in some European Countries and registered in Poland (Tektrotyd—Polatom, Poland) and for the 99mTc-EDDA/HYNIC-Tyr3-octreotate (99mTc-EDDA/HYNIC-TATE) [23]. The clinical indication is for SR imaging in staging, restaging and follows up of GEP NET, pulmonary NETs, other forms arising from the skin as Merkel cell tumours. This radiopharmaceutical is also proposed for the study of tumours originating from the sympathoadrenal system. Moreover, this imaging is mandatory to select patients for peptide radio-receptor therapy (PRRT).

A gamma camera equipped with medium-energy parallel-hole collimator is needed; planar and SPECT images are acquired at 4 and 24 h, sometimes up to 48 h after injection (when at 24 h the activity in the bowel is still significant). CT hybrid imaging has shown increased sensitivity over gamma camera alone and planar imaging.

Different 68Ga-labelled peptides are available for SR PET-CT imaging, which differ in the affinity to the different SSTR subtypes. The most relevant radiopharmaceuticals in use are [68Ga-DOTA-Tyr3]-octreotide (68Ga-DOTA TOC), [68Ga- DOTA-Tyr3]-octreotate

(68Ga-DOTATATE) and [68Ga-DOTA-1-Nal3]-octreotide (68Ga-DOTANOC). We will generally speak of 68Ga-DOTA-peptide PET-CT [24].

Clinical applications of 68Ga-DOTA-peptide imaging are the detection and staging of the primary tumour, the restaging of recurrent or progressive disease and the assessment of somatostatin receptor expression to candidate patients for somatostatin analog and peptide radionuclide receptor therapy (PRRT) [25].

Breastfeeding should be interrupted and can be restarted when the radiation dose to the child would be lower than one mSv. Discontinuation of "cold" analogues is suggested by some authors in the weeks before the exam when "long-acting" analogues are used. Images are usually acquired between 45 and 60 min after intravenous injection of the tracer.

The heterogeneity of NETs and the different degree of differentiation may influence the affinity for 68Ga-DOTA-peptides and thereby the diagnostic performance. The reported pooled sensitivity and specificity of 68Ga-DOTA-peptide PET imaging is 96% and 100%, respectively [26].

High tracer uptake at this imaging reflects the increased density of somatostatin receptors, rather than malignant disease.

NETs usually do not show a high glucose turnover rate. Therefore 18F-FDG PET-CT is not routinely used to assess these tumours. However, FDG finds application in studying poorly differentiated forms and metastatic disease, then contributing to define the aggressiveness of the lesions, in a prognostic framing [27].

As for future perspectives, we would like to mention imaging based on glucagon-like peptide-1 receptor (GLP-1R), using 68Ga-DOTA-exedin-4 PET-CT. These receptors are overexpressed at a high incidence, and density in almost all benign insulinomas is, therefore, an ideal target for these tumours for which SR scintigraphy and PET can give suboptimal results. 68Ga-DOTA-exen-din-4, however, is not a state-of-the-art tracer, but an experimental and promising probe [28].

Other novel imaging radiopharmaceuticals, not in clinical use but showing impressive preliminary results, are the somatostatin antagonists. First-in-human studies showed the high potential of radiolabelled antagonists for imaging and also targeted radionuclide therapy. 111In- DOTA-BASS and 111In-DOTA-JR11 are such gamma-emitting tracers using somatostatin antagonists, whereas 68Ga-NODAGA-JR11 is one of the antagonists under evaluation for PET-CT imaging [29].

As seen for conventional imaging, there is a rising interest in the study of texture analysis and radiomics in PET-CT imaging as well, and to date, the impact of these researches is purely academic; still, they appear very intriguing.

6.3 NETs of the Lungs

Pulmonary NETs account for approximately 1–2% of all lung malignancies and approximately 20–30% of all NETs and display significant heterogeneity, ranging from well-differentiated to poorly differentiated neoplasms. In addition to the historical classification in typical carcinoid (TC) and atypical carcinoid (AC), the World Health Organization (WHO) classification of bronchial NETs distinguishes large-cell neuroendocrine lung carcinoma (LCNEC), small-cell lung carcinoma (SCLC) and mixed neuroendocrine/non-neuroendocrine forms (miNEN) [30].

Lung NETs (L-NETs) are also classified according to their origin in respect of the bronchial tree, into central and peripheral, but they can also occur throughout the lung parenchyma.

The central forms commonly present respiratory symptoms, such as recurrent chest infections, cough, haemoptysis, chest pain, dyspnoea and wheezing. The peripheral lesions more often are incidental findings at radiological procedures carried out for other reasons.

Rarely, lung NENs can be associated with carcinoid or Cushing's syndrome.

A full imaging work up with a combination of both morphological and functional imaging is necessary during the initial diagnosis, staging and therapeutic assessment.

Bronchoscopy, if necessary, with additional endoscopic ultrasonography and biopsies, is the

best procedure to study central bronchial NETs [31].

L-NETs can be detected already at standard chest x-ray in up to 40% of cases [32]. However, contrast-enhanced CT of the thorax is widely considered the gold standard, usually with a 20 s delay between contrast injection and image acquisition to allow better visualisation of the mediastinal structures. High-resolution CT must be considered in patients with clinical contraindication to contrast media (allergies or renal failure) [33]. The CT appearance of L-NETs is often similar to the that of adenocarcinoma, presenting as round-shaped peripheral lung nodules with smooth or lobular margins, usually with a slow growth pattern and high vascularity following intravenous contrast administration.

The level of contrast enhancement depicts the angiogenetic characteristics of the lesions.

Ground-glass appearance is also reported, usually as a sign of oedema around the lesions rather than intra-alveolar invasion.

At CT images, the intermediate forms are frequently associated with atelectasis and air trapping, indirect signs of obstruction; sometimes obstructive pneumonitis, bronchiectasis and lung abscess can be part of the imaging presentation. The typical CT presentation is with rounded or elongated nodules; the latter usually have their long axis parallel to the bronchi and vessels. Complete obstruction of the bronchus is rarely seen, as the extra-bronchial component is more often predominant to the endo-bronchial part [3].

Calcifications are detected in one-third of all cases, especially in the intermediate forms.

In the rare event of multiple synchronous carcinoids, high-resolution CT with an expiration study can help to show mosaic attenuation or air trapping in addition to multiple nodules [34].

Nodal involvement (particularly in the atypical carcinoids), as well as the presence of distant metastases, influences the prognosis and the treatment options, and imaging assessment of the spreading of disease is then crucial for the patient management.

Apart from mediastinal nodes, liver and bones are the most common sites of metastasis.

Multiphase CT, including arterial and portal phases, must be acquired to image the liver status accurately; CT with appropriate bone window setting may be useful to reveal bone metastases.

MRI should include dynamic acquisition and diffusion-weighted sequences for the study of the liver metastasis. In case spinal metastasis is suspected, MR is preferable to CT [35].

L-NETs, as well as NETs arising in other sites, are characterised by the ability to take up and concentrate amine precursors in order to produce amines and peptides and also express different membrane peptide hormone receptors (e.g. somatostatin receptors, SSTRs). These uptake mechanisms and the presence of membrane peptide receptors represent the basis for functional imaging of NETs [36].

Combined functional imaging using SSTR imaging and metabolic imaging allows in vivo demonstration of the overall biological behaviour of NETs [37].

Since 80% of typical bronchial carcinoids express SSTRs, somatostatin receptor scintigraphy (SRS) and 68Ga-DOTA-peptide PET-CT may be very informative.

Scintigraphy with 111I-labelled somatostatin analogue has been the most widely used method to assess somatostatin receptor expression in the last decades, but 68Ga-DOTA-somatostatin analogue PET-CT recently became the nuclear medicine test of choice for staging [38].

Well-differentiated NETs are typically not FDG avid and overexpress membrane receptors for somatostatin [39]. On the contrary, more aggressive bronchial NETs such as LCNEC and SCLC are characterised by higher FDG uptake and lower expression of somatostatin membrane receptors. Therefore, for poorly differentiated NETs, FDG PET-CT may result more sensitive and informative than somatostatin receptor imaging.

MIBG scintigraphy has no clinical role in the management of lung neuroendocrine cancer, while PET-CT with 18F-dihydroxy-L-phenylalanine and 11C-hydroxy-L-tryptophan might potentially be used in the future for therapy response evaluation (Figs. 6.1 and 6.2).

