Imaging of NETs

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4.1 Introduction

Cross-sectional imaging plays an important role for the diagnosis and the staging of neuroendocrine tumors (NETs). Radiological studies are critical to identify the location of the tumor as well as metastases in order to guide appropriate management.

As well as the clinical presentation, imaging findings can be extremely variable [1]. Many neuroendocrine tumors are found through imaging studies performed for other health issues. Diagnosis of functional NETs usually relies upon biochemical and imaging studies, given the smaller size of these tumors, while nonfunctional NETs are more readily detected with radiology.

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V. Ambrosini, S. Fanti (eds.), *PET/CT in Neuroendocrine Tumors*,
Clinicians' Guides to Radionuclide Hybrid Imaging: PET/CT,
DOI 10.1007/978-3-319-29203-8_4

4.2 Indications to Radiological Imaging

Imaging studies are performed for three main reasons: to identify the primary lesion, its local extension and relationships with surrounding structures; to assess the TNM staging, therefore to discriminate between surgical and medical therapeutic options; during the follow-up to evaluate radiological response to therapy (restaging) as well as the need for additional treatments [2]. Computed tomography (CT) and magnetic resonance imaging (MRI) are the main imaging modalities employed for detection, staging and treatment response evaluation. Transabdominal ultrasound (US) is usually performed for directing biopsies of the tumoral mass in order to obtain histological diagnosis; on the other hand, contrast-enhanced ultrasound (CEUS) shows high accuracy for the visualization of microvascularization in pancreatic lesions (PNETs) and the detection of liver metastases [3]. Endoscopic ultrasound (EUS) is highly sensitive for the characterization of PNETs and tumors located in the foregut; in addition it allows EUS-guided biopsy of the lesion through fine needle aspiration (EUS-FNA).

4.3 CT

CT is the most used anatomic imaging technique for NET evaluation, due to high spatial resolution, low scan time (especially for what concerns the newest multidetector CT), and an accurate bolus tracking of intravenous (IV) contrast medium.

Patients should be fasted and drink water as an oral contrast agent right before the examination, in order to distend gastric and duodenal walls. An initial precontrast scan is important to detect the primary lesion that can appear as a hypodense area with calcifications (in PNETs and pulmonary NETs). Arterial phase should be started by an accurate bolus tracking of IV contrast or following a delay of 25–30 s after the start of contrast injection. Portal venous phase images should be obtained after a delay of 60–70 s and sometimes can more easily identify the lesion.

NETs are usually hypervascular lesions that enhance during early arterial phase (Fig. 4.1), when the tumor-to-parenchyma contrast is maximized, although the vascular blush is often transient; the delayed portal venous phase usually shows washout of contrast medium.

The detection of small primary tumors of the small bowel is very challenging; therefore the use of a negative oral contrast agent may be helpful. Larger tumors are usually malignant and/or nonfunctioning neoplasms; their typical pattern includes necrosis, calcifications and infiltration of surrounding structures.

CT scan is not recommended in pregnant or lactating women, children, people allergic to iodinated IV contrast media, and nephropathic patients.

Main pitfalls in the use of CT scan are poor ability in the differential diagnosis between small metastatic and reactive lymph nodes and the evidence that Response Evaluation Criteria in Solid Tumors (RECIST) is not sufficient alone to assess response to medical therapy in patients affected by NETs [4].

Detection of the primary tumor depends on size and location: sensitivity range in detecting PNETs is 57–94 %. 85 % of gastrointestinal NETs are visualized through CT enteroclysis, and 44–82 % of liver metastases are detected by CT [5].

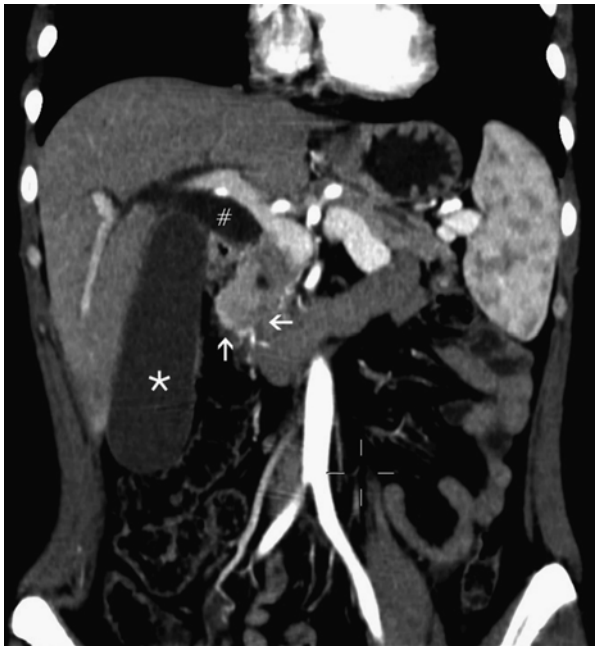

Fig. 4.1 CT scan: arterial phase in coronal view of a neuroendocrine tumor located in the head of the pancreas (*arrows*); it appears as a hypervascularized lesion compared to the rest of the pancreatic gland. * hydropic gallbladder, # dilated main bile duct

