review

The multidisciplinary team for gastroenteropancreatic neuroendocrine tumours: the radiologist's challenge

Vincenza Granata[1], Roberta Fusco[1], Sergio Venanzio Setola[1], Elisabetta de Lutio di Castelguidone[1], Luigi Camera[2], Salvatore Tafuto[3], Antonio Avallone[3], Andrea Belli[4], Paola Incollingo[5], Raffaele Palaia[4], Francesco Izzo[4], Antonella Petrillo[1]

[1] Division of Radiology, "Istituto Nazionale Tumori IRCCS Fondazione Pascale – IRCCS di Napoli", Naples, Italy
[2] Division of Radiology, "Università degli Studi di Napoli Federico II", Naples, Italy
[3] Division of Gastrointestinal Oncology, "Istituto Nazionale Tumori IRCCS Fondazione Pascale – IRCCS di Napoli", Naples, Italy
[4] Division of Hepatobiliary Surgical Oncology, "Istituto Nazionale Tumori IRCCS Fondazione Pascale – IRCCS di Napoli", Naples, Italy
[5] Operative Unit of Genaral surgery and Kidney Transplantation, Advanced Biomedical Science Department University Federico II of Naples, Italy

Radiol Oncol 2019; 53(4): 373-387.

Received 30 March 2019
Accepted 15 July 2019

Correspondence to: Dr. Roberta Fusco, Department of Radiology, Istituto Nazionale Tumori Fondazione G. Pascale. Phone: +390 81 590 714; Fax: +390 815 903 825; E-mail: r.fusco@istitutotumori.na.it

Disclosure: No potential conflicts of interest were disclosed.

Background. Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are a heterogeneous group of tumours. An effective diagnosis requires a multimodal approach that combines evaluation of clinical symptoms, hormonelevels, radiological and nuclear imaging, and histological confirmation. Imaging plays a critical role in NETs diagnosis, prognosis and management, so the radiologists are important members of the multidisciplinary team. During diagnostic work-up two critical issues are present: firstly the need to identify tumor presence and secondly to define the primary site and assess regional and distant metastases.

Conclusions. The most appropriate imaging technique depends on the type of neuroendocrine tumour and the availability of specialized imaging techniques and expertise. There is no general consensus on the most efficient imaging pathway, reflecting the challenge in reliably detection of these tumours.

Key words: neuroendocrine tumours; ultrasound; contrast-enhanced ultrasound; computed tomography; magnetic resonance imaging

Introduction

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are a heterogeneous group of tumours, arising from neuroendocrine cells present in the gastrointestinal tract and into the islets of Langerhans of the pancreas.[1] Thanks to their capability to synthesize and secrete peptides and hormones, these tumours can cause clinical syndromes, although more often may be asymptomatic and discovered as an incidental finding.[2] Functioning tumours usually reveal themselves relatively early, so it might be difficult for the radiologist to localize the lesions since they are often too small to be detected. Non-functioning tumours generally present non-specific symptoms and frequently manifest as locally advanced or metastatic desease. The neuroendocrine tumour of the gastroenterict tract can cause vague abdominal symptoms and may be diagnosed as an irritable bowel syndrome (IBS).[3] Between 60% and 90% of GEP-NETs of pancreas (p-NETs) are non-functioning tumors, so they can be diagnosed at advanced stages because of their relatively indolent nature and slow

growth.[4] The diagnosis of functional (F)-p-NETs is clinical with laboratory test that should confirm the hypothesis. An effective diagnosis of NET requires a multimodal approach that combines evaluation of clinical symptoms, hormone levels, radiological and nuclear imaging, and histological confirmation.[3] Imaging plays a critical and indispensable role in NETs diagnosis, prognosis and management; therefore radiologists are important members of the multidisciplinary NET team.[5] Two critical issues are present in diagnostic work-up of NETs: firstly the need to identify tumor presence and secondly to define the primary site and assess regional and distant metastases.[6] In fact, primary site, stage, grade and functionality are prognostic factors that the radiologist should assess in order toguide prognosis and management.[6-7] Although imaging itself is not able to discriminate between a functioning and a non-functioning NET, the imaging identification of a large tumor burden in a patient without specific symptoms strongly suggests a non-functional tumor (Figure 1). Functional imaging can also suggest tumor grade.[7] The most appropriate imaging technique depends on the type of neuroendocrine tumour and the availability of specialized imaging techniques and expertise.[8]

Anatomical and functional imaging

Imaging modalities can be anatomic, which assess the physical characteristics of the tissue, or functional, which assess the biochemical characteristics.[7] The increase of knowledge about these tumours andNETs' characteristic of expressing somatostatin receptors (SSTRs) make them target of specific therapy (target therapy) and functional imaging. Currently, five main subtypes of SSTR have been identified (SSTR-1, SSTR-2A and SSTR-2B, SSTR-3, SSTR-4, and SSTR-5). SSTR-2 is the predominantly expressed one. The expression of SSTR is especially high in well-differentiated NETs compared to poorly differentiated ones.[9-10] In this scenario, molecular imaging techniques, with the ability to acquire informations on the SSR expression, have a pivotal role in diagnosis, staging, treatment selection and follow-up of NETs.[11] However, the technique should always be complemented with computed tomography (CT) or magnetic resonance imaging (MRI), inasmuch as these tecniques allow the exact identification of the tumor site, vascular and or biliary involvement and detection of metastatic disease, all parameters that impact on surgical planning and prediction of the response to treatment.[11-12]

The European Neuroendocrine Tumor Society (ENETS) has proposed a tumor–node–metastasis staging and grading system for various types of GEP-NETs.[4,5,13-19] Preoperative staging should include, whenever possible, somatostatin receptor scintigraphy (SSRS).[11] Although SSRS is highly efficient for whole-body imaging, detection of lesions is difficult in organs with intense physiologic uptake, with low receptors' density, or small size. 68Ga-DOTATATE PET/CT is more efficient than SSRS to evaluate small NET lesions, also considering that the affinity of 68Ga-DOTATATE to bind somatostatin receptor 2 is higher than 111In-octreotide's one.[20] However, the higher costs and the 68Ga generators limitated availability to specialized centers, due to the short half-life of 68Ga that requires in-house labelling of the tracer, still remain impediments to its routine use in clinical care.[21] MRI of the liver is complementary to 68Ga-DOTATATE PET/CT and is highly recommended

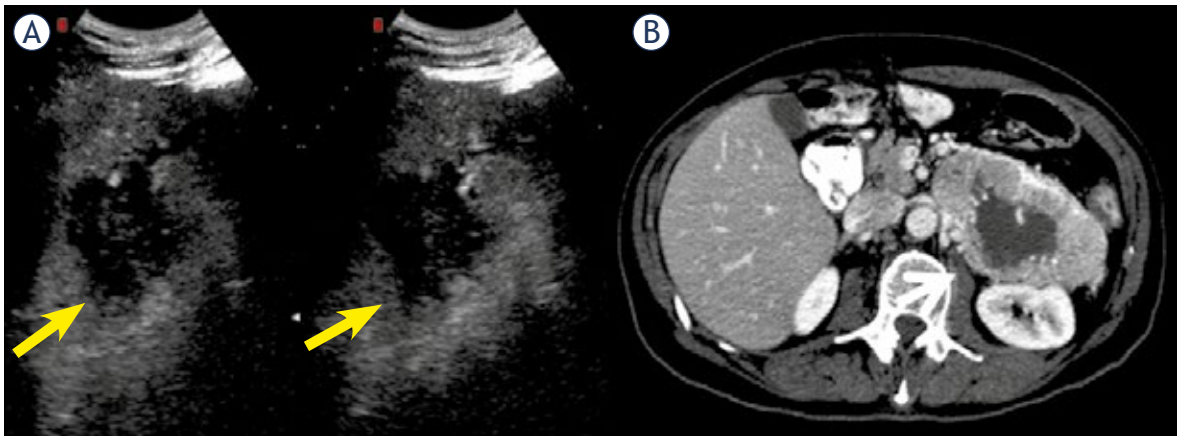

FIGURE 1. A 45 yrs old female: CEUS study of inhomogeneous pancreatic lesion **(A)**, with necrotic central area (arrow). CT **(B)**, during late arterial phase of contrast study shows the same vascular profile (arrow) seeing during CEUS study.

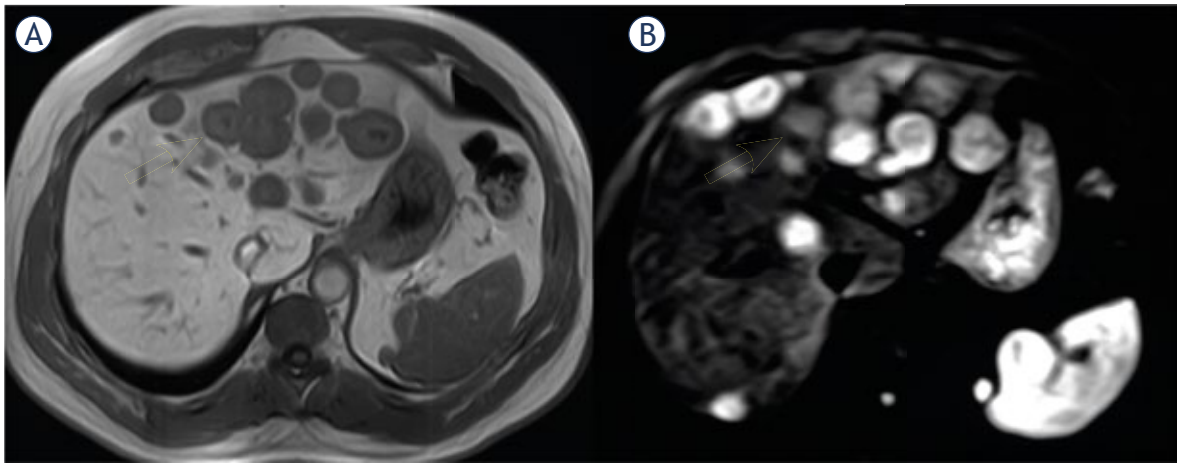

FIGURE 2. A 64 yrs old male with pancreatic NET. Liver metastases in IV, II and III segment, with a "target" appearance (arrow) during hepatobiliary phase of EOB-MR study **(A)** and restricted diffusion (arrow) on b800 s/mm^2**(B)**.