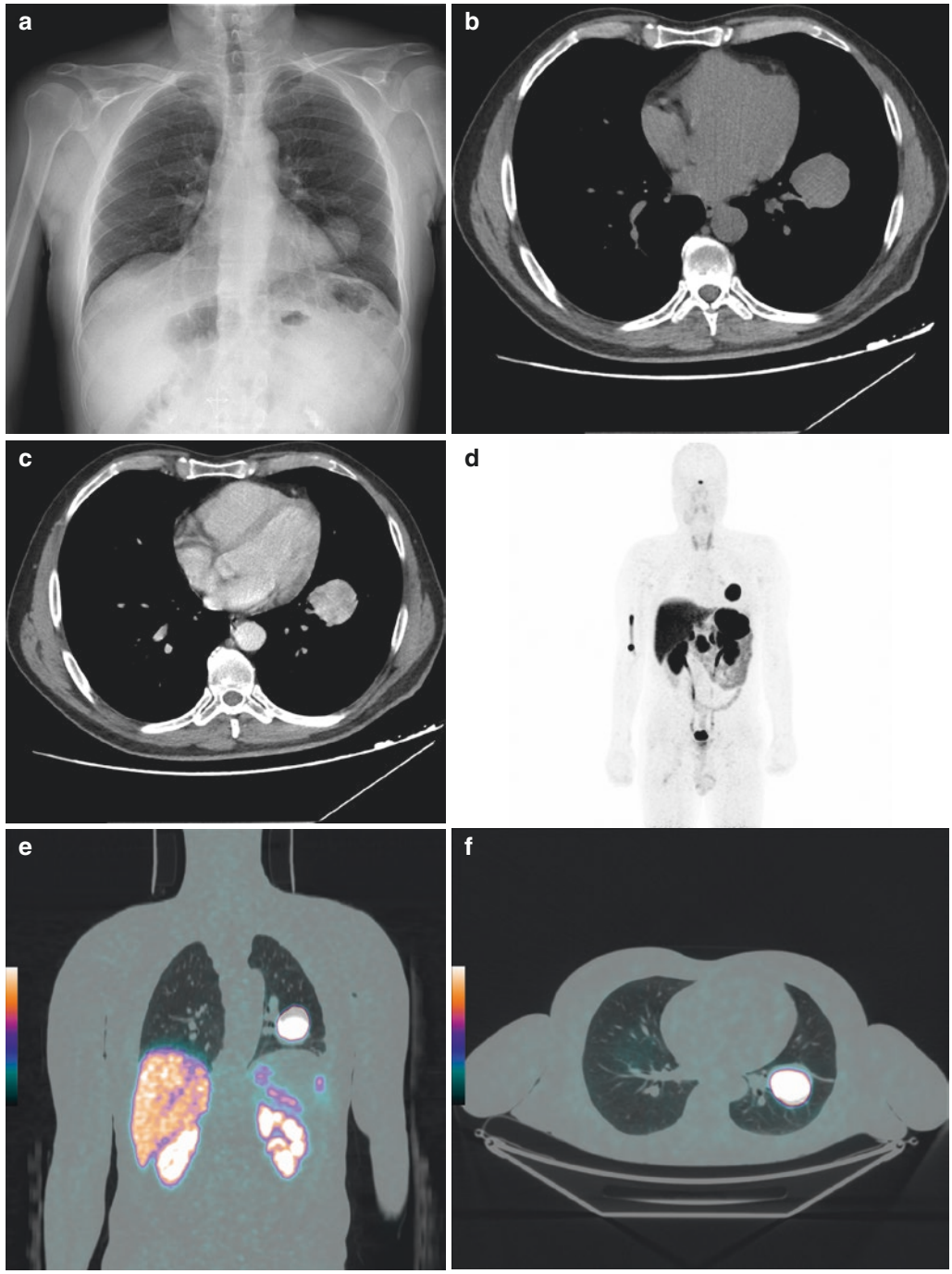


Fig. 6.1 A 50-year-old male patient referred to the hospital for pulmonary embolism. Chest x-ray (**a**) revealed an inferior left pulmonary mass. (**a**) Chest x-ray. The following CT of the thorax confirmed the lesion (**b**) that was characterised significant contrast enhancement (**c**). The intense contrast enhancement of the lesion documented at the CT scan coupled with the clinical data arose the suspect of a neuroendocrine tumour. (**b**) CT basal acquisition. (**c**) CT after contrast injection. A 68GaDOTATOC PET-CT (**d**, MIP, **e**, coronal, **f**, axial) was then performed showing intense tracer uptake of the lesion. Histology confirmed the diagnosis of typical carcinoid, ki67 = 8%. (**d**) 68Ga-DOTA-peptide PET-CT MIP. (**e**) 68GaDOTApeptide PET-CT coronal. (**f**) 68GaDOTApeptide PET-CT axial

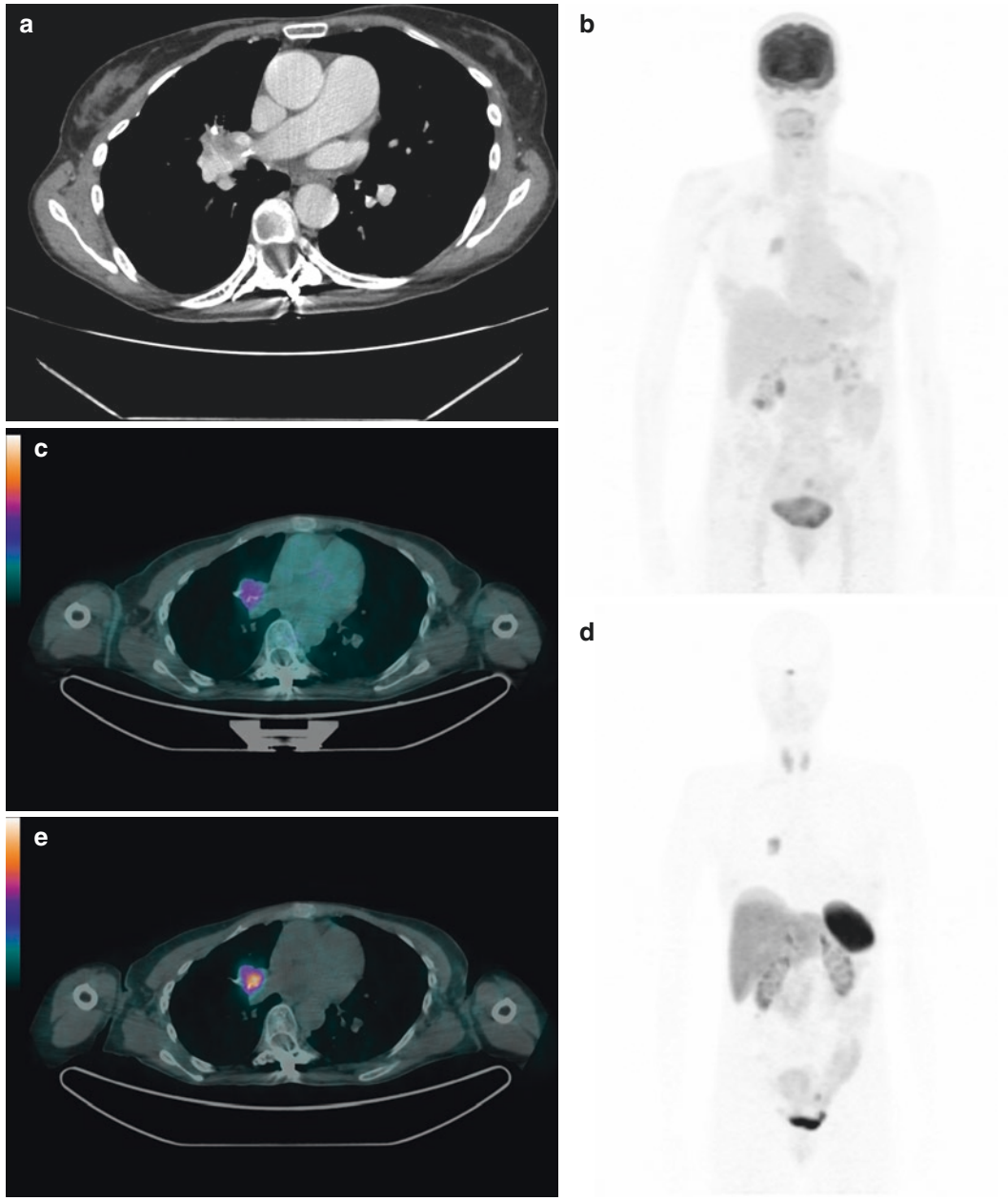


Fig. 6.2 A 50-year-old lady affected by atypical thoracic pain was scheduled to undergo a CT scan that showed a para-hilar right pulmonary node, with inhomogeneous contrast enhancement and some calcifications. (**a**) CT scan transaxial. At 18F-FDG PET-CT, the mass was confirmed, but the tracer uptake was mild (**b**, MIP and **c**, transaxial). Therefore, a fibro-bronchoscopy with biopsy was performed. Results were orientative towards a low-grade neuroendocrine tumour. (**b**) 18F-FDG PET-CT MIP. (**c**) 18F-FDG PET-CT transaxial. A 68 Ga-DOTATOC PET-CT was then requested. A focus of moderate tracer uptake was seen within the mass (**d**, MIP and **e**, transaxial). The multidisciplinary discussion proposed surgery upfront as no other lesions were detected. (**d**) 68Ga-DOTATOC PET-CT MIP. (**e**) 68Ga-DOTATOC PET-CT transaxial

6.4 GEP NETs

NETs arising in the gastrointestinal tract are the most represented forms (67%), with the most common origin in the distal tract of the ileum (up to 30% of GEP). These tumours are often quite small in size, making their identification challenging, especially for the ileal localisations [40].

