

Topographic diagnosis: Respective roles of morphological and functional imaging[☆]

Diagnostic topographique : rôles respectifs de l'imagerie morphologique et fonctionnelle[◇]

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Recommendations

In sporadic context, imaging usually enables preoperative localization of insulinoma and guides the choice of the most appropriate surgical approach. Insulinoma being almost always benign, extrapancreatic extension does not necessarily need to be assessed. CT and endoscopic ultrasound seem to be sufficient in most cases to localize the insulinoma, determine its relation with Wirsung's duct and rule out other pancreatic lesions. MRI should be performed when CT is negative or in large or heterogeneous tumour. When morphologic imaging is negative, OctreoScan[®] scintigraphy or PET scan with one of the ⁶⁸Ga-labelled DOTA-peptides may be performed. [18F]-FDOPA may also be contributive in some cases. [18F]-FDG PET is not indicated. Other tracers are still in the experimental stages.

In multiple endocrine neoplasia type-1, the search for multiple pancreatic lesions makes cross-sectional imaging (notably MRI) a logical attitude of first intention. Search for extra-pancreatic locations requires combined morphologic and functional imaging. The standard order for nuclear imaging examinations applies: somatostatin receptor imaging (OctreoScan[®] or PET), followed if necessary by [18F]-FDOPA PET. [18F]-FDG PET is not indicated.

In metastatic forms, conventional imaging enables extension assessment. Functional imaging may be performed if there is some potential therapeutic benefit; the order of examination is somatostatin receptor imaging followed by [18F]-FDOPA PET. Somatostatin receptor imaging also allows patient selection for adjuvant targeted radiation therapy. [18F]-FDG PET may be indicated in rapidly progressive forms or in case of elevated proliferation index.

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1. Role of radiologic imaging and endoscopic ultrasound

1.1. Ultrasound

Pancreatic endocrine tumour has a rounded, well-contoured or oval aspect and is hypoechogenic with clear margins. It may be hetero- or homogeneous and shows as hypervascular under contrast enhancement.

Malignancy is suspected in case of peri-pancreatic adenopathies and liver metastases. Hepatic lesions are typically

hyperechogenic, or occasionally hypoechogenic or with a bulls-eye aspect. The detection sensitivity of abdominal ultrasound for endocrine tumour ranges from 20% to 80% [1].

1.2. CT scan

Multislice CT is essential to diagnosis of pancreatic endocrine tumour (insulinoma).

Acquisition has to be precise. Firstly, slices of 0.6 mm, reconstructed at 1 mm thickness with overlap every 0.7 mm for multiplanar reconstruction, are taken without contrast enhancement.

100 ml of contrast medium with 350 mg of iodine per millilitre is then injected at a rate of 3 to 5 cc/s.

Acquisition then begins with automatic detection of contrast medium in the aorta at 25 s (early arterial phase), followed by programmed sequences at 40 s (late arterial pancreatic phase), and 60 s (portal phase). Examination thus comprises four acquisitions. The effective radiation dose ranges between 8 and 12 mSv.

Another 3-step protocol has a late arterial phase at 30 to 45 seconds then a 70-second portal phase [2].

A low-density oral contrast medium such as water can enhance visualisation of pancreatic endocrine tumours near the digestive tract wall.

Typically, the lesion shows as a spontaneously hypodense nodule, becoming hyperdense in the arterial phases and isodense with respect to the pancreatic parenchyma in the portal phase.

When the lesion measures more than 3 cm or has an unusual aspect (necrosis, haemorrhage, calcification or cyst), a late sequence may be performed at 5 min to detect a fibrous component taking up contrast medium.

When endocrine tumours are cystic, they have a hypervascularised wall, differentiating them from other cystic tumours.

Arterial phase imaging is more sensitive than portal venous phase imaging, with respectively 83 to 88% and 11 to 76% sensitivity. The two phases are complementary. When a pancreatic phase is performed 35 to 45 seconds after injection, sensitivity can reach 100%.

Certain tumours, more difficult to diagnose, may have heterogeneous impregnation, remain hypo- or iso-dense or lie in contact with a vascular structure or the small intestine or be pediculated.