before any liver surgery and for monitoring liver metastases (Figure 2).[11]

The optimization of imaging techniques

The optimization of techniques is mandatory to assess GEP-NETs patients. CT is a widely available technique with high spatial and temporal resolution. Therefore, it represents the most common initial tool to assess suspected abdominal lesions. Contrast-enhanced CT protocols are mandatory for NET imaging. To achieve a good separation of the contrast phases, short scan times and high flow rates of the contrast agent (above 3 ml/s) should be used. Scans before contrast (calcifications), in the arterial phase (typical NET enhancement) and the portal phase should be carried out. Correct timing of the arterial phase is crucial for successful NET imaging. As GEP-NETs and their metastases are often hypervascular, they are easily detected in the early arterial phase of contrast study protocol (Figure 3).[21] For small-bowel tumors, CT enterography or enteroclysis can be performed.[23] The performance of CT is related to the study protocol, as well as the lesion size, location, and contrast with the surrounding tissue.[24,25] MR imaging offers higher intrinsic soft-tissue contrast[22]; moreover, recent advances in the hardware and software have also improved the spatial resolution and acquisition time for each sequence, resulting in shorter breath holds. Furthermore, MR imaging does not use ionizing radiation. Thanks to its capability to provide functional data by diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging, MRI is a valuable tool in oncologic patient as perfusion dual energy CT.[26-30] However,

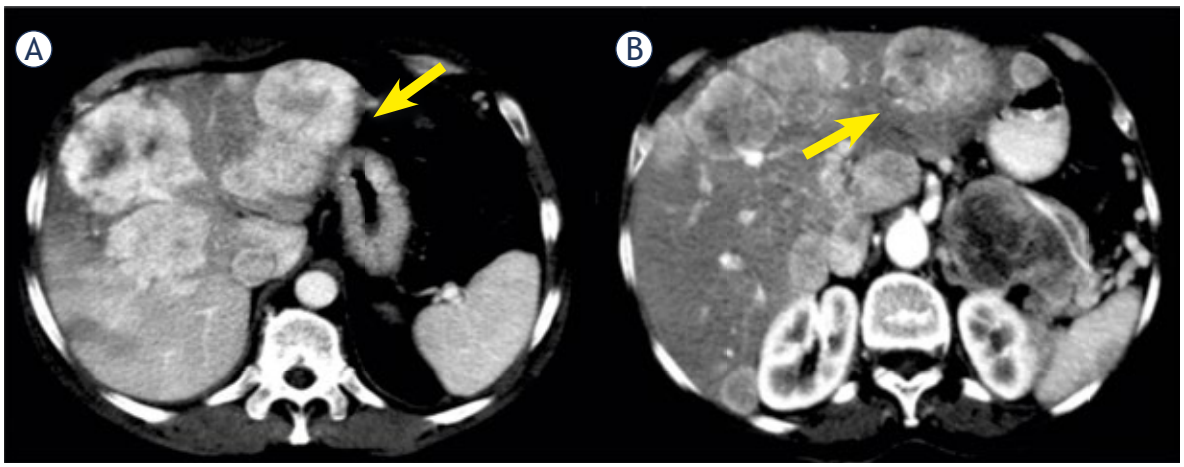

FIGURE 3. A 52 yrs old female with pancreatic NET. Liver metastases show hypervascular appearance (arrow) during arterial phase of contrast study on CT **(A, B)**.

MR imaging is less readily available, is more expensive, and often requires more time and patient cooperation.[22] MR abdominal acquisition protocols for NET imaging should include T1-weigthed and T2-weighted sequences and multiphase contrast enhancement studies, including unenhanced, arterial, venous and delayed phases Nowadays, the inclusion of DWI for the upper abdomen seems to be indispensable.[22] DWI is a relatively mature non-invasive imaging modality that could display functional information without contrast media.[22] DWI signal depends on the water mobility that reflects indirectly tissue biological characteristics. DWI has been applied to liver imaging as an excellent tool for detection and characterization of lesions, increasing clinical confidence and decreasing false positives.[22] Oncology is one of the main fields of application of DWI.[22] Water mobility is restricted in malignant tissue due to the increase of cellular density. Diffusion is quantified by ADC diffusion coeficient. The ADC map is the graphical representation of the ratio of DW signal intensities and its measurements may discriminate between benign and malignant lesions. The ADC measurements are related to the sequence acquisition protocol and suffer from a lack of reproducibility, especially in respiratory triggering techniques.[22] The main technical limits of MR imaging are costs, lack of availability and long examination time.[12]

Detection and localization of the primary tumour

Gastroduodenal neuroendocrine neoplasms

According to Delle Fave *et al.*, gastric neuroendocrine neoplasms (g-NENs) represent the most frequent digestive NENs and are increasingly recognized due to expanding indications of upper gastrointestinal endoscopy.[14] G-NENs may be divided into three types: type 1 and 2 are ECLomas, due to chronic hypergastrinemia, respectively associated with chronic atrophic gastritis (CAG) and Zollinger-Ellison's syndrome; type 3 g-NENs are rare and sporadic tumors not consequent to underlying gastric mucosal abnormality, the latter are mostly single large lesions with high metastatic potential and with high grade (often G3 NEC).[14] Duodenal neuroendocrine neoplasms (d-NENs) may be sporadic or associated with multiple endocrine neoplasia type 1 (MEN-1) and may present with a functional syndrome.[14] Gastroscopy and endoscopic US (EUS) are essential to localize the primary lesion and usually sufficient in small Type I and II g-NENs. Furthermore, the invasiveness of the gastric wall can be assessed with a EUS.[31] In gastric tumours larger than 1 cm and duodenal NETs, EUS is used to detect invasion and regional lymph node metastases.[32] For invasive gastric NETs, all Type III tumours and duodenal NETs staging is performed by CT and MRI.[14]

Ileal NETs

Ileal NETs are usually sporadic and multiple in 26%–30% of cases.[33] At the time of diagnosis hepatic metastases are already present in 20% of cases.[34-36] The lesion is indolent with non-specific symptoms (vague pain, bleeding, intermittent partial bowel obstruction). The classic carcinoid syndrome is present in 6%–30% of patients, and it is associated with hepatic metastases in more than 95% of cases.[37] CT or MR scan are often the preferred imaging tests, and small-bowel distention (enterography or enteroclysis) is desirable. The lesions are small, hypervascular, polypoid; high lesions can appear as asymmetric or concentric bowel wall thickening (Figure 4).[22] More often the radiologist easily detects secondary features, such as desmoplastic reaction in the mesentery and lymphadenopathy with or without calcification, these features are re-

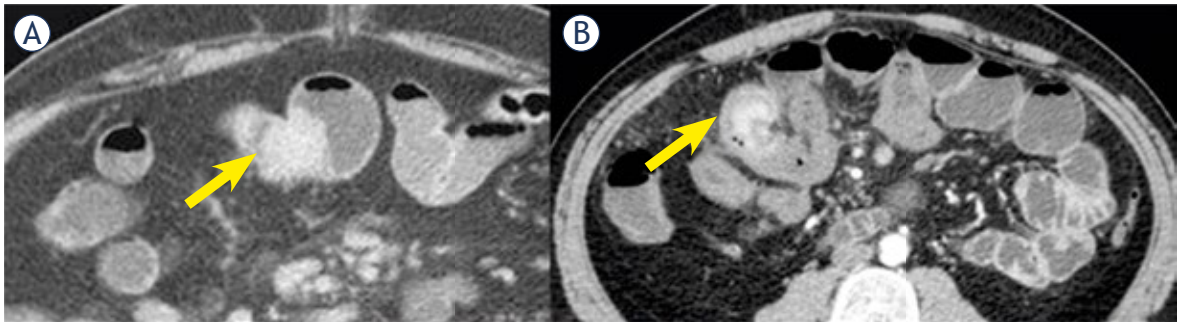

FIGURE 4. A 41 yrs old male. CT enteroclysis examination shows lesion, in **(A)**, as small, hypervascular, polypoid (arrow) and, in **(B)**, as an asymmetric bowel wall thickening (arrow).

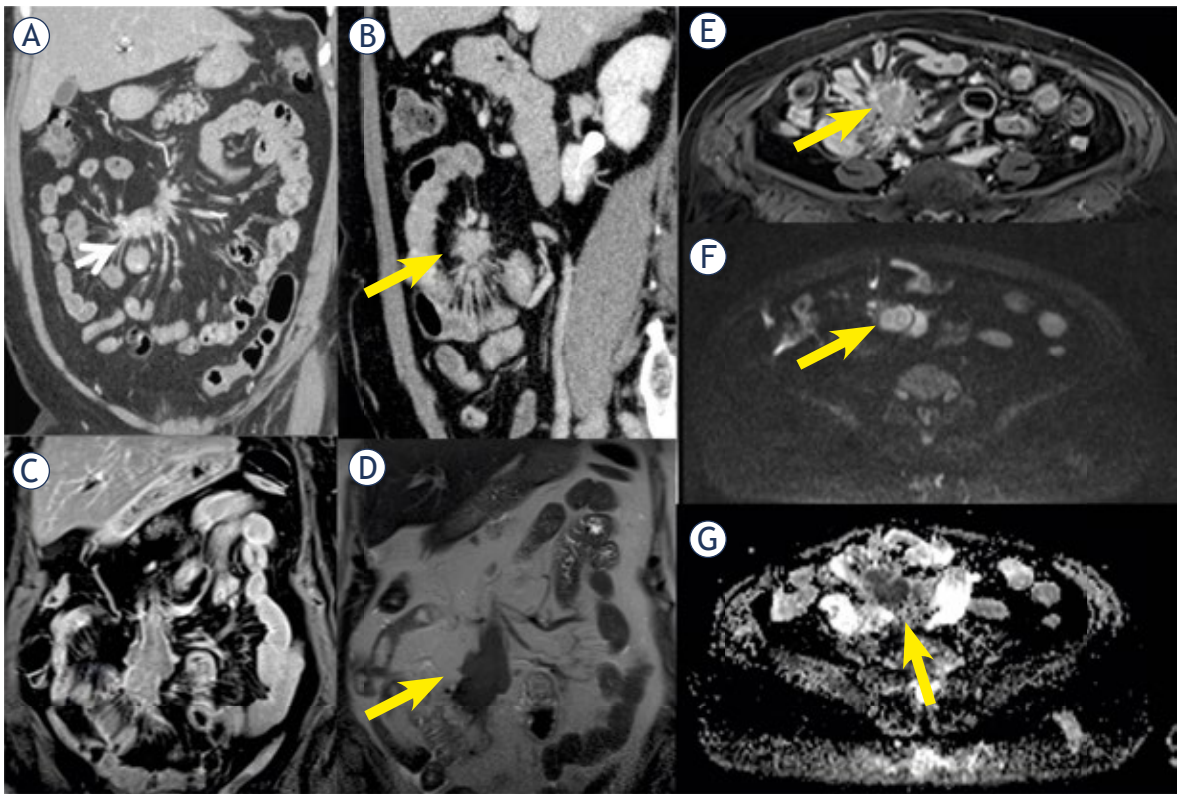

FIGURE 5. A 48 yrs old male with ileal net. CT during portal phase shows **(A**, coronal plane and **B** sagittal plane) desmoplastic reaction in the mesentery and lymphadenopathy (arrow); these features in T1-W post contrast study **(C** and **E** portal phase) show hypointense signal (arrow) and hypintense signal (arrow) in T2- W sequence **(D)** with restricted diffusion (arrow) in b800 s/mm^2 **(F)** and hypointense signal in ADC **(G)** map.