The clinical presentation and tumour location, as already mentioned, profoundly influence the investigations required to achieve the final diagnosis.

The presence of hormonal hypersecretion must be assessed using laboratory analyses and endocrinological tests. Pathological analysis, whether possible, is required to confirm the diagnosis.

Functioning GEPs can either arise from the pancreas or the gastrointestinal tract, exhibiting specific hormonal syndromes according to the secreting abilities of the proliferating clone of cells. The clinical presentation can play a fundamental role in recalling the correct diagnosis, but from the imaging point of view it is not possible to discriminate functioning from non-functioning tumours; however, some general features are common findings in GEP NETs, such as the hyper-vascular attitude.

Usually, in case of non-functioning GEPs, the symptoms are mainly related to the compressive/obstructive effect of the mass on the surrounding structures and organs and include abdominal pain, obstructive jaundice, presence of abdominal mass, weight loss and intestinal obstruction. Therefore, the typical findings occurring in the clinical scenarios of abdominal discomfort are common to GEP NETs as well.

Well-differentiated, slow-growing GEP NETs are, nonetheless, quite often already metastatic at the moment of the diagnosis, hence the detection of primary together with the assessment of the disease extent is of paramount importance to guide staging and treatment.

Conventional imaging and functional imaging complement each other in the definition of these tumours, being nuclear medicine more effective in the biological characterisation of the lesions [41].

As a first step in the diagnostic workup, there is trans-abdominal ultrasonography (US), a non-invasive and widely available screening technique for the abdominal parenchyma. NETs typically appear on US images as a hypoechoic mass surrounded by a hyperechoic halo. US is mainly suitable for the investigation of solid organs but results inefficient at examining the gastrointestinal tract and mesentery.

The role of US seems to be limited, though, especially in the evaluation of the pancreas where it can turn out suboptimal due to partial obscuration by bowel gas, with an overall reported sensitivity of 13–27% [41].

Computed tomography shows high spatial and temporal resolution. Thanks to the multiplanar reconstructions and image display, and in consideration of the variety of protocols of contrast media injection and acquisition studies, it can survey different parts of the body in a more tailored fashion, providing detailed information on the tumour and its relationship with vascular structures and other close tissues and organs. These features gained its fortune, particularly in the pre-surgical evaluation.

Because of the known hyper-vascular aspect of the metastasis from GEP NETs, multiphase acquisition protocols are recommended for a more appropriate investigation of these lesions, usually more conspicuous in the early arterial phase of the acquisition [42].

It is also possible to perform basal scans with no contrast media injection to assess the presence of calcification and haemorrhage within the mass [43].

Multiphasic and multiplanar CT is usually performed at first. On average, arterial phase imaging is performed at 20–25 s following contrast injection. This timing takes into account the time for the contrast to reach the descending aorta at the level of the thoracoabdominal tract. Afterwards, a venous phase at approximately 50–60 s is scanned. All the phases must be performed for a complete examination and detection of eventual metastases, typically at the hepatic level.

Magnetic resonance (MR), even though more expensive, time-consuming and demanding either on patients cooperation or professional efforts to carry out a high-quality examination, together with the multiplanar acquisitions, offers superior intrinsic soft-tissue contrast and does not use ionising radiation. Multiphasic and multiplanar MRI is recommended for the study of

GEPs and considered superior to CT for lesion assessment in solid visceral organs.

At MRI, NET lesions are hypointense in T1-weighted sequences and hyperintense in T2-weighted sequences and, usually after contrast media injection, show a diffuse pattern of enhancement in the arterial phase. Typically, fat-suppressed contrast-enhanced T1-weighted sequences provide the best accuracy.

Molecular imaging techniques, especially with PET tracers, have a significant impact on patient management, including better localisation of occult tumours in the small intestine and pancreas as well as improved staging and restaging. Especially somatostatin receptor imaging continues to have a central role in the diagnostic workup of patients with well-differentiated GEP-NETs owing to its high accuracy and the theranostic potential [44].

111In-octreotide scintigraphy has a high sensitivity for detecting typical carcinoids and gastrointestinal pancreatic NETs, particularly, gastrinomas, non-functioning NETs, and functioning endocrine pancreatic tumours except insulinomas (because of the lack of expression of type 2 somatostatin receptor subtype) [45].

Somatostatin receptor scintigraphy (SRS) shows high accuracy in the diagnosis and localisation of primary NETs and secondary lesions. There is a consolidated experience on the use of SRS in GEP-NETs. It is well known for its usefulness in detecting small lesions of the small bowel that are difficult to identify on conventional imaging with a sensitivity of 80–100% [20].

Nonetheless, it is limited by low spatial resolution, low sensitivity in the detection of small tumours and high background activity in healthy organs, especially the liver, kidney and spleen.

The upgrade has introduced several improvements to tomographic and hybrid imaging by means of SPECT and SPECT/CT.

Finally, the development of PET tracers specifically designed for NETs originated a new paradigm in the staging and restaging of these tumours. Excellent signal-to-noise ratio, spatial resolution and high-quality imaging as early as 45 min after injection of the radiotracer are evident advantages.

Good sensitivity of 68Ga-DOTANOC was reported especially for cases with an unusual anatomic localisation and small lesions, particularly at the node and bone level. It also enables absolute quantification of tracer uptake (determination of the standard uptake value, SUV) and provides relevant information of SSTR expression, which has a direct therapeutic implication with PRRT [23, 46].

Regarding potential pitfalls in image interpretation, we would like to mention reactive nodes, benign meningiomas, accessory spleens, the physiological activity in the pancreatic uncinate process and physiologic activity at the adrenal level can cause false-positive results.

As already seen in general for NETs, GEP-NETs usually do not show a high glucose turnover rate. Therefore, the sensitivity of 18F-FDG PET/CT is low, especially in well-differentiated forms (G1 and G2).

FDG is useful in the poorly differentiated forms, which also seem to express lower levels of somatostatin receptors. Information deriving from the 18F-FDG PET seems to provide valuable prognostic elements that may contribute to select patients affected by a more aggressive disease.

MIBG is generally not used in the routine workup of GEP-NETs.

6.4.1 Gastric and Intestinal NETs

Gastric NETs (G-NETs) originate from enterochromaffin-like cells located in the gastric glands and are divided into three categories:

- Type 1 arises as neuroendocrine hyperplasia and ultimately neoplasms in the context of achlorhydric hypergastrinemia due to chronic atrophic (autoimmune) gastritis.
- Type 2 appears as a result of hypochlorhydria (hyper acidic) hypergastrinemia due to Zollinger-Ellison syndrome caused by one (or several) duodenal or pancreatic gastrinoma(s), usually in the context of MEN1 syndrome.
- Type 3 occurs sporadically and is not related to any gastric mucosal abnormality.

Type 1 and 2 mainly present as multiple small lesions due to the underlying diffuse (systemic)

growth stimulus; type 3 usually presents as a large-size solitary tumour with upper GI bleeding and is often characterised by more aggressive behaviour and worse prognosis with an increased risk of diffusion to regional lymph nodes and liver metastases [46].

Endoscopy, with biopsy, is the first imaging choice, but to assess the invasion of the surrounding structures and the spread of disease contrast-enhanced CT is required. Validated protocols exist: the patient should fast before the exam and have a couple of glasses of water right before the exam starts. This protocol enables the stomach to distend and its walls to be more visible. Also, water acts as a negative contrast allowing for better visualisation of the ampulla and thus identification of periampullary tumours. The thickness of the sections should be 1.25–2 mm as thin collimation of the scan is useful at identifying millimetric lesions. Iodinated contrast media is injected intravenously after an unenhanced scan is performed, particularly in case of lesions smaller than 2 cm.

Type 1 and type 2 tumours appear as numerous enhancing submucosal lesions similar to other small gastric tumours and polyps; type 3 lesions demonstrate an infiltrative morphology similar to that seen in adenocarcinomas and often show avid contrast enhancement [47].

Contrast-enhanced CT and MR are most crucial for staging distant metastases [48].

In G-NETs functional imaging, especially using PET-CT can contribute to staging and identification of disease spread. FDG PET-CT is most useful in the type 3 forms, to assess the diffusion of metastasis.