In such cases, multiplanar reconstruction is essential, to separate the lesions from vessels and other digestive structures. CT determines the anatomic relation between the tumour and the pancreatic ducts; when lesions are superficial, enucleation may be considered.

Large lesions tend to show as heterogeneous after injection, with central necrosis. Necrosis, lymph-node invasion or nodular calcifications suggest malignancy. Tumours exceeding 5 cm are also generally malignant.

The liver of patients with pancreatic endocrine tumour should be assessed, so as to reveal any secondary lesions. Lymph nodes and liver lesions are also hypervascularised in the arterial phase.

Liver metastases typically show early central nodule contrast uptake followed by centrifugal filling, forming a hypervascular crown-like aspect in the portal phase.

No modalities are 100% sensitive. According to the algorithm, multislice CT scan is the main imaging examination, because of its excellent spatial and temporal resolution.

When CT scan reveals a lesion of unusual heterogeneous aspect with suspected malignancy, or in case of negative CT despite proven hypoglycaemia syndrome, MRI may be performed.

1.3. MRI

Slice thickness is 5 mm; T1-weighted and T2-weighted fat-saturation sequences are taken. Dynamic 3D T1-weighted sequences use 1 to 2 mm slices in early arterial, portal and 3 and 5 min late phases.

Gadolinium is dosed at 0.4 ml/kg at a rate of 3 cc/s, followed by 40 cc serum.

MRI is as sensitive as multiphase CT in detecting pancreatic endocrine tumour. Normal pancreas shows in hypersignal on T1-weighted sequences.

Endocrine tumours appear relatively hypointense, round or oval and well-contoured on T1-weighted sequences with and without fat saturation.

Most pancreatic endocrine tumours show hypersignal on T2-weighted sequences. In collagen-rich lesions, the signal is intermediate or hypointense on T2-weighted sequences.

Dynamic fat-sat sequences are taken in an arterial, portal and then late phase, to reveal lesions with early hypervascularisation and hyperintensity, portal-phase with an isointense aspect at the pancreatic parenchyma, or late uptake in lesions with a fibrous component [3].

Typically, endocrine tumours not exceeding 2 cm in size are hyperintense and homogeneous in the arterial phase. Larger lesions may have a heterogeneous cystic or necrotic aspect with a hypervascular crown.

Liver metastases show as hypointense on T1-weighted sequences, and hyperintense on T2 fat-suppression sequences. After injection, they appear hyperintense, with a crown-like aspect. Contrast enhancement also helps reveal peripancreatic adenopathies.

In case of heterogeneous nodule exceeding 3 cm in size and suspected of malignancy, MRI is completed by diffusion-weighted sequences from b-50 to b-800 s/mm², with calculation of the apparent diffusion coefficient (ADC) [4].

On diffusion-weighted sequences with low b-values, benign endocrine tumours show hypersignal with high ADC.

In contrast, malignant endocrine tumours maintain hyperintensity on diffusion-weighted sequences with high b-values (800 to 1000s/mm²) and reduced ADC.

This aspect is caused by restriction of water movement due to cell density.

Even so, diffusion-weighted sequences are of limited diagnostic use in differentiating between benign and malignant tumours. Endocrine tumours have variable ADCs depending on their components: necrosis, calcifications.

Diffusion-weighted sequences are useful for revealing locoregional diffusion and liver metastases undetected on other sequences and pathological lymph nodes.

Recent MRI studies have reported favourable results, with 85% detection at 1.5 T.

1.4. Arteriography and venous sampling

Superselective catheterisation of the superior mesenteric artery and celiac trunk with calcium injection allows selective transhepatic portal or suprahepatic venous sampling, to localize the tumour within a pancreatic region by demonstrating hormonal response to a secretagogue. Positive results are obtained in 77 to 94% of cases. With the progress of cross-sectional imaging, this invasive technique is no longer used.