lated to the presence of the primary lesion in the neighboring small-bowel (Figure 5). Some times, the radiologists work in emergency setting with the patient affected by a bowel obstruction, intussusception or ischemia due to desmoplastic response compromising bowel lumen or mesenteric circulation.[12,22,24] Some researches have shown that CT enterography and MR enteroclysis improved sensitivity (100% and 86%–94%, respectively) and specificity (96.2% and 95%– 98%, respectively) for tumor diagnosis.[23,38-40] In addition, MR enterography (MRE) is one of the few imaging modalities that can provide an accurate evaluation of the small-bowel loops, as well as the whole abdominal cavity, without any radiation exposure and at reasonable healthcare costs. Owing to the undoubted advantages, it is realistic to look with a fresh eye at MRE, beyond the well-established role in the intestinal assessment of Crohn's disease (CD) patients. According to ENETS guidelines enteroclysis is beneficial to assess small bowel in patients with NET, in case of failure of CT scan in the localization ofthe primary tumour.[18] Nowadays, thanks to the increasing use of 68Ga-DOTATOC-PET/CT the primary small bowel NET is more frequently detected.[18]

The appendix is the site of GEP- NETs in about 20% of cases, and up to 70% of cases are discovered at appendectomy.[41] These lesions are small and metastases to regional lymph nodes are uncommon, therefore, rarely detected on the basis of imaging findings.[41]

Colorectal NET

Neuroendocrine tumors of the colon are very rare. They involve more commonly the right colon and appear as large lesions (5 cm or more), already metastatic at the time of diagnosis.[36] Rectal NEN are more common than colonic NEN, representing about 11% of all GEP-NET.[36] They are usually small and generally from low to intermediate grade.[19] Typically, rectal NET are single, sub-mucosal tumors, smaller than 1 cm. Metastases occur in tumors larger than 2 cm.[22] EUS evaluates the depth of tumor invasion in the rectal wall and regional

lymph nodes.[42] MR examination is increasingly used to assess local tumor spread and nodes involvement, and to guide surgical management for lesion larger than 1 cm.[19,43] For lesion larger than 2 cm or those with rectal wall invasion on EUS, the spread of disease should be assessed using CT. SRS is not routinely recommended in rectal NETs smaller than 2 cm without invasion of the muscularis propria.[43]

Pancreatic NET

PNETs are the second most common pancreatic cancer, exhibiting a heterogeneous spectrum of clinical symptoms and behaviors.[44] Between 60% and 90% of p-NETs are non-functional and are generally diagnosed at more advanced stages.[4] Imaging is fundamental during the work-up of these patients, for the detection of the primary tumor, its characterization and prognosis determination, for the local and distant assessment, as well as for the evaluation of treatment.[44] Functioning PNETs are generally small (1–2 cm) and manifest as well-defined, hypervascular lesions, owing to their rich capillary network. Non-functioning tumors are larger in size (4 cm) at the time of detection, often well defined, encapsulated and show a heterogeneous enhancement. Rarely, they can be completely cystic, with a hypervascular rim in up to 90% of cases. Malignant tumors often show local invasion into the retroperitoneum and metastases (regional nodes and liver), and they can rarely involve the main pancreatic duct.[22] According to ENETS guideline, PET/CT with 68Ga-labelled somatostatin analogs DOTA-TOC/TATE/NOC is now the method of choice to localize and stage the disease in non-insulinoma P-NETs patients.[4] In addition, functional imaging plays a role in targeted therapy selection.[22] In case of rapid tumor growth in earlier diagnosed G1-G2 tumors, 18-FDG-PET/CT may be considered for the assessement of tumor burden and prognosis.[4] In a small percentage of patients with insulinomas (<5–10%) all conventional imaging studies are negative. Receptor scintigraphy with radio-labelled Glucagon-like peptide-1 (GLP-1) receptor's analogues is a sensitive method to detect insulinomas as they frequently overexpresses this receptor.[4] Unfortunately this method is not routinely available anywhere and it has been mainlyused in research applications. The preoperative imaging assessment of p-NET may establish the anatomical position of the lesion, its relation to the pancreatic duct and the main bile duct, as well as, encasement of the hepatic, splenic and mesenteric artery and vein and the portal vein. When MRI is performed, MR cholangiopancreatography should be included (Figure 6).[45]

EUS is the most advantageous imaging technique to detect pNETs with a sensitivity mean of the 90% (range 77–100%). For insulinomas, the sensitivity is less (84%).[4] Some researches showed that EUS improves sensitivity for the detection of small tumours and multiple lesions in MEN1 or VHL syndromes compared to CT or MRI.[46,47] The primary aims of EUS are to guide a biopsy in order to obtain a tissue sample and also to guide the decision-making process between an enucleation and a Whipple's procedure.[48]

CT is the first-line imaging modality employed in the evaluation of patients with suspected PNETs, allowing the study of the pancreas as well as the assessment of the disease extension. The study protocol should consist of a multiphase imaging, including unenhanced, arterial/pancreatic, venous and delayed phase. The late arterial (30 s) or pancreatic phase (40 s) is mandatory in order to increase the detection of small functioning PNET, in particular insulinoma. Moreover, it also increases the detection of hepatic metastases and assesses the encasement of the hepatic, splenic and mesenteric artery. The venous phase allows to assess the hepatic parenchyma and the encasement of mesenteric and portal vain. The delayed phase is complementary of the all other phases, allowing the detection of delayed enhancement presented by some fibrous tumors.[44] PNETs are expected to be hypervascular, and benign tumours show a homogenous hypervascular pattern followed by early wash-out in the venous phase.[49] Progression towards malignancy is associated with derangement in vessel architecture and function. Although these tumours remain hypervascular, their anarchic vasculature reflects into their less homogenous CEP; delayed contrast enhancement may be considered as a sign of malignancy in pNETs.[50,51] Cappelli *et al.*[49] showed that CEP might preoperatively suggest the behavior of pNETs. Even Takumi *et al.*[52] assessed the relation between contrast-enhanced computed tomography features and tumour aggressiveness, showing that non-hyperattenuating P-NETs during the venous phase were suggestive of G2. In the quantitative analysis, tumor contrast enhancement and tumor-to-pancreas contrast during the venous phase were significantly higher in G1 than in G2 tumors.[52] To improve the conspicuity of pancreatic tumor and reduce radiation dose, Marin *et al.*[53] assessed the low-tube-voltage, high-tube-current CT technique, demonstrating that it improves the enhancement