Moreover, radiologists should be aware of indirect signs and concomitant findings typical of this kind of tumours. In the case of gastrinomas, for example, a common accessory finding is represented by small-bowel mural thickening or oesophageal hyperenhancement (Figs. 6.3 and 6.4).

Duodenal NETs are rare tumours and comprise 1–3% of all duodenal neoplasms; they are generally small (<2 cm) and usually confined to mucosa or submucosa but in approximately 40–60% and 10% lymph node and liver metastases, respectively, have been reported.

The majority (90%) of duodenal NENs are non-functional, but an association with Zollinger–Ellison is reported as well as with carcinoid syndrome.

Upper gastrointestinal endoscopy is the most sensitive method of detection and diagnosis, while EUS can help determine the extension of the tumour invasion. CT, MRI and SSTRs functional imaging can be used in order to determine

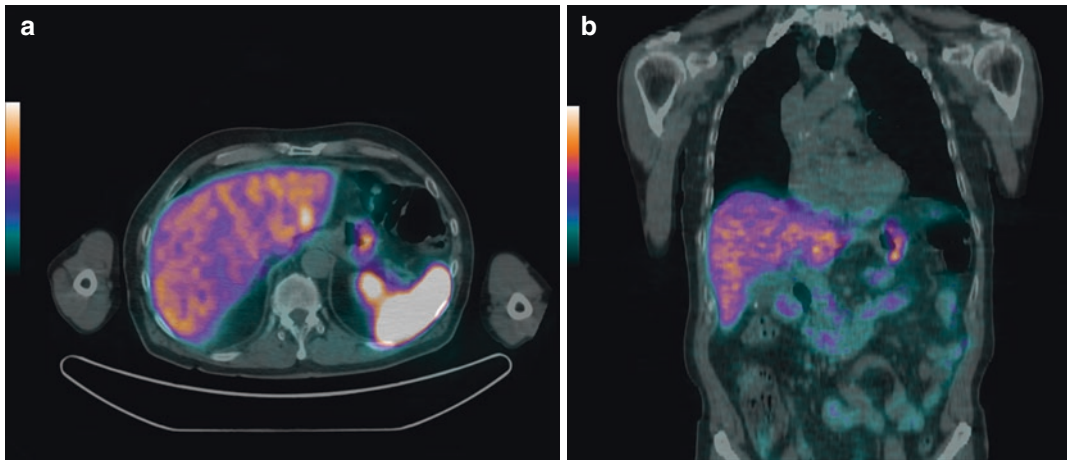


Fig. 6.3 A 72-year-old patient affected by anaemia, loss of B12 and gastritis. A biopsy of a polypoid mass seen at endoscopy demonstrated a well-differentiated NET G1 of the gastric body, ki67 = 1%. A 68Ga-DOTATOC PET-CT was performed for staging, confirming the gastric lesion and highlighting a hepatic metastasis in the third segment (**a**, axial, **b**, coronal). (**a**) 68Ga-DOTATOC PET-CT axial. (**b**) 68Ga-DOTATOC PET-CT coronal

the presence and the extent of metastatic disease [5] (Fig. 6.5).

Small intestinal neuroendocrine tumours (siNETs) derive from serotonin-producing enterochromaffin cells, and frequently they present with non-specific symptoms (abdominal pain, weight loss, bleeding or intermittent partial bowel obstruction). At the same time, 20–30% of patients develop carcinoid syndrome that is associated with liver metastases in more than 95% of cases.

SiNETs frequently present as multiple small lesions and have a high propensity to metastasise, as liver metastases are already seen at the moment of diagnosis in 80–90% of patients. However,

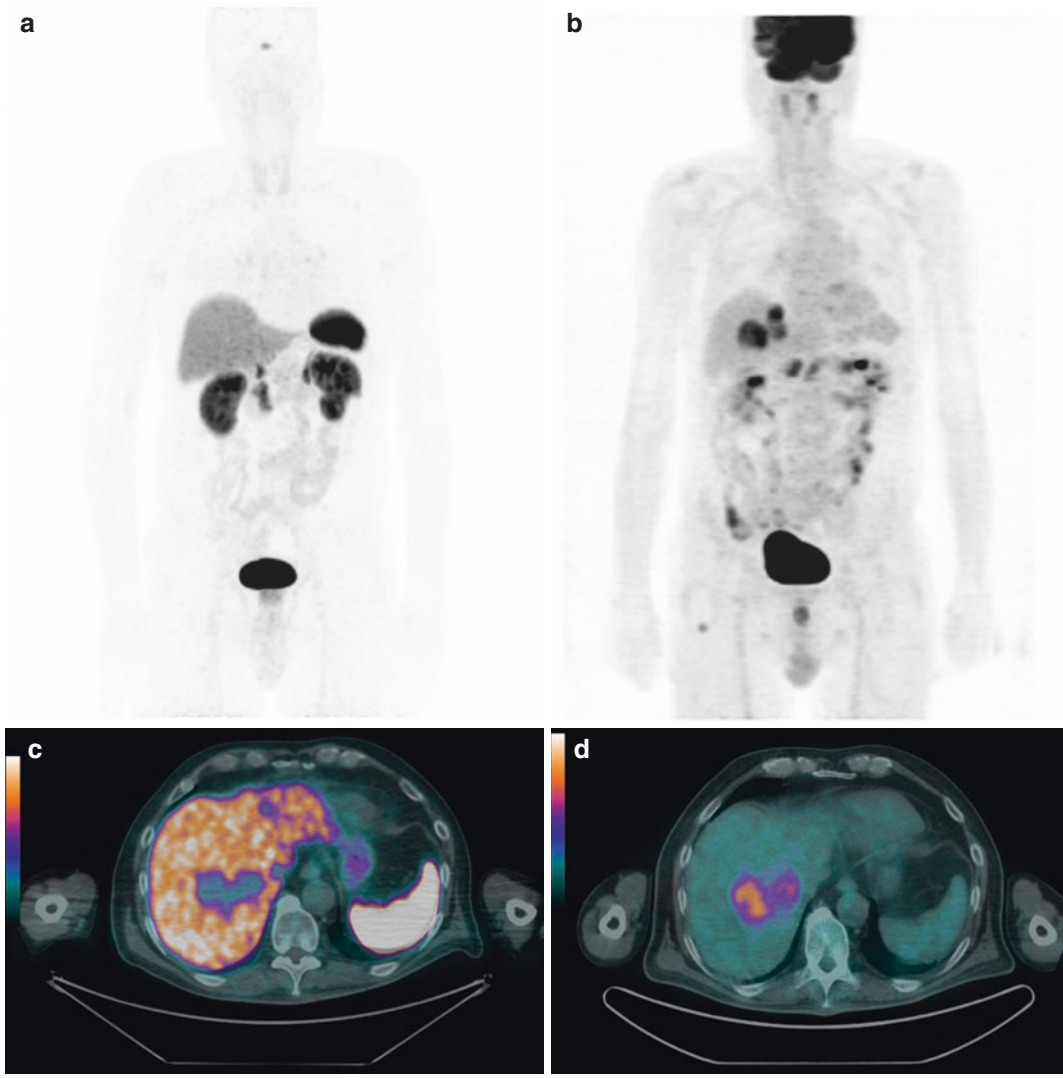


Fig. 6.4 A 76-year-old gentleman restaged for gastric NET (G2) relapsed after 3 years from surgery. 68Ga-DOTANOC PET-CT (**a**, MIP) and 18F-FDG PET-CT (**b**, MIP) were performed because of the clinical history and because of the moderate differentiation (G2). The residual gastric wall (after surgery) suspected for relapse of disease showed intense tracer uptake at the receptor PET-CT, whereas was not FDG avid. (**a**) 68Ga-DOTANOC PET-CT MIP. (**b**) 18F-FDG PET-CT MIP. Several liver lesions appeared as areas of no-uptake at 68Ga-DOTANOC PET-CT (**c**, axial) and as intense foci of uptake at the FDG images (**d**, axial). (**c**) 68Ga-DOTANOC PET-CT axial. (**d**) 18F-FDG PET-CT axial. Moreover, only FDG PET-CT revealed a bone lesion in the right femur neck (**e**, coronal and **f**, axial). (**e**) FDG PET-CT coronal. (**f**) FDG PET-CT axial