1.5. Endoscopic ultrasound

The interest of endoscopic ultrasound (EUS) in insulinoma exploration has been recognised since the early 1990s. It is a high-resolution ultrasound technique in which the probe can be brought in contact with the digestive tract wall, to examine it and neighbouring structures with a depth of 2 to 4 cm and a precision within a few millimetres. EUS enables the entire pancreas to be explored by moving the probe along the duodenum (uncinate process, head and isthmus) then along the posterior side of the stomach (isthmus, body and tail). EUS can thus identify a tumour by its acoustic characteristics, locate it within the pancreas and with respect to Wirsung's duct and determine its vascular relationships and lymph-node extension, as well as taking a sample for pathologic analysis.

EUS can be performed under light sedation, although the standard practice in France is general anaesthesia by propofol. Complications are rare if no guided biopsy is associated, and mainly consist in gastroduodenal perforation, which is slightly more frequent (1 to 2%) in case of biopsy, with an added risk of pancreatitis.

The success of EUS in diagnosing digestive and pancreatic endocrine tumour, and insulinoma in particular, lies in its considerably greater sensitivity than alternative techniques [5]. The usually small size of insulinoma and its almost exclusively intra-pancreatic location make EUS the exploration of choice.

The ultrasound characteristics of insulinoma are common to all endocrine tumours: good peripheral contouring and homogeneous predominantly moderately hypoechogenic acoustic structure. Insulinoma may, however, be isoechogenic with respect to the adjacent pancreatic parenchyma, or slightly hyperechogenic. Cystic or calcified forms are rare. There is frequently a hyperechogenic reinforcement of the posterior edge of the tumour (distal to the US transducer), due to the hypervascularisation of insulinoma.

1.5.1. Diagnostic performance of endoscopic ultrasound

According to certain reports, insulinoma is harder to identify in the tail than in the head or body of the pancreas, with a clear gradient of diagnostic sensitivity [6,7]; not all reports concur, and the lower sensitivity of left pancreas exploration seems partly to

Table 1
EUS Diagnostic Performance in Studies mainly dating from the 1990s.

	Sensitivity of EUS (identification and location)
Glover et al., 1992 [9]	79%
Palazzo et al., 1992 [10]	77%
Rösch et al., 1992 [11]	81%
Zimmer et al., 1994 [12]	87%
Schumacher et al., 1996 [6]	57% (head 83%, tail 37%)
Pitre et al., 1996 [13]	91%
Zimmer et al., 1996 [14]	93%
Proye et al., 1998 [15]	79%
Anderson et al., 2000 [16]	93%
Sotoudemanesh et al., 2007 [7]	89.5% (head 92.6%, body 78.9%, tail 40.0%)

be a question of operator experience and exploration quality. According to one study, sensitivity is lower with young patient age, female gender and low body-mass index [8].

Table 1 summarises EUS diagnostic performance in studies mainly dating from the 1990s. The data remain roughly valid, despite considerable progress in cross-sectional imaging (CT and MRI), the performance of which is now close to that of EUS. One of the most robust of these studies is that by Anderson et al., systematically comparing EUS results and the pathology findings in a large series of 54 patients.

1.5.2. Role of biopsy

EUS-guided biopsy plays a limited role in the management of insulinoma, which is usually a secreting symptomatic tumour. It is, on the other hand, essential in non-secreting endocrine tumour, often discovered incidentally. The diagnostic precision of biopsy is greater than 80% in pancreatic endocrine tumour, although this is slightly lower than in pancreatic adenocarcinoma [17]. Immunolabelling enables determination of tumour grade and can identify rare non-secreting forms.

1.5.3. Recent advances

Contrast ultrasound has recently been adapted for EUS, and for EUS diagnosis of endocrine tumour in particular; Ishikawa et al. reported a gain of 15% in sensitivity over multislice CT scan in a series of 41 patients [18].

As the small size and intra-pancreatic location of most insulinomas hinders peroperative detection, peroperative ultrasound is usually required. Peroperative tattooing of the tumour by fine-needle injection of India ink or equivalent substance under EUS control has recently been described [19].