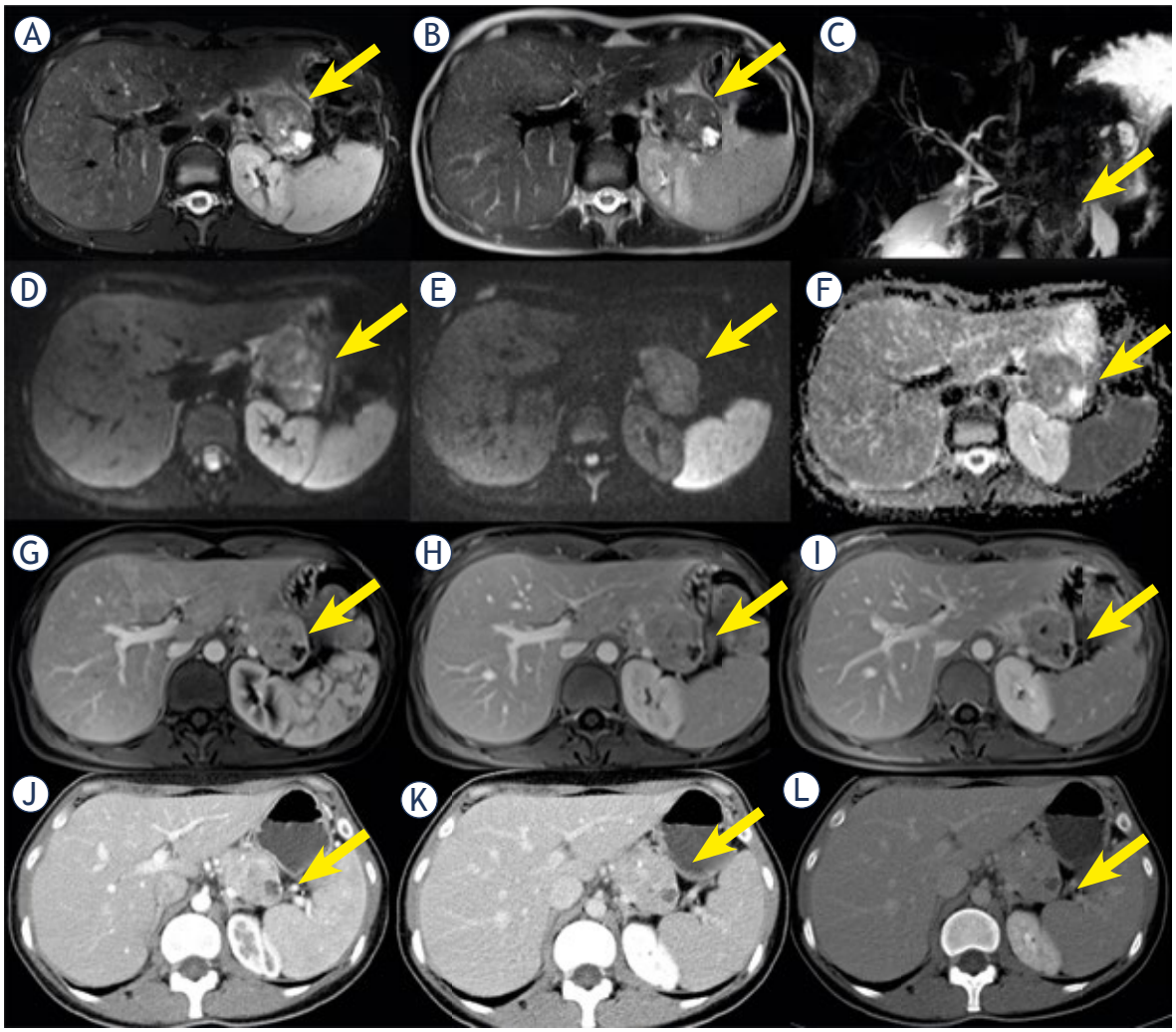

FIGURE 6. A 29 yrs old female with p-Net of pancreatic tail. The lesion shows inhomogeneous signal with cystic component (arrow) on T2-W sequences **(A, B)**. MR cholangiopancreatography **(C)** sequence show its relation to the pancreatic duct and the main bile duct (arrow). The lesion shows restricted diffusion **(D, E, F)** and inhomogeneous contrast enhancement during arterial **(G, J)**, venus **(H, K)** and late **(I, L)** phase as in MR as in CT (arrow).

of the pancreas and peripancreatic vasculature, increasing tumor conspicuity and reducing patient's radiation dose. The use of dual energy CT (DECT) has potential clinical implications for pancreas imaging.[54] However, there are limited data assessing the utility of DECT for other pancreatic masses excluding adenocarcinomas.[55] Potential benefits include the evaluation of enhancement in neuroendocrine tumours. DECT has shown a higher sensitivity for the detection of pancreatic insulinomas compared to conventional CT (95.7 *vs.* 68.8%).[56]

MRI shows higher diagnostic accuracy than CT. For MRI the sensitivity is 93% (range 85–100%) and specificity 88% (range 75–100%).[57] In a recent study, the sensitivity of MRI was similar to that of EUS 95%.[58] The advantages of MRI over CT are:the lack of ionizing radiation and the utilization of gadolinium chelate contrast agents, which have a better safety profile in terms of allergic reactions. Moreover, MRI provides functional data extracted by DWI to evaluate the distribution of water molecules in the interstial space and the blood motion in the capillaries.[59] MR imaging protocol should include: T1-Weigthed (T1-W) and T2-Weigthed (T2-W) sequences, dynamic three-dimensional (3D) sequences before and after cm multi arterial, venous and delayed (> 5 min) acquisitions, DWI and cholangiopancreatic sequences.[44,58] DWI increases the sensitivity for detection of the lesion as well as of the liver metastases. The Apparent Diffusion Coefficient (ADC) value has been recently identified as biomarker of tumor aggressiveness related

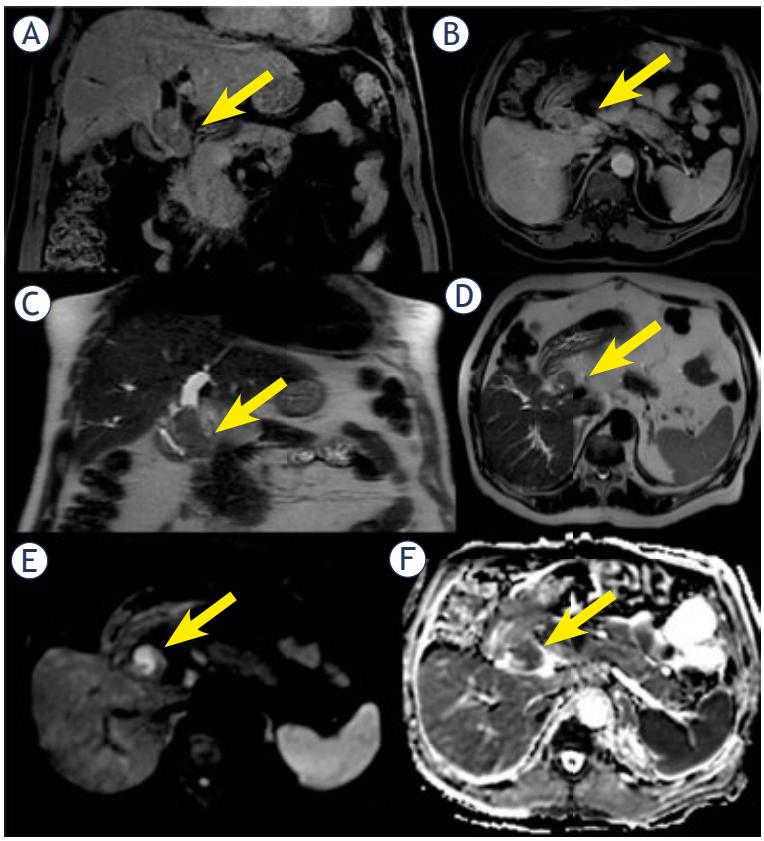

FIGURE 7. A 58 yrs old male wih primitive NET of biliary tree. The lesion shows hypointense signal (arrow) during portal phase of contrast study **(A, B)**, hyperintense signal (arrow) on T2-W sequences **(C, D)** and restricted diffusion (arrow) on DW sequences **(E, F)**.

to the histological grade of PNET: low ADC is a strong predictor of high tumor grade.[44,58] MR cholangiopancreatography, assessing the involvement of the biliary and pancreatic ducts, is useful in the surgical planning and should always precede resection of a pancreatic NET.[58] Hypervascular tumors (typically insulinomas) are often better depicted in T2W with fat suppression sequences, whereas hypovascular tumors are better depicted in T1-W sequences during the arterial phase.[22] Wang *et al.* assessed an inverse correlation between tumor's Ki-67 index on pathology and ADC values, supporting the role of DWI in predicting tumor biology.[60] DCE-MRI should be used to assess microvascular structures.[61,62] The DCE-MRI can be assessed semi-quantitatively or quantitatively. Bol *et al.*[63] evaluated the role of DCE-MRI to assess the therapy in a murine model, showing that DCE-MRI-derived parameters predict peptide uptake better than the "contrast amount-related" parameters. Consequently, DCE-MRI elucidates the correlation between vascular characteristics, peptide delivery and therapy efficacy, and may predict targeting efficiency.[63] Huh *et al.*[64] tested, in a clinical study, DCE-MRI for pancreatic lesions, showing that between pancreatic adenocarcinomas and neuroendocrine tumours, there were significant differences in the Ktrans (0.073 ± 0.058 *vs.* 0.308 ± 0.062, respectively; $p = 0.007$) that represent the contrast rate between the vascular space and the extracellular extravascular space and initial area under time intesitu curve (iAUC) (1.501 ± 0.828 *vs.* 3.378 ± 0.378, respectively; $p = 0.045$).[64] Furthermore, the quantitative values of Ktrans and the contrast rate between the extracellular extravascular space and the vascular space (kep), are helpful for differentiating G2 NET from G1 ones.[65]

Recently, the term of "Radiomics" has been introduced to define a mathematical process to extract innumerable quantitative features from medical images (including each diagnostic technique) with high-throughput computing for diagnosis and prediction.[66] Compared to traditional visual interpretation of medical images, the deep mining of medical images by computer technology from radiomics makes features uptake more efficient, relatively objective and rich in features types. Radiomics is promising for tumor screening, early diagnosis, accurate grading and staging, treatment and prognosis, molecular characteristics and so on.[66,67] De Robertis *et al.* assessed MRI derived whole-tumour histogram analysis parameters in predicting pNEN grade and aggressiveness.[68] They showed that whole-tumour histogram analysis of ADC maps might be helpful in predicting tumour grade, vascular involvement, nodal and liver metastases in panNENs. $ADC_{entropy}$ and $ADC_{kurtosis}$ are the most accurate parameters for identification of panNENs with malignant behaviour.[68]

According to ENETs Consensus Guidelines, CEUS is the suggested technique for the diagnosis of neuroendocrine neoplasms.[4] Although CEUS is not indicated for the detection of focal solid or cystic pancreatic lesions, it improves the characterization of nodules detected on US.[69] So that,according to recommendation 26 of EFSUMB Guidelines, CEUS can be used to distinguish between pancreatic ductal adenocarcinomas and neuroendocrine tumors (Figure 1).[69]

Liver involvement

Primary hepatic NET

Primary hepatic NETS (PHNETs) are extremely rare. When a NET is detected in the liver, great care must be taken to exclude metastasis from an extra-