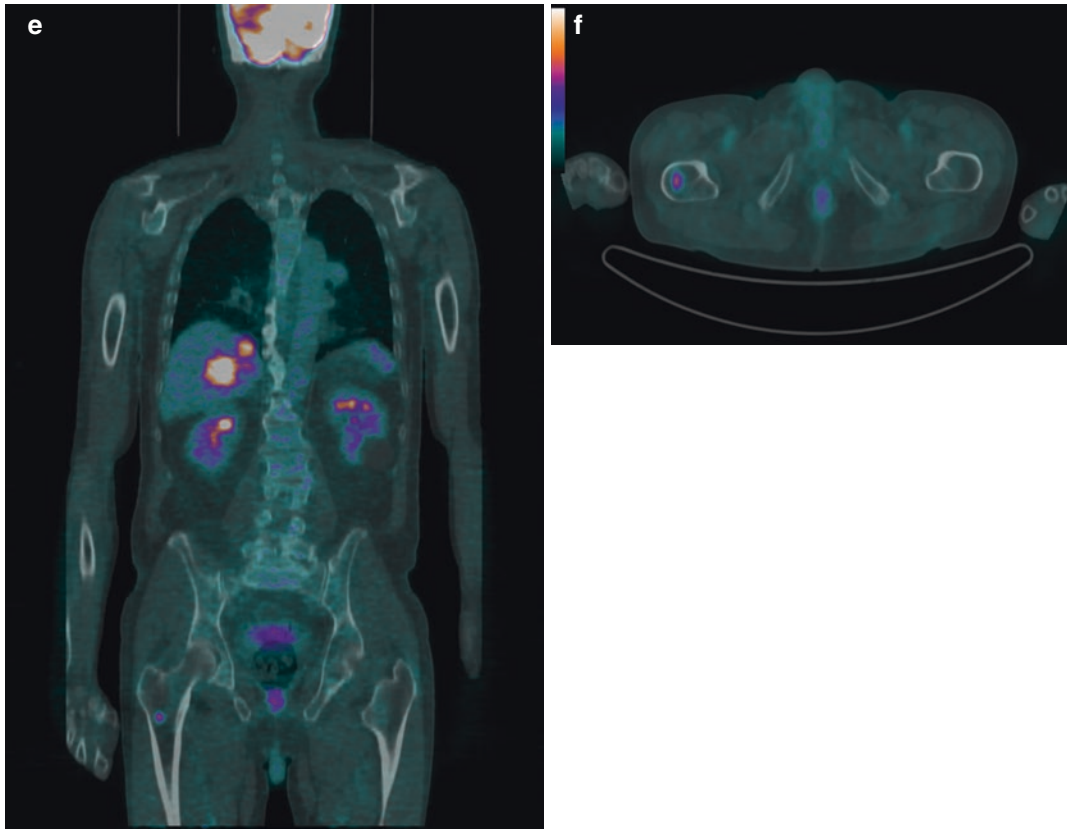


Fig. 6.4 (continued)

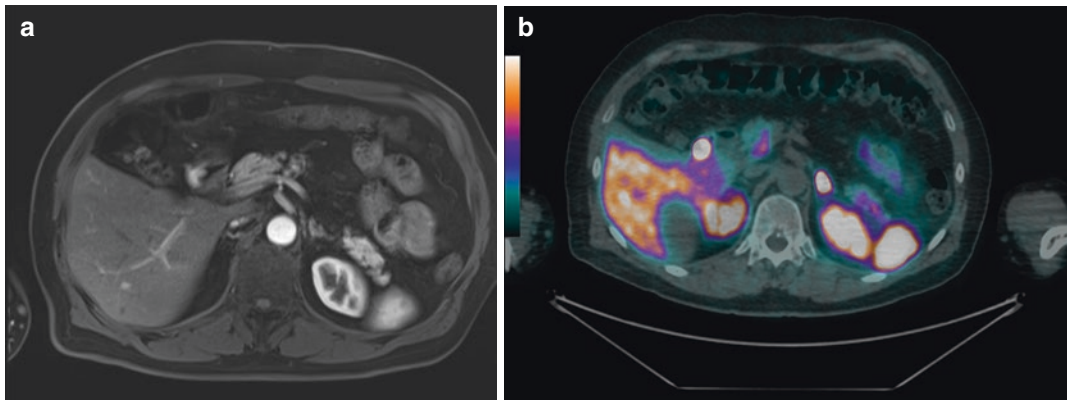


Fig. 6.5 A 67-year-old male patient was operated for gallbladder stones. Histology revealed the presence of a small amount of tissue with immune-reactivity orienting for the presence of a neuroendocrine tumour. Endoscopic ultrasound was performed, showing a lump in the distal part of the duodenum. The following MRI detected an area with early contrast enhancement in the duodenum, in keeping with a neuroendocrine lesion (**a**, axial, arterial phase); confirmed as an area of intense focal uptake at 68Ga-DOTATOC PET-CT (**b**, axial fused). (**a**) MRI axial, arterial phase. (**b**) 68Ga-DOTATOC PET-CT axial fused

despite their malignant behaviour, most of them belong to the G1 histopathological group.

CT or MRI, CT/MRI water enteroclysis or endoscopic techniques and SRS or 68Ga-DOTATOC PET can be helpful for the detection of the primary tumour and probable metastatic lesions while colonoscopy can detect tumours located in the terminal ileum.

Contrast-enhanced CT or MR imaging is often the preferred imaging techniques.

Small-bowel distention is often advisable to improve lesion detection using CT enterography and MR enteroclysis that have shown improved sensitivity (100% and 86%–94%, respectively) and specificity (96.2% and 95%–98%, respectively) for tumour detection [49].

These tumours usually appear as small, hypervascular, polypoid masses or as asymmetric or concentric bowel wall thickening. Another meaningful indirect sign is represented by mesenteric retraction (desmoplastic reaction), especially in the case of small-bowel lesions. This sign is crucial, and it may be more easily recognised than the primary lesion, at CT but also at MRI.

As with CT, multiphasic and multiplanar MRI is recommended for the study of GEPs and considered superior to CT for lesion assessment in solid visceral organs. Typically, fat-suppressed contrast-enhanced T1-weighted sequences provide the best accuracy.

A steep differential diagnostic consideration in these patients, concerning CT and MR, is chronic mesenteric panniculitis (also known as sclerosing mesenteritis) [50].

Given the technical difficulties to diagnose such small lesions at conventional imaging, functional imaging has gained over the past years an increasing role for siNETs, with an overall sensitivity of 80–90% for somatostatin receptor imaging [51] (Fig. 6.6).

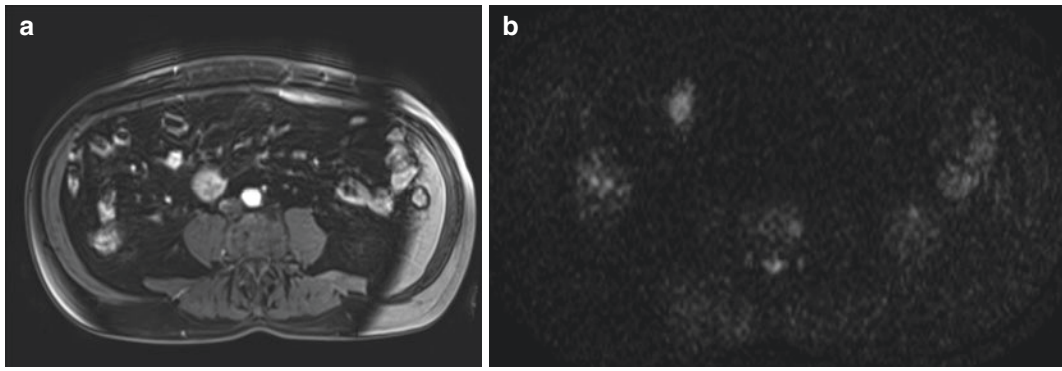


Fig. 6.6 A 79-year-old male patient with a 10-year history of a low-grade, multifocal, neuroendocrine tumour of the ileum. He was treated with surgery on the ileum and on the metastatic liver lesions that aroused in the second year after diagnosis. After 5 years of negative follow-up, an abdominal MRI for follow-up showed multiple solid nodules in the mesenteric adipose tissue with significant arterial contrast enhancement, thus suspicious for carcinoid tumour (**a**, MRI, dynamic sequence, arterial phase fat-saturated; **b**, MRI, DWI sequence b 800). (**a**) MRI, dynamic sequence, arterial phase fat-saturated. (**b**) MRI, DWI sequence b 800. After multidisciplinary consultation, a new surgery was performed on the mesenterial nodules and lymph nodes. No further treatment was suggested. Three years after surgery, during which the patient was negative for residual disease, a 68Ga-DOTATOC PET-CT scan was asked in the follow-up, detecting a pathological uptake in the mesenterial adipose tissue (**c**, axial fused). An area of uptake was also seen in the temporal region consistent with meningioma (**d**, axial fused). (**c**) 68Ga-DOTATOC PET-CT axial fused, mesenterial node. (**d**) 68Ga-DOTATOC PET-CT axial fused, meningioma. Also, MRI confirmed the presence of a mesenterial node (**e**, axial dynamic sequence "Lava MPh"). (**e**) MRI axial dynamic sequence "Lava MPh". Treatment with "cold" analogues of somatostatin was started, and MRI was the imaging chosen for follow-up, recording a progressive dimensional increase in the peritoneal lesion in the following 2 years, until the last MRI performed in November 2019 (**f**, MRI dynamic sequence, arterial phase fat-saturated; **g**, MRI axial dynamic sequence "Lava MPh"). (**f**) Dynamic sequence, arterial phase fat-saturated. (**g**) Axial dynamic sequence "Lava MPh". Subsequent multidisciplinary decision: "watch and wait" approach and continue with follow-up imaging studies