1.6. Morphologic imaging guidelines

The problem in diagnosing insulinoma in a context of hypoglycaemia is generally quite simple: clinical and biological findings point to a secreting insulinoma, which then has to be detected and located precisely for surgery [20,21]. Insulinoma is almost always benign and single, so that locoregional and remote extension assessment is not indispensable. EUS, having the best spatial resolution, could thus be the one necessary and

sufficient first-line examination, as suggested by various authors [22–24]. Economically, the efficiency of EUS was demonstrated by American studies in the 1990s [25] and its use is associated with a considerable gain in cost-effectiveness compared to the use of selective venous sampling. However, with recent improvements in the spatial resolution of CT and MRI, combined with vascular contrast agents, the respective sensitivities of the different techniques are now closer. EUS is still probably more effective in detecting small tumours of about 5 mm or less and in determining their relationship to Wirsung's duct (distance between tumour edge and duct wall), which is important for pancreas-sparing surgery (enucleation) in head or isthmus locations. Cross-sectional imaging, on the other hand, is more precise than EUS in terms of longitudinal location. In multiple endocrine neoplasia (MEN) type-1, the search for multiple pancreatic lesions makes cross-sectional imaging a logical attitude of first intention.

Finally, CT combined to EUS appears to be sufficient in most cases. If the tumour appears heterogeneous on CT scan, has a diameter exceeding 3 cm, and in case of type-1 MEN or when CT scan fails to reveal an endocrine tumour, then MRI should be performed.

2. Role of nuclear imaging in insulinoma

2.1. "Routine" examinations

2.1.1. Somatostatin receptor scintigraphy (SRS) or OctreoScan®

SRS is the reference scintigraphic examination. OctreoScan® is a radiolabeled (indium 111) somatostatin analogue that binds preferentially to type 2 somatostatin receptors (SST2). Clinical studies in insulinoma have had small series, but results as a whole are fairly concordant. Diagnostic sensitivity is usually between 40% and 60%, which is lower than for other pancreatic endocrine tumours, whether secreting or not (>80%) [14,15,26–28]. This is due to the low expression of SST2 (<60%) [29] and possibly to the limited spatial resolution of the cameras used for detecting these tumours, which are generally small. Somatostatin receptor imaging also allows patients to be selected for targeted radiation therapy, which can be highly effective on clinical hypoglycaemia [30].

SRS uses a classic widely-available gamma camera, often coupled to a CT scanner (SPECT-CT). According to some teams, examination requires digestive preparation and glucose perfusion to prevent hypoglycaemia following the radiopharmaceutical injection. Whole-body acquisitions (6 to 8 cm/min) are usually performed 4 and 24 hours after injection. Additional SPECT/CT images centred over the abdomen are also required

2.1.2. [18F]-FDOPA PET

[18F]-FDOPA is concentrated in tissues which are able to capture and decarboxylate amino acids, a property of tumours deriving from the APUD (Amine Precursor Uptake and Decarboxylation) system. Uptake requires membrane expression of transporters (notably, LAT-1) and storage is intracytoplasmic

within neurosecretory vesicles, which requires expression of vesicular monoamine transporter (VMAT).

[18F]-FDOPA is available from various suppliers and should be ready for use in all PET centres in the coming months under a French market authorisation.

[18F]-FDOPA PET was successfully applied in neonatal hyperinsulinaemia, to distinguish focal from diffuse involvement [31–36]. Kauhanen et al. reported that [18F]-FDOPA (without Carbidopa premedication) detected 9 in 10 hyperfunctional lesions (insulinoma or nesidioblastosis) although with a relatively low tumour/pancreas fixation ratio. Results were disappointing in another study, with intense global physiological fixation in the adult pancreas [37]. The potential interest of using Carbidopa premedication in adults needs further study.

2.1.3. [18F]-FDG PET

[18F]-fluoro-2-deoxy-D-glucose ([18F]-FDG) is the most widely used tracer in oncology. It enables quantification of glucose uptake and phosphorylation which, indirectly, reflects tissue energy metabolism. It penetrates tumour cells by glucose membrane transporters (mainly GLUT-1) and accumulates after hexokinase action as [18F]-FDG-6P. Well-differentiated endocrine tumours are known to have low proliferation indices and thus show low [18F]-FDG uptake. There is no literature specific to insulinoma. However, [18F]-FDG PET shows very low sensitivity for well-differentiated pancreatic endocrine tumour [38]. In insulinoma, moreover, PET may be associated with intense muscle uptake, due to tumoral insulin secretion [39].