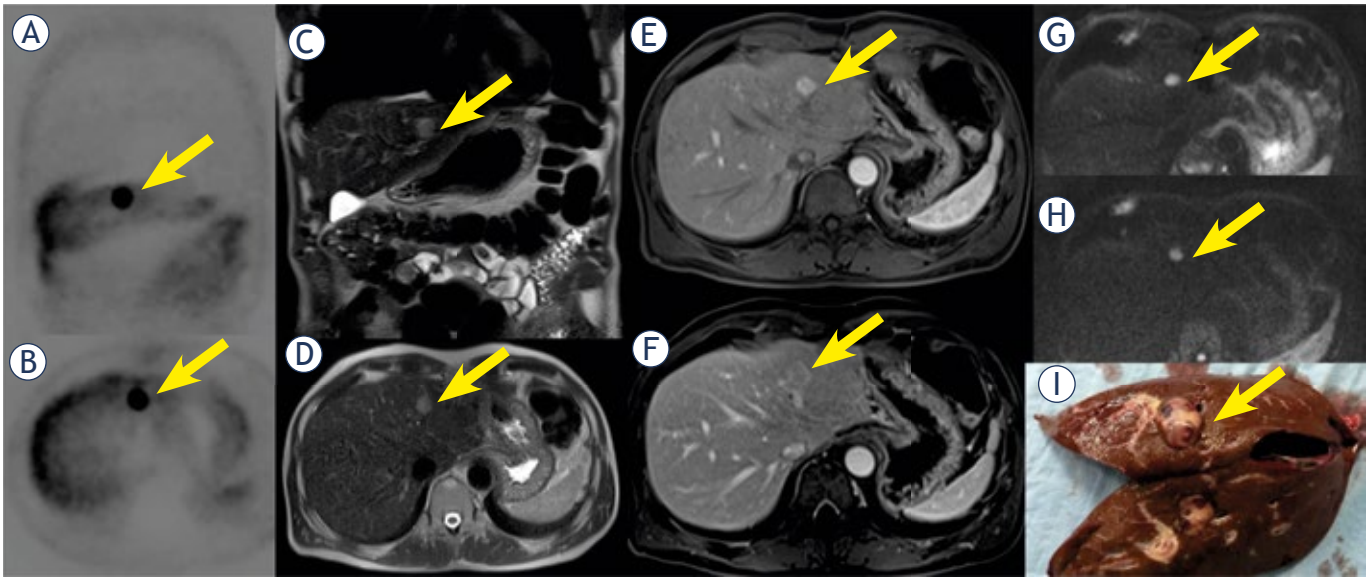

FIGURE 8. A 63 yrs old male with solitary liver lesion. The nodule is detected (arrow) by 68Ga-DOTATOC-PET/CT **(A, B)**, showing hyperintense signal (arrow) in T2-W sequences **(C, D)**. The lesion shows hypervascular appearance (arrow) during arterial phase **(E)** and "target" appearance (arrow) during portal phase **(F)** of contrast study, with restricted diffusion **(G, H)**. In **(I)** it is shown speciemen.

hepatic unknown site.[70] The clinical features and treatment outcomes of PHNETs are still unclear.[70] This tumour occurrs in middle-aged patients and it is more common in women.[71-73] More than 80% of the NETs found in the liver are metastatic and fewer than 150 cases of PHNET have been reported in the literature.[74] Even rarer is the biliary tree involvement (Figure 7).[74-76] The radiologic findings of PHNETs have not been well defined, but the cases reported show that the lesions are typically solid with necrotic components.[71] The cross-sectional imaging features usually consist of a solitary hepatic mass with a diameter of up to 25 cm (Figure 8). The lesion may be solid (60% of cases), partially solid with cystic areas (25% of cases), or mainly cystic and may demonstrate peripheral enhancement after the administration of an iodinated CM. PHNETs have low signal intensity on T1-W and high signal intensity on T2-W and their enhancement characteristics at MR imaging are similar to those at contrast-enhanced CT.[70]

Liver metastases

Approximately 30–80% of GEP-NET will develop synchronous or metachronous liver metastases (NELM).[77] NELM is the most important prognostic factor of GEP-NETs, in fact liver failure is the most common cause of death, followed by bowel obstruction and ischemia, with 5-year overall survival rates are around 50% for those with liver involvement, compared to 70–80% for those without it.[77] Surgery is the most effective approach for the majority of well-differentiated NELM. Due to frequently bilobar and multifocal manifestation of NELM, not more than 20–30% of patients may be candidates for resection with curative intent (Figure 9). Liver transplantation is a therapeutic option in selected patients with unresectable metastases. Moreover, ablative therapies, in addition to surgical resection, can offer improved survival and quality of life at 5 years as compared with patients who do not undergo surgery (70%–90% *vs.* 50%).[78] In this scenario, it is therefore important to identify the exact number, anatomical side and size of NELM, their proximity to vascular and biliary structures, and the volume of the future liver remnant.[77-78] According to Ronot *et al.* MRI is the most accurate imaging modality for NELM detection and characterization. DWI is more sensitive in detecting NELM than T2-W while dynamic gadolinium-enhanced MR sequences should be systematically performed. Gadoxetic acid-enhanced MRI ismore sensitive for detecting liver metastases than conventional MR sequences.[77] Flechsig *et al.* assessed the role of MRI in NELM compared to CT and ^{68}Ga-DOTATOC PET, showing that contrast-enhanced (CE) MRI using Gd-EOB-DTPA in combination with DWI was superior to non-contrast MR-sequences and arterial- and portal-venous phase CT in lesion conspicuity, likewise CE-MRI

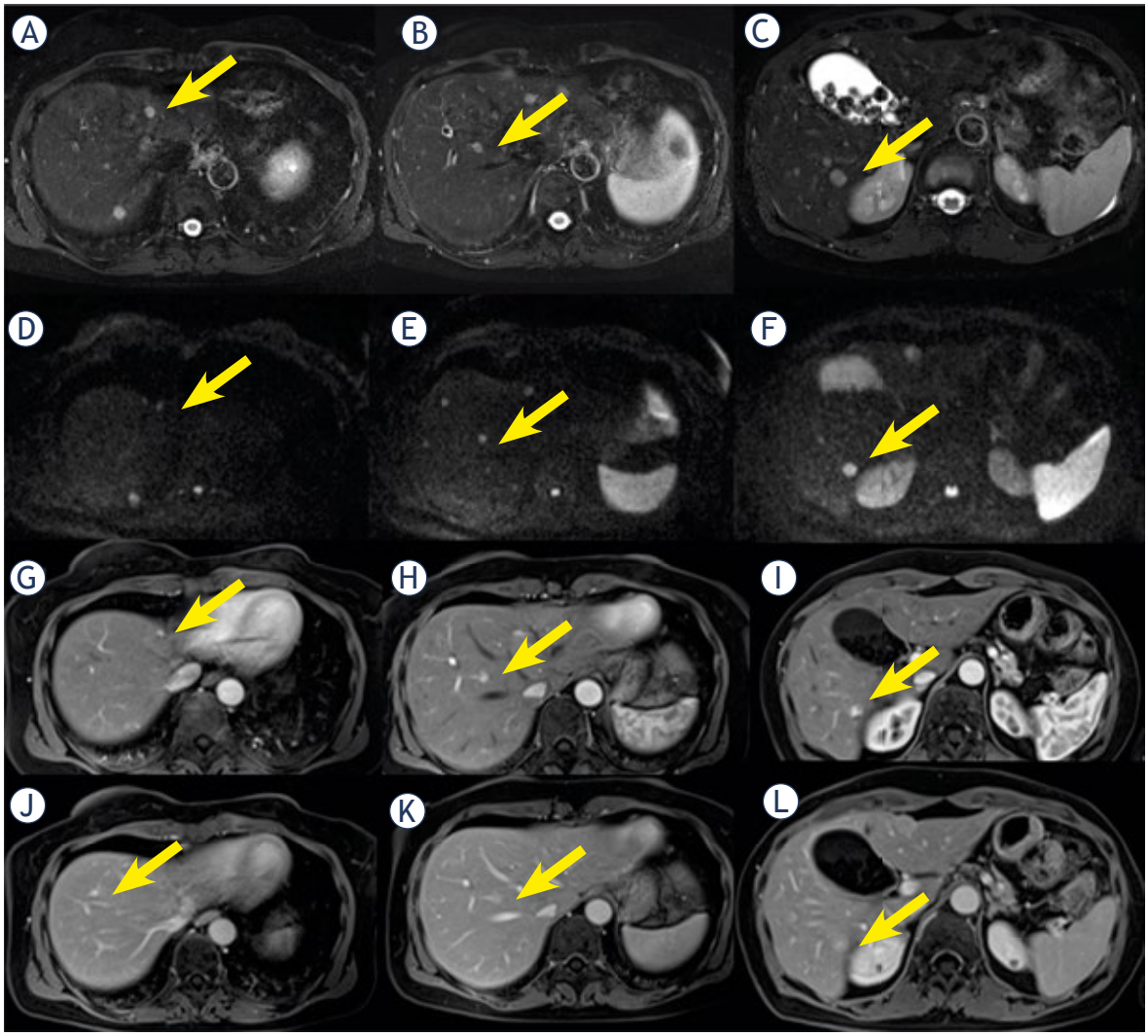

FIGURE 9. A 46 yrs old female with p-Net and bilobar liver metastases. The metastases show hyperintense signal (arrow) in T2-W sequences **(A, B ,C)**, restricted diffusion (arrow) in DW sequences **(D, E, F)**, hypervascular appearance (arrow) during arterial phase of contrast study **(G, H, I)** and hyperintense signal (arrow) during portal phase of contrast study **(J, K, L)**.

was superior to all other modalities concerning detectability of lesions.[78] Therefore, the researchers think that in the future PET/MR might replace the current standards of PET/CT or octeriotide scintigraphy/SPECT in liver metastasis detection of GEP-NET patients.[78] Up to the present, the best modality to detect vascular and biliary invasion is still unclear (Figure 10). CT and MRI should be considered the best imaging modalities in preoperatively detecting of vascular and biliary invasion.[77] According to Granata *et al.*, in the work-up of patients with liver colorectal metastases, the different phases should be considered by the radiologist; the same should be evaluated in the work-up of NELM.[26] In particular, in the preoperative setting, the radiologist should assess the functionality of the future liver remnant[26]; MRI with EOB may be a promising tool to assess this parameter, in order to avoid hepatic failure post surgery or ablative therapies.[26]

Treatment and follow-up

The aim of treatment should be curative when possible. The extention of the tumour, its metastases, histological grade and functional profile should be assessed before planning treatment**.** In fact**,** the choice of the therapy is related to symptoms, stage of disease, degree of uptake of radionuclide and histological features of NEN.[21]

According to ENETS guidelines, surgery with curative intent and/or locoregional or ablative