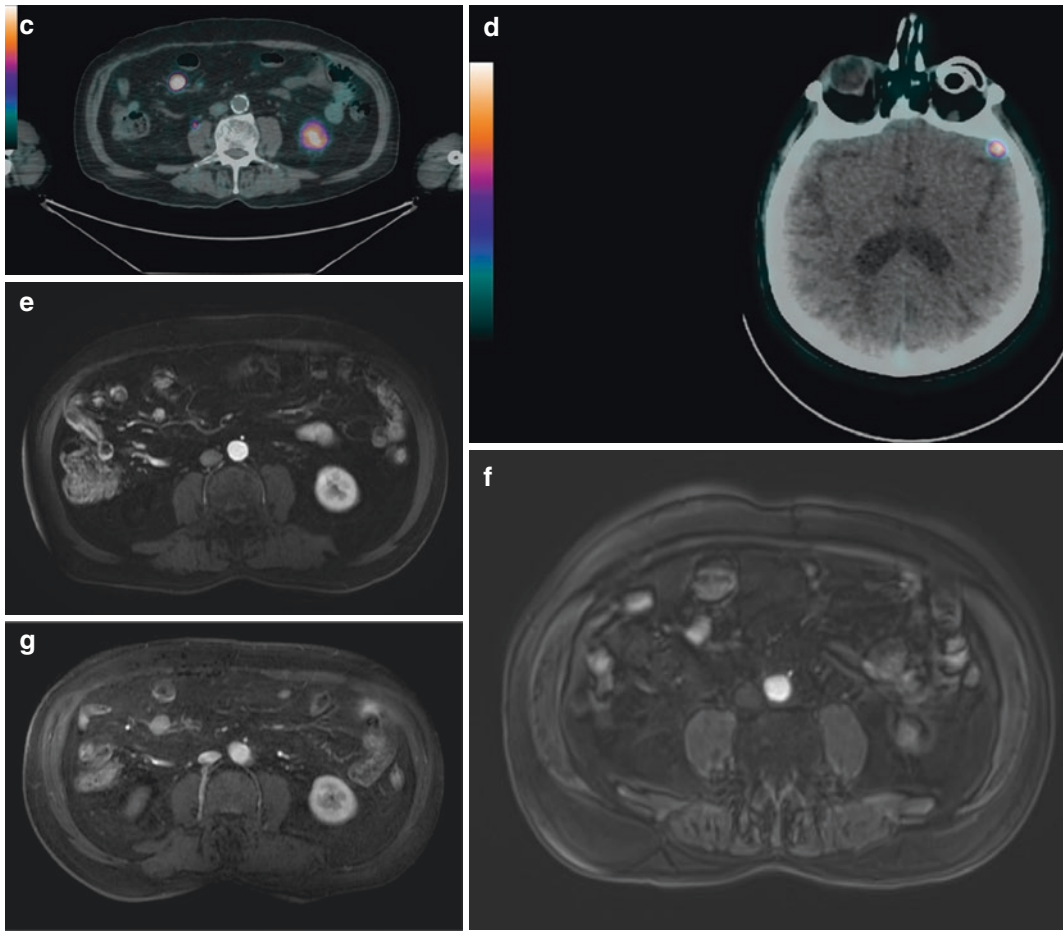


Fig. 6.6 (continued)

Appendix NETs are often incidentally discovered during appendicectomy and represent the most common neoplasm of the appendix. Despite they are generally considered indolent, approximately 49% display lymph node metastases while 9% present with distant metastases. The risk of distant metastases is associated with tumour size and is considered significantly increased for tumours >2 cm. For tumours >2 cm or with angioinvasion and infiltration of the mesoappendix, further imaging with abdominal CT/MRI and SRS or 68Ga-DOTATOC PET is recommended.

Colon NETs are often aggressive and metastatic at diagnosis while rectal neuroendocrine tumours are frequently low to intermediate grade and are associated with long-term survival.

EUS should be used to determine the depth of invasion while pelvic MRI is considered to be most accurate in determining local lymph node status [52] (Fig. 6.7).

6.4.2 Pancreatic NETs

Pancreatic neuroendocrine tumours are rare but represent the second most common pancreatic cancer. They can be functioning or non-functioning with a heterogeneous pattern of clinical presentation. They are often slow-growing lesions associated with prolonged survival, even in the presence of distant metastases.

Non-functioning pancreatic NETs show no symptoms as they are non-secreting lesions and are often detected when already of large size and usually in an advanced stage. Interestingly, the majority of non-functioning tumours are likely to

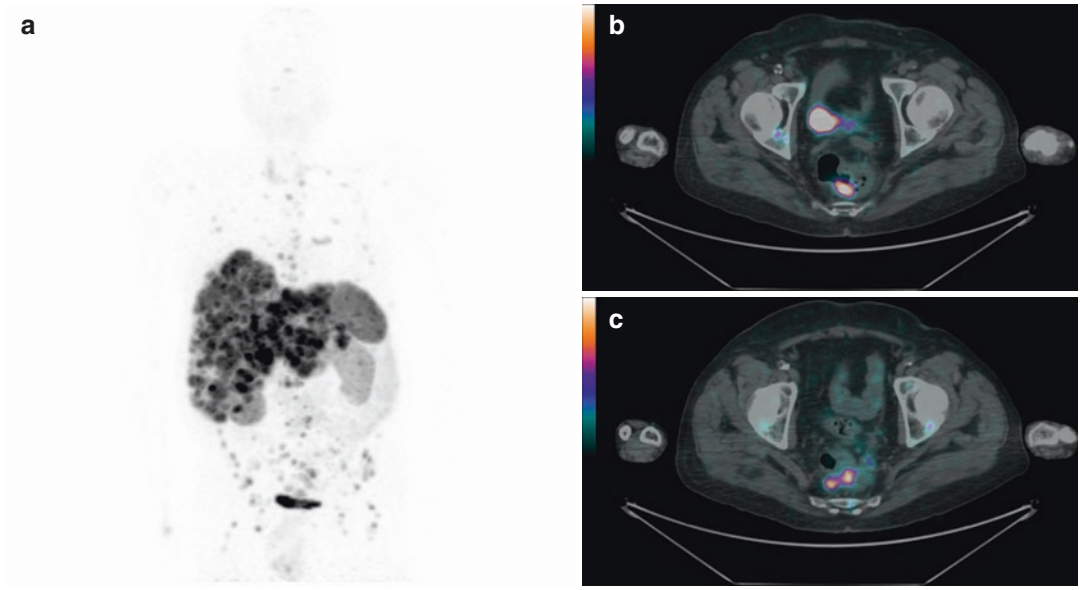


Fig. 6.7 A 68-year-old gentleman affected by a rectal mass revealed as moderately differentiated NET with an endoscopic biopsy. A 68Ga-DOTATOC PET-CT was performed for staging showing intense focal uptake of the primary lesion, regional lymphadenopathies, multiple liver and bone metastasis (**a**, MIP, **b**, axial fused, **c** axial fused). (**a**) 68Ga-DOTATOC PET-CT MIP. (**b**) 68Ga-DOTATOC PET-CT axial fused. (**c**) 68Ga-DOTATOC PET-CT axial fused

be malignant while functioning tumours, which have typical hormone-secreting clinical presentations, are benign [53].

Imaging techniques for the diagnosis of pancreatic NETs are the same already outlined for GEPs and especially in these tumours, the endoscopic US is of paramount importance due to its role for identification and histologic characterisation of lesions.

Multiphase multi-detector CT examination represents the first-line imaging test to evaluate pancreatic tissue with a detection rate rating between 69% and 94% in recent studies [4].

Functioning NETs are usually small in size (1–2 cm) and have a vibrant capillary network; therefore, present as homogeneously hypervascular lesions. When greater than 2 cm, they may show heterogeneity and degeneration patterns. Non-functioning tumours are instead well-defined, larger (> 4 cm) and show heterogeneous enhancement. This imaging characteristic is due to the possible cystic, necrotic or calcific components within the lesions.

Pancreatic NET secondary lesions are commonly seen in liver and locoregional lymph nodes, but retroperitoneal localisation can also occur. Moreover, as for pancreatic adenocarcinomas, also in the case of pancreatic NETs, the evaluation of locoregional vascular structures is mandatory. Pancreatic NETs tend to have a high rate of neoplastic vein thrombosis (splenic, portal and superior mesenteric veins) even though they show a lower rate of vascular encasement, more typical for pancreatic adenocarcinoma [54].