4.4 MRI

MRI study of NETs should be performed on 1.5 or 3 T field strength magnets, including T1-weighted (T1w) and T2-weighted (T2w) sequences with and without fat suppression, diffusion-weighted imaging (DWI), and post-contrast dynamic imaging on arterial, portal venous and delayed phases.

NETs usually appear hypointense on T1w images (Fig. 4.2), while on T2w sequences primary lesions have hyperintense signal; both weighing are more useful when fat suppressed because of the high tumor-to-parenchyma contrast. DWI sequences can be helpful in distinguishing between well- and poorly differentiated NETs, showing the latter lower ADC values probably due to increased tumor cellularity. Post-contrast images show the same features as CT.

MRI has a higher sensitivity than CT in the detection of liver metastases (high signal on T2w sequences, sensitivity 82–95 %) (Fig. 4.3); in particular it has great potential in distinguishing between metastases and benign hepatic lesions especially when performed with hepatocyte- and Kupffer-cell-specific contrast media.

Limitations are those typical of magnetic resonance instrumentation (presence of pacemakers, metallic prosthetic devices, claustrophobia, patient's collaboration, etc).

Main pitfalls are connected to tumor size and to the fact that liver metastases present at diagnosis can be disguised at follow-up examinations, due to fibrotic effects on the liver of medical therapies (chemotherapy, radionuclide therapy, etc.).

Up to 94 % of pancreatic lesions are correctly diagnosed by MRI, while for what concerns primary gastrointestinal NETs, sensitivity of MRI with enteroclysis is 86 % [5].

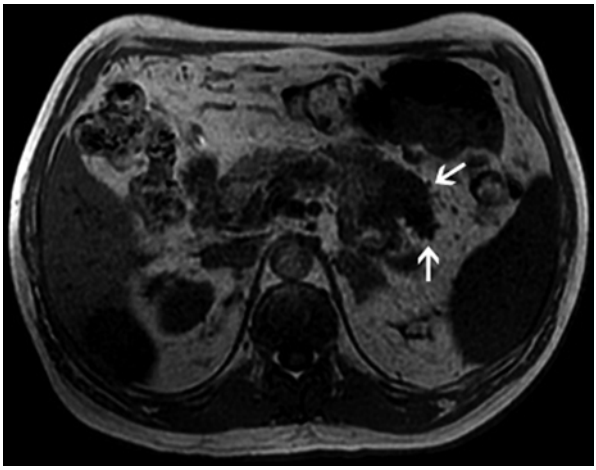

Fig. 4.2 MRI scan: T1w image showing a hypointense lesion of the pancreatic tail (*arrows*)

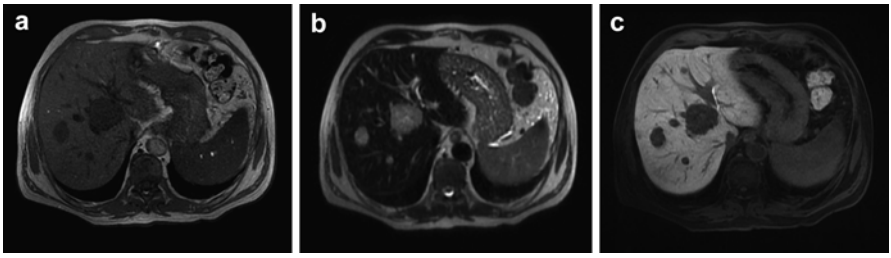

Fig. 4.3 MRI scan: T1w (**a**), T2w, (**b**) and 3D liver acquisition volume acceleration (LAVA sequence) after hepatospecific contrast medium (**c**) show several PNET's liver metastases

4.5 US-CEUS-EUS

US plays a role only in the evaluation of abdominal NET in particular pancreatic tumors (PNET) [6].

Nonfunctional tumors can grow and create a large abdominal mass; in this case US is usually the first imaging technique used for the diagnosis and can guide the transabdominal biopsy.