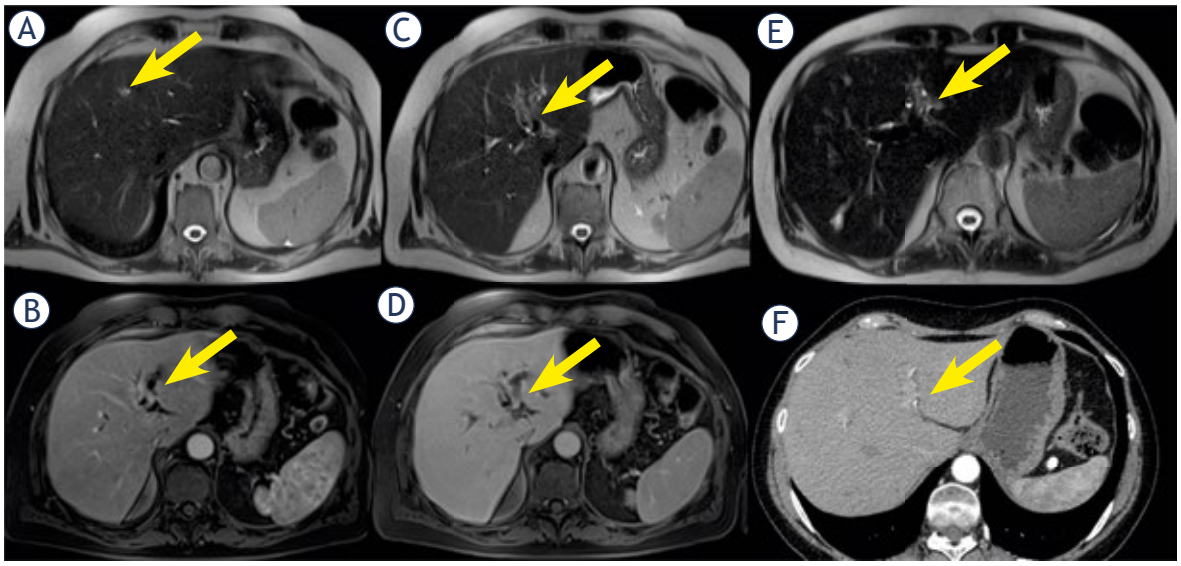

FIGURE 10. Man 51 y with p-Net and peribiliary metastasis. The lesion is hyperintense (arrow) in T2-W sequences **(A, C, E)** with progressive contrast enhancement (arrow) during contrast study **(B, D, F)** both in MR and in CT.

therapies should be considered at initial diagnosis and during the course of disease as an alternative approach to systemic therapies. Debulking surgery is indicated in patients with functional lesion with predominant liver disease for syndrome control. Liver transplantation is indicated in highly selected patients, with functional syndromes demonstrating early resistance to medical therapy. SSA, octreotide and lanreotide, are effective drugs for syndrome control in functional NET. SSA is recommended as a first-line therapy in midgut NET and can be considered in pancreatic NET as a first-line therapy (up to a Ki-67 of 10%). IFN-alpha is an established and approved therapy for syndrome control, and primarily used as second-line therapy in refractory carcinoid syndrome or functional pancreatic NET. Everolimus and sunitinib are approved antiproliferative therapies in progressive pancreatic NET, and they are one of the different options next to SSA and systemic chemotherapy. In G3 NEC, platinum-based chemotherapy is recommended as a first-line therapy. PRRT is recommended after failure of medical therapy.[4] There is no consensus on the optimal follow-up for completely resected gastroenteropancreatic neuroendocrine tumors. Published guidelines for follow-up are complex and emphasize closer surveillance in the first 3 years after resection. Neuroendocrine tumors have a different pattern and timescale of recurrence, and thus require more practical and tailored follow-up.[80,81] According to ENETS guidelines, in the follow-up of patients the pathological grade should be considered; for Grade1:US, CT, or MRI at 6 and 12 month (mo), then yearly or longer; octreoscan (or gallium-68–based PET) at baseline and every 2 y. Grade 2-3: US, CT, or MRI every 3 mo indefinitely; octreoscan (or gallium-68–based PET) at 3 mo and yearly.[80,81] Anyway, follow-up for NETs requires a multidisciplinary approach. CT or MR imaging plays a central role in long-term assessment after surgery. The follow-up protocol includes imaging studies every 6 months for the 1st year and then at yearly intervals if negative. The follow-up interval is shorter (3 months) for intermediate- and high-grade NETs and in patients undergoing chemotherapy or biologic therapies.[21] During follow-up, CT is the standard imaging method, to detect recurrent disease after surgery and locally ablative procedures, and to monitor systemic therapy. In young patients, MRI is generally preferred to CT.[45] RECIST (Response Evaluation Criteria In Solid Tumours) are utilized for therapy monitoring in general oncology and rely on morphological imaging to measure the longest diameter of a set of chosen target lesions.[82] The currently used criteria (RECIST 1.1) state that a maximum of two lesions per organ and five in total should be measured.[82] Some issues still remain in the application of RECIST to monitor NETs' therapy due to the fact that tumours have generally slow-growth, can have cystic components and that the various available therapies, especially the new targeted agents, such as everolimus and sunitinib, generally do not result in tumour shrinkage

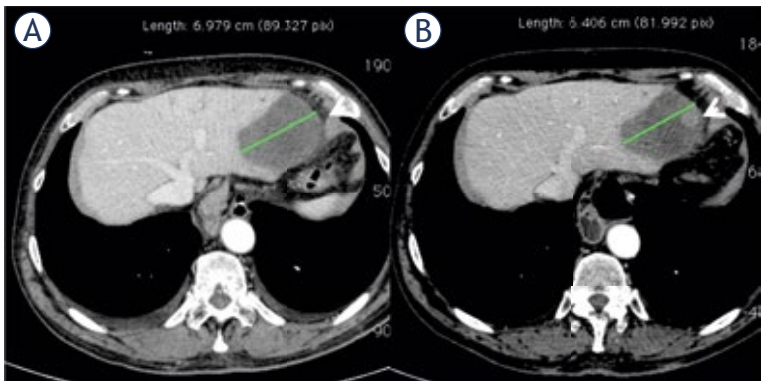

FIGURE 11. Nodule in nodule appearance (arrow) during follow-up of p-NET, indicating progressive disease.

but rather in stabilization of the disease. RECIST is, therefore, less suited for therapy monitoring of NETs than the one of other cancers.[45] Therefore, the radiologists should be aware of patients therapy in order to evaluate the real efficacy of the treatment. They should consider that the common and expected imaging response pattern of metastatic GEP-NETs to somatostatin analogues is a stable disease with no changes in tumor size. The typical imaging response pattern to targeted agents (Sunitinib and everolimus) is a decrease in tumor attenuation and enhancement and a stable to mild decrease in tumor size. Sometimes tumors have decreased density suggestive of response to treatment but show an increased size, which may lead to a misinterpretation of tumor progression according to size criteria (Figure 11). Sometimes target therapies cause intratumoral hemorrhage, which can result in an increase of density with a variable size change. If tumor size and density are increased by hemorrhage, an accurate interpretation of treatment response is difficult and may be confused with progression, even when new criteria, such as the Choi criteria and mRECIST, are used.[83]

Conclusions

NETs are a considerable diagnostic challenge since their clinical presentation is protean, nonspecific and usually late, often when hepatic metastases are already evident. An effective diagnosis requires a multimodal approach that combines evaluation of clinical symptoms, hormone levels, radiological and nuclear imaging, and histological confirmation.

The radiologists are important members of the multidisciplinary NET team both in the assessment of tumor staging and in the treatment follow up. In diagnostic work-up of NETs two critical issues are present: firstly the need to identify tumor presence and secondly to define the primary site and to assess regional and distant metastases. The most appropriate imaging technique depends on the type of neuroendocrine tumour.

The role of somatostatin receptor-based ^{68}Ga-PET–CT imaging is well established and is recommended for diagnosis and follow-up of NETs. MRI of the liver with hepatocyte-specific contrast media and DWI areused to detect liver metastases with high sensitivity. MRI of the liver is highly recommended before any liver surgery and for monitoring liver metastases. Enteroclysis-CT or MR is mandatory to assess small bowel in patients with NET. PET/CT with 68Ga-labelled somatostatin analogs DOTA-TOC/TATE/NOC is the method of choice to fully stage and localize the extent of disease in patients with non-insulinoma P-NETs. The preoperative imaging assessment of p-NET needs to establish the anatomical position of the lesion, its relation to the pancreatic duct and the main bile duct, as well as the encasement of the hepatic, splenic and mesenteric artery and vein and the portal vein. The treatment follow-up requires a multidisciplinary approach, including biochemical (chromogranin A, hormones, vasoactive amines), radiologic, and histologic investigations and an important role is assumed by radiologist. CT or MR imaging plays a central role in long-term assessment after surgery. RECIST is less suited for therapy monitoring of NETs than of other cancers.

References

1. Fraenkel M, Kim MK, Faggiano A, Valk GD. Epidemiology of gastroenteropancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol* 2012; **26:** 691-703. doi: 10.1016/j.bpg.2013.01.006

2. Oberg K, Akerström G, Rindi G, Jelic S; ESMO Guidelines Working Group. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21 (Suppl 5):** v223-7. doi: 10.1093/annonc/mdq192

3. Modlin IM, Moss SF, Chung DC, Jensen RT, Snyderwine E. Priorities for improving the management of gastroenteropancreatic neuroendocrine tumors. *J Natl Cancer Inst* 2008; **100:** 1282-9. doi: 10.1093/jnci/djn275

4. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS Consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine Tumors. *Neuroendocrinology* 2016; **103:** 153-71. doi: 10.1159/000443171

5. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS Consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016; **103:** 172-85. doi: 10.1159/000443167

6. Sundin A. Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol* 2012; **26:** 803-18. doi: 10.1016/j.bpg.2012.12.004

7. Yu R, Wachsman A. Imaging of neuroendocrine tumors: indications, interpretations, limits, and pitfalls. *Endocrinol Metab Clin North Am* 2017; **46:** 795-814. doi: 10.1016/j.ecl.2017.04.008

8. Rockall AG, Reznek RH. Imaging of neuroendocrine tumours (CT/MR/US). *Best Pract Res Clin Endocrinol Metab* 2007; **21:** 43-68. doi: 10.1016/j.beem.2007.01.003

9. Gatto F, Hofland LJ. The role of somatostatin and dopamine D2 receptors in endocrine tumors. *Endocr Relat Cancer* 2011; **18:** R233-R251. doi: 10.1530/ERC-10-0334

10. Rust E, Hubele F, Marzano E, Goichot B, Pessaux P, Kurtz JE, et al. Nuclear medicine imaging of gastro-entero-pancreatic neuroendocrnne tumors. The key role of cellular differentiation and tumor grade: from theory to clinical practice. *Cancer Imaging* 2012; **12:** 173-84. doi: 10.1102/1470-7330.2012.0026

11. Auernhammer CJ, Spitzweg C, Angele MK, Boeck S, Grossman A, Nölting S, et al. Advanced neuroendocrine tumours of the small intestine and pancreas: clinical developments, controversies, and future strategies. *Lancet Diabetes Endocrinol* 2018; **6:** 404-15. doi: 10.1016/S2213-8587(17)30401-1

12. Bodei L, Sundin A, Kidd M, Prasad V, Modlin IM. The status of neuroendocrine tumor imaging: from darkness to light? *Neuroendocrinology* 2015; **101:** 1-17. doi: 10.1159/000367850.