On MRI, most pancreatic NETs are hyperintense on T2-weighted images and hyper- or isointense during the arterial phase of the dynamic study. MR-DWI and ADC maps play an important complementary role to the other sequences, particularly at localising non–hyper-vascular tumours [55].

Despite the advances in the diagnostic approaches, in general, NETs are difficult to identify, and no single imaging test fulfils all the clinical expectations. For this reason, it is crucial to have a multimodal diagnostic approach that comprises invasive and non-invasive techniques.

Somatostatin receptor imaging, using scintigraphy or PET-CT is recommended because of the high expression of somatostatin receptors

generally occurring in these tumours, especially in the well-differentiated forms.

The reported sensitivity of somatostatin receptor scintigraphy, to detect islet cell tumours, is between 70% and 90%. However, it appears to be generally lower, ranging between 20% and 60% for insulinomas. Enthusiastic results with a detection rate of 100% for glucagonomas, 88% for VIPomas, 72% for gastrinomas, 82% for non-functioning islet cell tumours and 87% for other carcinoids is seen in some European experiences [20].

SRS has been widely adopted for diagnosis but also for the clinical management in the restaging after surgery to assess the therapy response and to plan further treatments.

The detection of unexpected sites of diseases, not found at other imaging modalities, is crucial to delineate the therapeutic strategy in the management of the patient. 68GaDOTA-peptide PET-CT has shown to be more sensitive than to SRS in the detection of primary pancreatic NETs, with sensitivity reported around 80–90%.

Versari et al. found similar figures for 68GaDOTATOC (sensitivity 92%) compared to multi-slice CT (sensitivity 91%) in detecting a duodenal-pancreatic tumour in a series of 19 patients [56].

Data on the comparison between 68Ga-DOTA-peptide PET-CT and MRI, particularly the diffusion-weighted MRI, are discordant on the superiority of one to the other, thus suggesting that the association of the two techniques is recommended to obtain the best performance [57].

68Ga-DOTA-peptide PET-CT also demonstrated to be superior to F-DOPA with a sensitivity of 96% and 56%, respectively [58].

FDG PET-CT is most indicated in patients affected by poorly differentiated or more aggressive forms and to complete staging when the disease is already metastatic, to assess the possible different behaviour of the different lesions.

MIBG scintigraphy has no clinical role in the study of pancreatic NETs (Figs. 6.8, 6.9, and 6.10).

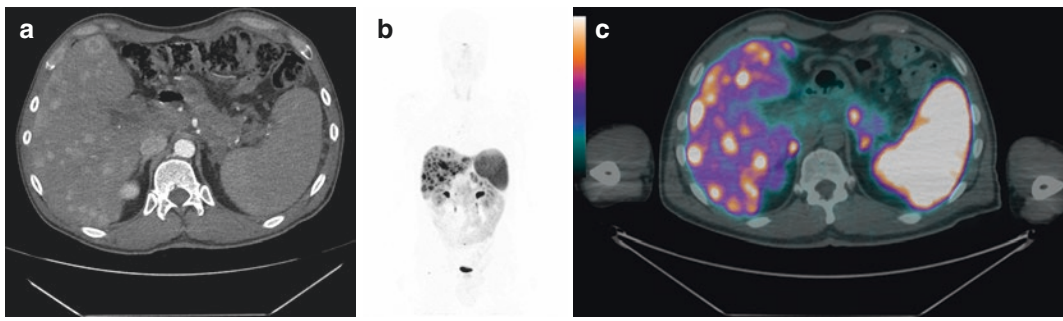
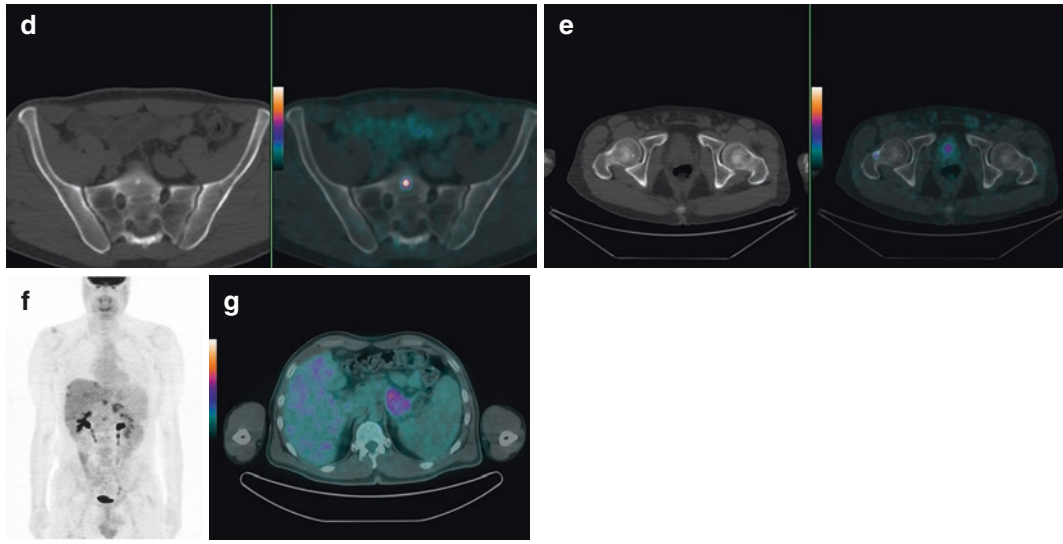


Fig. 6.8 A 44-year-old man suffered from weight loss in several months and a mild and unfocused abdominal pain. He underwent an abdominal ultrasound that showed multiple hepatic lesions, confirmed at a CT scan, particularly at the arterial phase for intense contrast enhancement. CT images also showed a 5 cm lesion in the pancreatic tail infiltrating the splenic hilum structures (**a**, CT axial, arterial phase). (**a**) CT axial, arterial phase. An ultrasound-guided biopsy was done on the liver. Histology revealed localisation of the well-differentiated NET tumour, with G1 aspects, ki67 = 2%, in keeping with the pancreatic origin. To complete staging a receptor PET-CT was performed and, because of the extension of disease, and FDG PET-CT was also scheduled. At 68Ga-DOTATOC PET-CT (**b**, MIP), the voluminous pancreatic mass in the organ tail was confirmed, showing inhomogeneous uptake of the radiopharmaceutical for a necrotic area in its context. Multiple foci of intense uptake were seen in the liver. The left adrenal appeared increased and almost fused with the pancreatic lesion; however, given the physiological adrenal uptake at receptor imaging, no conclusion was made on the effective adrenal pathological involvement (**c**, axial). Two bony lesions were seen, only at the receptor PET-CT, in the sacrum (**d**, CT of PET and fused) and the right femur (**e**, CT of PET and fused). (**b**) 68Ga-DOTATOC PET-CT MIP. (**c**) 68Ga-DOTATOC PET-CT axial pancreas and liver lesions. (**d**) 68Ga-DOTATOC PET-CT axial (CT of PET and fused) lesion in the sacrum. (**e**) 68Ga-DOTATOC PET-CT axial (CT of PET and fused) lesion in the right femur. At 18F-FDG PET-CT (**f**, MIP), the pancreatic mass appeared with moderate tracer uptake around a central area of necrosis. Only some of the multiple liver lesions were detectable. The left adrenal did not show pathological uptake (**g**, coronal). The patient was scheduled for systemic chemotherapy. (**f**) 18F-FDG PET-CT MIP. (**g**) 18F-FDG PET-CT axial



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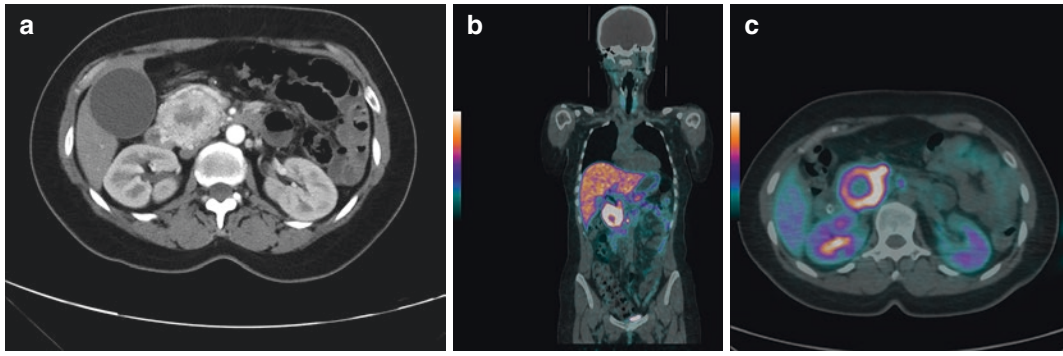