In the suspicion of functional tumors, which are often small, US has a low sensitivity (ranging from 20 to 86%) [7], which increases with the size of the lesion, while endoscopy with EUS and EUS-FNA has become a cornerstone in the diagnosis of these tumors. Given the limitations also of CT and MRI for small lesions, EUS has become an integral part of the diagnosis of PNETs because of its high sensitivity (from 83 to 94%) [7, 8] in detecting, localizing, and diagnosing pancreatic PNETs.

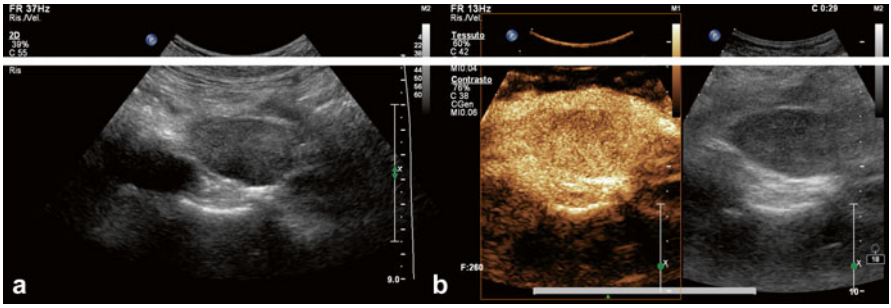

Fig. 4.4 (**a**) Transabdominal ultrasound: hypoechoic, well-defined, homogeneous, pancreatic NET. (**b**) At CEUS the lesion shows enhancement in the arterial phase (29 s after injection of SonoVue)

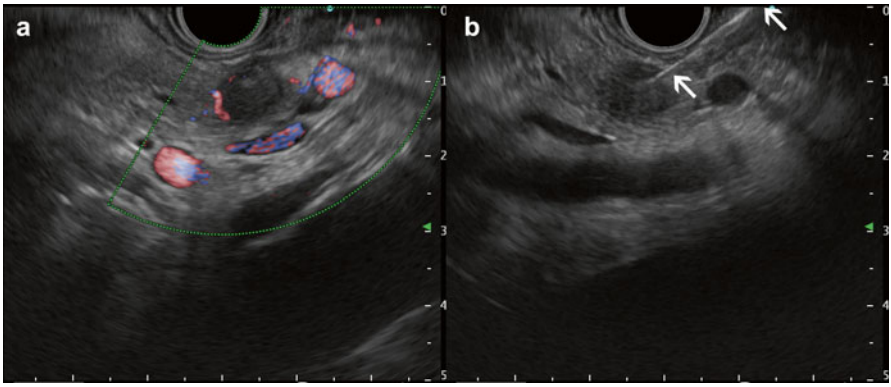

Fig. 4.5 (**a**) EUS: hypoechoic, well-defined, homogeneous, pancreatic NET. (**b**) FNA of the lesion using a 22-gauge needle (*arrows*) (Courtesy of Dr. Pietro Fusaroli, University of Bologna)

Despite EUS and improved radiological imaging, small PNETs may be difficult to localize. Intraoperative palpation combined with intraoperative ultrasound is over 95 % sensitive [9].

Most commonly, PNETs appear hypoechoic, round, homogeneous, and well defined on US (Fig. 4.4a), though they may be isoechoic and, rarely, hyperechoic with irregular margins. Malignant PNETs are larger, with irregular margins, compared to benign PNETs. Classically CEUS, as well as CT and MRI, shows hypervascular enhancement during the arterial phase due to their vascular nature [3] (Fig. 4.4b).

Cystic lesions are the least common presentation, accounting for 8–17 % of PNETs, and may be unilocular, septated, microcystic, or mixed solid-cystic [10].

The addition of FNA to EUS using a 22- or 25-gauge needle enables tissue diagnosis, which allows differentiation from pancreatic adenocarcinoma and is more relevant for diagnosis of nonfunctioning or cystic PNETs (Fig. 4.5).

To improve FNA yield, ideally onsite cytopathology examination should be performed. This examination significantly reduces the rate of unsatisfactory cytology specimens.

Key Points

- NETs are vascularized tumors in the arterial phase of all contrast imaging techniques.
- Small PNETs and gastrointestinal NET can be visualized only during EUS or surgical examination.
- MRI has better diagnostic capabilities in comparison to CT, but it is less available and has several technical limitations.
- The integration of the different imaging modalities available nowadays allows higher sensitivity and specificity in diagnosing NETs.

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