13. Sundin A, Arnold R, Baudin E, Cwikla JB, Eriksson B, Fanti S, et al. ENETS Consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine & hybrid imaging. *Neuroendocrinology* 2017; **105:** 212-44. doi: 10.1159/000471879

14. Delle Fave G, O'Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, et al; Vienna Consensus conference participants. ENETS consensus guidelines update for gastroduodenal neuroendocrine neoplasms. *Neuroendocrinology* 2016; **103:** 119-24. doi: 10.1159/000443168

15. Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, et al. ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine zumors and neuroendocrine carcinomas. *Neuroendocrinology* 2016; **103:** 186-94. doi: 10.1159/000443172

16. Klöppel G, Couvelard A, Perren A, Komminoth P, McNicol AM, Nilsson O, et al. Mallorca consensus conference participants; European Neuroendocrine Tumor Society. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. *Neuroendocrinology* 2009; **90:** 162-6. doi: 10.1159/000182196

17. O'Toole D, Kianmanesh R, Caplin M. ENETS 2016 consensus guidelines for the management of patients with digestive neuroendocrine tumors: an update. *Neuroendocrinology* 2016; **103:** 117-8. doi: 10.1159/000443169

18. Niederle B, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U, et al. ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. *Neuroendocrinology* 2016; **103:** 125-38. doi: 10.1159/000443170

19. Ramage JK, De Herder WW, Delle Fave G, Ferolla P, Ferone D, Ito T, et al. ENETS consensus guidelines update for colorectal neuroendocrine neoplasms. *Neuroendocrinology* 2016; **103:** 139-43. doi: 10.1159/000443166

20. Etchebehere EC, de Oliveira Santos A, Gumz B, Vicente A, Hoff PG, Corradi G, et al. 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. *J Nucl Med* 2014; **55:** 1598-604. doi: 10.2967/jnumed.114.144543

21. Sahani DV, Bonaffini PA, Fernández-Del Castillo C, Blake MA. Gastroenteropancreatic neuroendocrine tumors: role of imaging in diagnosis and management. *Radiology* 2013; **266:** 38-61. doi: 10.1148/radiol.12112512

22. Baumann T, Rottenburger C, Nicolas G, Wild D. Gastroenteropancreatic neuroendocrine tumours (GEP-NET) - Imaging and staging. *Best Pract Res Clin Endocrinol Metab* 2016; **30:** 45-57. doi: 10.1016/j.beem.2016.01.003

23. Kamaoui I, De-Luca V, Ficarelli S, Mennesson N, Lombard-Bohas C, Pilleul F. Value of CT enteroclysis in suspected small-bowel carcinoid tumors. *AJR Am J Roentgenol* 2010; **194:** 629-33. doi: 10.2214/AJR.09.2760

24. Tan EH, Tan CH. Imaging of gastroentero- pancreatic neuroendocrine tumors. *World J Clin Oncol* 2011; **2:** 28-43. doi: 10.5306/wjco.v2.i1.28

25. Woodard PK, Feldman JM, Paine SS, Baker ME. Midgut carcinoid tumors: CT findings and biochemical profiles. *J Comput Assist Tomogr* 1995; **19:** 400-5.

26. Granata V, Fusco R, Avallone A, Catalano O, Piccirillo M, Palaia R, et al. A radiologist's point of view in the presurgical and intraoperative setting of colorectal liver metastases. *Future Oncol* 2018; **14:** 2189-206. doi: 10.2217/fon-2018-0080

27. Granata V, Fusco R, Catalano O, Avallone A, Palaia R, Botti G, et al. Diagnostic accuracy of magnetic resonance, computed tomography and contrast enhanced ultrasound in radiological multimodality assessment of peribiliary liver metastases. *PLoS One* 2017; **12:** e0179951. doi: 10.1371/journal.pone.0179951

28. Granata V, Fusco R, Catalano O, Avallone A, Leongito M, Izzo F, et al. Peribiliary liver metastases MR findings. *Med Oncol* 2017; **34:** 124. doi: 10.1007/s12032-017-0981-7

29. Granata V, Fusco R, Catalano O, Filice S, Avallone A, Piccirillo M, et al. Uncommon neoplasms of the biliary tract: radiological findings. *Br J Radiol* 2017; **90:** 20160561. doi: 10.1259/bjr.20160561

30. Granata V, Cascella M, Fusco R, dell'Aprovitola N, Catalano O, Filice S, et al. Immediate adverse reactions to Gadolinium-Based MR contrast media: A retrospective analysis on 10,608 examinations. *Biomed Res Int* 2016; **2016:** 3918292. doi: 10.1155/2016/3918292

31. Kulke MH, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas* 2010; **39:** 735-52. doi: 10.1097/MPA.0b013e3181ebb168

32. Cambruzzi E, Azeredo AM, Kronhart A, Foltz KM, Zettler CG, Pêgas KL. The presence of metastases in regional lymph nodes is associated with tumor size and depth of invasion in sporadic gastric adenocarcinoma. *Arq Bras Cir Dig* 2014; **27:** 18-21. doi: 10.1590/S0102-67202014000100005

33. Scherübl H, Jensen RT, Cadiot G, Stölzel U, Klöppel G. Neuroendocrine tumors of the small bowels are on the rise: Early as- pects and management. *World J Gastroin- test Endosc* 2010; **2:** 325-34. doi: 10.4253/wjge.v2.i10.325

34. Oberg K, Castellano D. Current knowledge on diagnosis and staging of neuroendocrine tumors. *Cancer Metastasis Rev* 2011; **30 (Suppl 1):** 3-7. doi: 10.1007/s10555-011-9292-1

35. Turaga KK, Kvols LK. Recent progress in the understanding, diagnosis, and treatment of gastroenteropancreatic neuroendocrine tumors. *CA Cancer J Clin* 2011; **61:** 113-32. doi: 10.3322/caac.20097

36. Chang S, Choi D, Lee SJ, Lee WJ, Park MH, Kim SW, et al. Neuro-endocrine neoplasms of the gastrointestinal tract: classification, pathologic basis, and imaging features. *RadioGraphics* 2007; **27:** 1667-79. doi: 10.1148/rg.276075001

37. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; **97:** 934-59. doi: 10.1002/cncr.11105

38. Masselli G, Polettini E, Casciani E, Bertini L, Vecchioli A, Gualdi G. Small-bowel neo- plasms: prospective evaluation of MR en- teroclysis. *Radiology* 2009; **251:** 743-50. doi: 10.1148/radiol.2513081819

39. Van Weyenberg SJ, Meijerink MR, Jacobs MA, Van der Peet DL, Van Kuijk C, Mulder CJ, et al. MR enteroclysis in the diagno- sis of small-bowel neoplasms. *Radiology* 2010; **254:** 765-73. doi: 10.1148/radiol.09090828

40. Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, et al. World Federation for Ultrasound in Medicine; European Federation of Societies for Ultrasound. Guidelines and good clinical practice recommendations for Contrast Enhanced Ultrasound (CEUS) in the liver - update 2012: A WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultrasound Med Biol* 2013; **39:** 187-210. doi: 10.1016/j.ultrasmedbio.2012.09.002

41. Shapiro R, Eldar S, Sadot E, Papa MZ, Zip- pel DB. Appendiceal carcinoid at a large tertiary center: pathologic findings and long-term follow-up evaluation. *Am J Surg* 2011; **201:** 805-8. doi: 10.1016/j.amjsurg.2010.04.016

42. Kobayashi K, Katsumata T, Yoshizawa S, Sada M, Igarashi M, Saigenji K, et al. Indications of endoscopic polypectomy for rectal carcinoid tumors and clinical use- fulness of endoscopic ultrasonography. *Dis Colon Rectum* 2005; **48:** 285-91. doi: 10.1007/s10350-004-0765-y

43. Anthony LB, Strosberg JR, Klimstra DS, Maples WJ, O'Dorisio TM, Warner RR, et al. The NANETS consensus guidelines for the diagnosis and management of gastro- intestinal neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum. *Pancreas* 2010; **39:** 767-74. doi: 10.1097/MPA.0b013e3181ec1261

44. Dromain C, Déandréis D, Scoazec JY, Goere D, Ducreux M, Baudin E, et al. Imaging of neuroendocrine tumors of the pancreas. *Diagn Interv Imaging* 2016; **97:** 1241-57. doi: 10.1016/j.diii.2016.07.012

45. van Essen M, Sundin A, Krenning EP, Kwekkeboom DJ. Neuroendocrine tumours: the role of imaging for diagnosis and therapy. *Nat Rev Endocrinol* 2014; **10:** 102-14.

46. Ueno N, Tomiyama T, Tano S, Wada S, Aizawa T, Kimura K, et al. Utility of endoscopic ultrasonography with color Doppler function for the diagnosis of islet cell tumor. *Am J Gastroenterol* 1996; **91:** 772e6. doi: 10.1038/nrendo.2013.246

47. Rösch T, Braig C, Gain T, Feuerbach S, Siewert JR, Schusdziarra V, et al. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography, and angiography. *Gastroenterology* 1992; **102:** 188e99. doi: 10.1016/0016-5085(92)91800-j

48. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* 2012; **61:** 6-32. doi: 10.1136/gutjnl-2011-300831

49. Cappelli C, Boggi U, Mazzeo S, Cervelli R, Campani D, Funel N, et al. Contrast enhancement pattern on multidetector CT predicts malignancy in pancreatic endocrine tumours. *Eur Radiol* 2015; **25:** 751-9. doi: 10.1007/s00330-014-3485-2

50. Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. *Nat Rev Cancer* 2003; **3:** 401-10. doi: 10.1038/nrc1093

51. Koito K, Namieno T, Nagakawa T, Morita K. Delayed enhancement of islet cell carcinoma on dynamic computed tomography: a sign of its malignancy. *Abdom Imaging* 1997; **22:** 304-6.