Fig. 6.9 A 47-year-old woman after an episode of jaundice was investigated using an abdominal ultrasound revealing a coarse mass in the pancreatic head. After an ultrasound-guided biopsy, the diagnosis of a well-differentiated pancreatic NET, G2, according to WHO 2000, Ki67 = 7%, was done. At contrast-enhanced abdominal CT, the lesion (4.2 × 4.8 cm and long 6.5 cm) early appeared in the arterial phase, with vivid contrast enhancement, an inhomogeneous aspect and a necrotic area within. Moreover, it appeared to have a compressive attitude towards the descending part of the duodenum (**a**, axial, arterial phase). (**a**) Contrast-enhanced abdominal CT, axial. At either 68Ga-DOTATOC (**b**, coronal, **c**, axial) or 18F-FDG PET-CT (**d**, coronal, **e**, axial), which followed the diagnostic CT, the lesion demonstrated to take up both tracers intensely and was characterised by a central area of no uptake due to necrotic changes. (**b**) 68Ga-DOTA-TOC PET-CT, coronal fused images. (**c**) 68Ga-DOTA-TOC PET-CT, axial fused images. (**d**) 18F-FDG PET-CT, coronal fused images. (**e**) 18F-FDG PET-CT, axial fused images

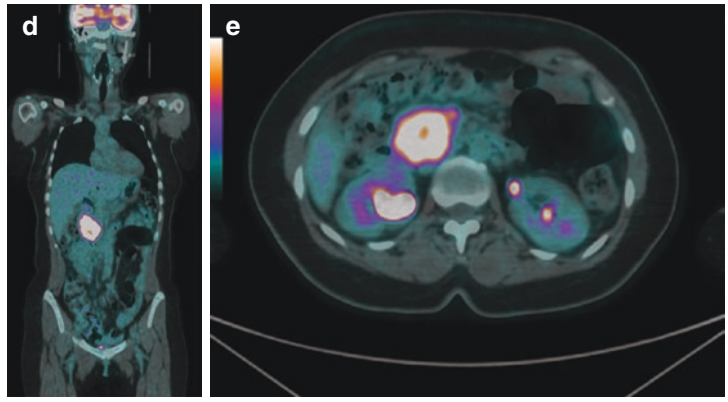
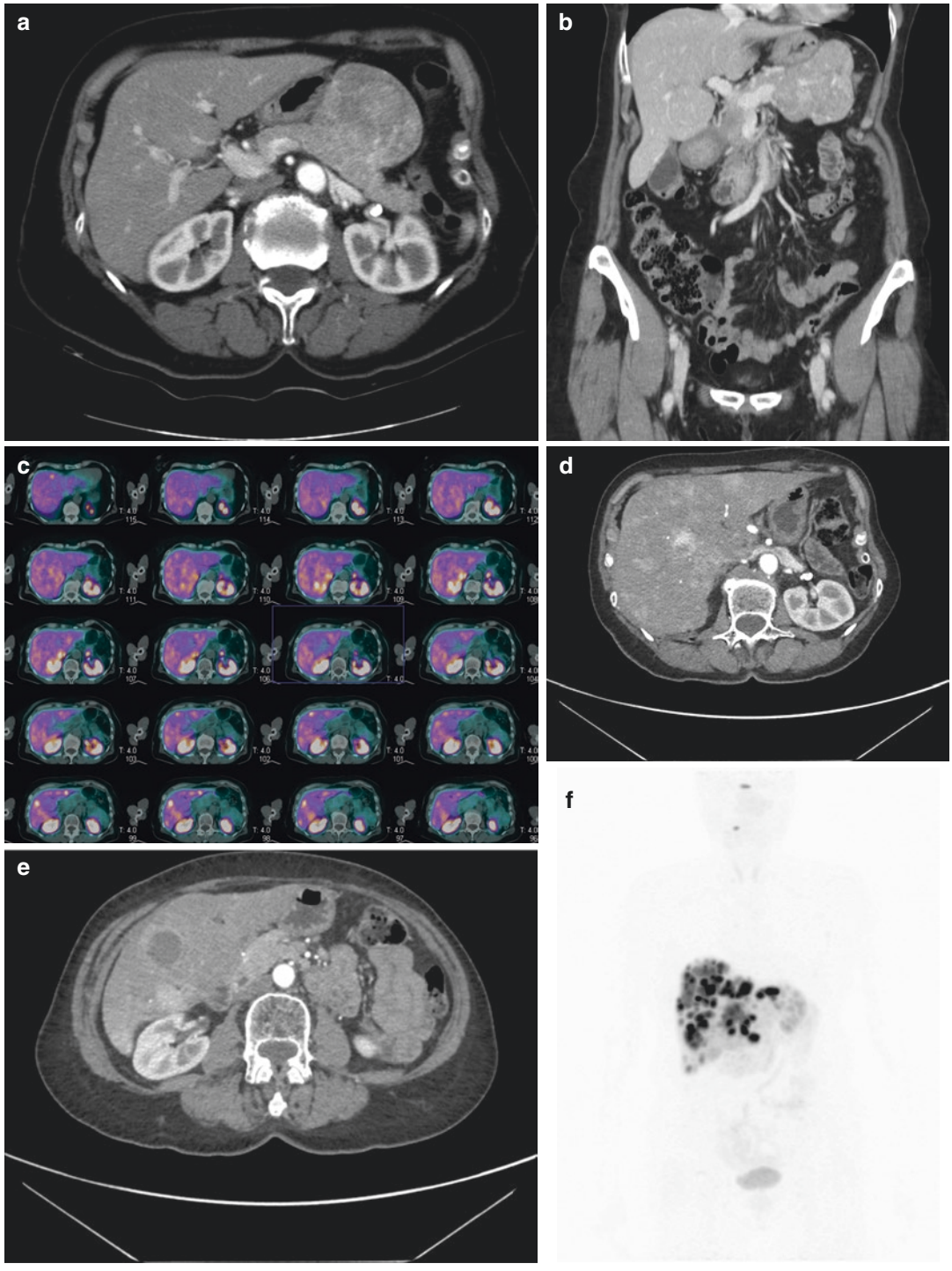


Fig. 6.9 (continued)

Fig. 6.10 In 2013 at the age of 71, this female patient had an incidental finding of a pancreatic lesion at CT scan done for abdominal pain (**a**, arterial phase axial and **b**, venous phase coronal). The following endoscopy and histological examination confirmed the presence of a pancreatic lesion, which resulted in a well-differentiated neuroendocrine tumour of the pancreatic gland, G2. After surgical evaluation, the patient was defined as suitable for resection and underwent distal splenic-pancreatectomy. (**a**) Abdominal CT scan, arterial phase axial. (**b**) Abdominal CT scan, arterial phase, venous phase, coronal view. Intraoperative US examination found bi-lobar liver lesions that were analysed histologically and resulted in metastatic localisations of the pancreatic NET (not seen at CT scan). A 68Ga-DOTA-NOC PET-CT was performed to complete staging after surgery with evidence of some foci of tracer uptake in the liver, in keeping with secondary localisation of the known neuroendocrine tumour of the pancreas (**c**, axials, fused). (**c**) 68Ga-DOTA-NOC PET-CT axial fused. After multidisciplinary discussion, treatment with somatostatin analogue was prescribed, with the progression of disease seen at 6 months of CT scan. Therefore, a treatment shift to chemotherapy was introduced. After the third cycle of chemotherapy, the follow-up CT scan showed a mixed response, but the treatment was stopped due to vascular complications, and 2 months later a substantial progression in number and size of the hepatic lesions was detected at CT (**d**, **e**), implying a new change of strategy with second-line chemotherapy. (**d**) Abdominal CT, arterial phase, axial view. (**e**) Abdominal CT, arterial phase, axial view. In the following 18 months, the disease remained stable. Then at the progression of liver disease seen at MRI, a palliative trans-arterial embolisation (TAE) of the accessible liver lesions was considered and performed. Successive follow-up CT scan: dimensional reduction of the liver lesions treated with TAE and stability of the other lesions; thus, a successive TAE was planned and performed. Follow-up abdominal MRI: progression in number and size of the untreated lesions, the stability of the treated lesions which appear inert. After further oncologic evaluation, taking into account the progression of the disease at a hepatic level even after TAE treatment, the latter was discontinued. In 2020, a new 68-GaDOTATOC was performed to evaluate the possibility to perform radio-receptor therapy (PRRT), which was started in April 2020. (**f**) 68-Ga-kDOTATOC MIP: multiple liver lesions and a bone lesion in C2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6.5 Conclusion

Imaging plays a fundamental role in the management of neuroendocrine tumours. Molecular and morphological information are available in a combined fashion and give a fundamental contribution to the diagnosis, staging, treatment election and treatment monitoring of these diseases.

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