2.2. Examinations used in clinical research

2.2.1. Gallium 68-labelled somatostatin analogue PET

Positron emission tomography (PET) has higher spatial resolution than a classic gamma camera. The PET tracers used also have a greater affinity for somatostatin receptors than does OctreoScan® [40]. Coupling to multi-detector CT now enables very complete examination including PET and multiphase CT [41]. All the peptides are labelled with gallium 68 (68Ga). 68Ga is obtained and the DOTA-peptides are labelled within suitably equipped nuclear medicine departments. Three agonists may be used: DOTATOC (Tyr3-octreotide), DOTATATE (Tyr3-octreotate) or DOTANOC (Nal3-octreotide). The first two have excellent affinity for SST2 receptors and the third has good affinity for subtype-5. This may be useful, as studies have demonstrated predominant SST5 expression in certain insulinomas [28]. Several interesting results have been reported with these radioligands [42–44]. There are as yet no reports specific to insulinoma. An oral communication was made of a preliminary study that showed better performance for [68Ga]-DOTATOC PET than SRS [45]. In practice, they are used in clinical research and suitably equipped PET centres. The examination is available in some French centres, and others are being equipped.

2.2.2. [11C]-hydroxytryptophan PET

[11C]-hydroxytryptophan PET was successfully assessed in pancreatic endocrine tumour [46,47]. Clinical application,

however, is hindered by its short half-life (20.4 min) compared to 18F (109.8 min), making an on-site cyclotron necessary.

2.2.3. GLP-1 receptor imaging

Strong overexpression of GLP1 (Glucagon-Like Peptide-1) receptors (GLP1R) in almost all insulinomas provides a promising target for imaging and vectorised radiation therapy. Two agonists (exendin 3 and 4) with longer half-life, labelled with indium 111 and gallium 68, have been studied. Preclinical studies on xenografted tumours or transgenic tumour models showed scintigraphy to have excellent sensitivity for GLP1 receptors.

These tracers are of interest, but application in humans is still under assessment. In the first clinical trial, indium-111-labelled exendin 4 ([Lys40(Ahx-DTPA)NH2]Exendin-4) located both of two insulinomas [48]. In another study by the same team, DOTA peptide ([Lys40(Ahx-DOTA)NH2]exendin-4) was contributive in all of six insulinomas [49].

2.2.4. Nuclear imaging guidelines

As the data in the literature are sparse, investigation strategies are best established by experts in multidisciplinary meetings. As sporadic insulinoma is generally single and benign, scintigraphy is not mandatory if the tumour is located using other techniques. Nuclear imaging demonstrates the endocrine nature of the pancreatic lesion thanks to the specificity of the tracers, and also allows whole-body exploration. If results are negative, OctreoScan® scintigraphy may be considered. If this in turn is negative, PET using a 68Ga-labelled DOTA-peptide can be used in clinical research. [18F]-FDOPA may be contributive in some cases, but physiological pancreatic fixation in adults greatly impairs detection. The use of Carbidopa premedication requires specific investigation. [18F]-FDG PET has no indications in non-metastatic forms. Finally, GLP1R imaging is not yet available, but is the clearly most promising option. In MEN-1, nuclear imaging may detect other neuroendocrine tumours (e.g., thymic NET).

In metastatic forms, conventional imaging enables extension assessment. Scintigraphy may be performed if there is some potential therapeutic benefit; the order of examination is somatostatin receptor imaging followed by [18F]-FDOPA PET. Somatostatin receptor imaging also allows patient selection for adjuvant vectorised radiation therapy. [18F]-FDG PET may be indicated in rapidly progressive forms or in case of elevated proliferation indexes (Ki-67, mitotic count).

Disclosure of interest

The authors have not supplied their declaration of conflict of interest.

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