52. Takumi K, Fukukura Y, Higashi M, Ideue J, Umanodan T, Hakamada H, et al. Pancreatic neuroendocrine tumors: Correlation between the contrast-enhanced computed tomography features and the pathological tumor grade. *Eur J Radiol* 2015; **84:** 1436-43. doi: 10.1016/j.ejrad.2015.05.005

53. Marin D, Nelson RC, Barnhart H, Schindera ST, Ho LM, Jaffe TA, et al. Detection of pancreatic tumors, image quality, and radiation dose during the pancreatic parenchymal phase: effect of a low-tube-voltage, high-tube-current CT technique-preliminary results. *Radiology* 2010; **256:** 450-9. doi: 10.1148/radiol.10091819

54. Granata V, Fusco R, Catalano O, Setola SV, de Lutio di Castelguidone E, Piccirillo M, et al. Multidetector computer tomography in the pancreatic adenocarcinoma assessment: an update. *Infect Agent Cancer* 2016; **11:** 57. doi: 10.1186/s13027-016-0105-6

55. George E, Wortman JR, Fulwadhva UP, Uyeda JW, Sodickson AD. Dual energy CT applications in pancreatic pathologies. *Br J Radiol* 2017; **90:** 20170411. doi: 10.1259/bjr.20170411

56. Lin XZ, Wu ZY, Tao R, Guo Y, Li JY, Zhang J, et al. Dual energy spectral CT imaging of insulinoma-Value in preoperative diagnosis compared with conventional multi-detector CT. *Eur J Radiol* 2012; **81:** 2487-94. doi: 10.1016/j.ejrad.2011.10.028

57. Van Binnebeek S, Vanbilloen B, Baete K, Terwinghe C, Koole M, Mottaghy FM, et al. Comparison of diagnostic accuracy of (111)In-pentetreotide SPECT and (68)Ga-DOTATOC PET/CT: a lesion-by-lesion analysis in patients with metastatic neuroendocrine tumours. *Eur Radiol* 2016; **26:** 900-9. doi: 10.1007/s00330-015-3882-1

58. Caramella C, Dromain C, De Baere T, Boulet B, Schlumberger M, Ducreux M, et al. Endocrine pancreatic tumours: which are the most useful MRI sequences? *Eur Radiol* 2010; **20:** 2618-27. doi: 10.1007/s00330-010-1840-5

59. Oberg KE, Reubi JC, Kwekkeboom DJ, Krenning EP. Role of somatostatins in gastroenteropancreatic neuroendocrine tumor development and therapy. *Gastroenterology* 2010; **139:** 742-53, 753.e1. doi: 10.1053/j.gastro.2010.07.002

60. Wang Y, Chen ZE, Yaghmai V, Nikolaidis P, McCarthy RJ, Merrick L, et al. Diffusion-weighted MR imaging in pancreatic endocrine tumors correlated with histopathologic characteristics. *J Magn Reson Imaging* 2011; **33:** 1071-9. doi: 10.1002/jmri.22541

61. Devries AF, Griebel J, Kremser C, Judmaier W, Gneiting T, Kreczy A, Ofner D, Pfeiffer KP, Brix G, Lukas P. Tumor microcirculation evaluated by dynamic magnetic resonance imaging predicts therapy outcome for primary rectal carcinoma. *Cancer Res* 2001; **61:** 2513-6.

62. DeVries AF, Kremser C, Hein PA, Griebel J, Krezcy A, Ofner D, et al. Tumor microcirculation and diffusion predict therapy outcome for primary rectal carcinoma. *Int J Radiat Oncol Biol Phys* 2003; **56:** 958-65. doi: 10.1016/s0360-3016(03)00208-6

63. Bol K, Haeck JC, Groen HC, Niessen WJ, Bernsen MR, de Jong M, et al. Can DCE-MRI explain the heterogeneity in radiopeptide uptake imaged by SPECT in a pancreatic neuroendocrine tumor model? *PLoS One* 2013; **8:** e77076. doi: 10.1371/journal.pone.0077076

64. Huh J, Choi Y, Woo DC, Seo N, Kim B, Lee CK, et al. Feasibility of test-bolus DCE-MRI using CAIPIRINHA-VIBE for the evaluation of pancreatic malignancies. *Eur Radiol* 2016; **26:** 3949-56. doi: 10.1007/s00330-016-4209-6

65. Zhao W, Quan Z, Huang X, Ren J, Wen D, Zhang G, et al. Grading of pancreatic neuroendocrine neoplasms using pharmacokinetic parameters derived from dynamic contrast-enhanced MRI. *Oncol Lett* 2018; **15:** 8349-56. doi: 10.3892/ol.2018.8384

66. Li Q, Ye ZX. [Radiomics: the process and applications in tumor research]. *Zhonghua Zhong Liu Za Zhi* 2018; **40:** 801-4. doi: 10.3760/cma.j.issn.0253-3766.2018.11.001

67. Napel S, Mu W, Jardim-Perassi BV, Aerts HJWL, Gillies RJ. Quantitative imaging of cancer in the postgenomic era: Radio(geno)mics, deep learning, and habitats. *Cancer* 2018; **124:** 4633-49. doi: 10.1002/cncr.31630

68. De Robertis R, Maris B, Cardobi N, Tinazzi Martini P, Gobbo S, Capelli P, et al. Can histogram analysis of MR images predict aggressiveness in pancreatic neuroendocrine tumors? *Eur Radiol* 2018; **28:** 2582-91. doi: 10.1007/s00330-017-5236-7

69. Sidhu PS, Cantisani V, Dietrich CF, Gilja OH, Saftoiu A, Bartels E, et al. The EFSUMB guidelines and recommendations for the clinical practice of Contrast-Enhanced Ultrasound (CEUS) in Non-c hepatic applications: Update 2017 (Long Version). *Ultraschall Med* 2018; **39:** e2-e44. doi: 10.1055/s-0044-101254

70. Wang LX, Liu K, Lin GW, Jiang T. Primary hepatic neuroendocrine tumors: comparing CT and MRI features with pathology. *Cancer Imaging* 2015; **15:** 13. doi: 10.1186/s40644-015-0046-0

71. Tan Y, Xiao EH. Rare hepatic malignant tumors: dynamic CT, MRI, and clinicopathologic features: with analysis of 54 cases and review of the literature. *Abdom Imaging* 2013; **38:** 511-26. doi: 10.1007/s00261-012-9918-y

72. Rückert RI, Rückert JC, Dörffel Y, Rudolph B, Müller JM. Primary hepatic neuroendocrine tumor: successful hepatectomy in two cases and review of the literature. *Digestion* 1999; **60:** 110-6. doi: 10.1159/000007635

73. Iwao M, Nakamuta M, Enjoji M, Kubo H, Fukutomi T, Tanabe Y, et al. Primary hepatic carcinoid tumor: case report and review of 53 cases. *Med Sci Monit* 2001; **7:** 746-50.

74. Li W, Zhuang BW, Wang Z, Liao B, Hong LY, Xu M, et al. Case report of contrast-enhanced ultrasound features of primary hepatic neuroendocrine tumor: A CARE-Compliant Article. *Medicine (Baltimore)* 2016; **95:** e 3450. doi: 10.1097/MD.0000000000003450

75. Iimuro Y, Deguchi Y, Ueda Y, Tanaka A, Iwasa Y, Ishihara M, et al. Primary hepatic carcinoid tumor with metachronous lymph node metastasis after long-term follow up. *J Gastroenterol Hepatol* 2002; **17:**1119-24. doi: 10.1046/j.1440-1746.2002.02663.x

76. Abdel Wahab M, Fathy O, Elghwalby N, Sultan A, Mostafa M, El-Baz M, et al. Primary hepatic carcinoid tumor: one Egyptian center experience. *Hepatogastroenterology* 2006*;* **53:** 33-8.

77. Ronot M, Clift AK, Baum RP, Singh A, Kulkarni HR, Frilling A, Vilgrain V. Morphological and functional imaging for detecting and assessing the resectability of neuroendocrine liver metastases. *Neuroendocrinology* 2018; **106:** 74-88. doi: 10.1159/000479293

78. Veenendaal LM, Borel Rinkes IH, Lips CJ, van Hillegersberg R. Liver metastases of neuroendocrine tumours; early reduction of tumour load to improve life expectancy. *World J Surg Oncol* 2006; **4:** 35. doi: 10.1186/1477-7819-4-35

79. Flechsig P, Zechmann CM, Schreiweis J, Kratochwil C, Rath D, Schwartz LH, et al. Qualitative and quantitative image analysis of CT and MR imaging in patients with neuroendocrine liver metastases in comparison to ^{68}Ga-DOTATOC PET. *Eur J Radiol* 2015; **84:** 1593-600. doi: 10.1016/j.ejrad.2015.04.009

80. Knigge U, Capdevila J, Bartsch DK, Baudin E, Falkerby J, Kianmanesh R, et al. ENETS consensus recommendations for the standards of care in neuroendocrine neoplasms: follow-up and documentation. *Neuroendocrinology* 2017; **105:** 310-9. doi: 10.1159/000458155

81. Singh S, Moody L, Chan DL, Metz DC, Strosberg J, Asmis T, et al. Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumors. *JAMA Oncol* 2018; **4:** 1597-604. doi: 10.1001/jamaoncol.2018.2428

82. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228-47. doi: 10.1016/j.ejca.2008.10.026

83. Kim KW, Krajewski KM, Nishino M, Jagannathan JP, Shinagare AB, Tirumani SH, et al. Update on the management of gastroenteropancreatic neuroendocrine tumors with emphasis on the role of imaging. *AJR Am J Roentgenol* 2013; **201:** 811-24. doi: 10.2214/AJR.12.10240