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IMAGING OF PANCREATIC NEUROENDOCRINE TUMORS: recent advances, current status and controversies

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Abstract

Introduction—To review recent the advances, current status and controversies in of imaging of pancreatic neuroendocrine tumors(panNETs).

Areas covered—Recently there have been a number of advances in imaging of panNETs, as well as other NETs, which have had a profound effect on the management and treatment of these patients, but in some cases also associated with controversies. These advances include result of numerous studies attempting to better define the roles of both cross-sectional imaging, endoscopic ultrasound(EUS) with or without fine needle aspiration(EUS-FNA) and molecular imaging in both sporadic and inherited panNET syndromes; the increased attempt to develop imaging parameters that correlate with tumor classification or have prognostic value; the rapidly increasing use of molecular imaging in these tumors and the attempt to develop imaging parameters that correlate with treatment/outcome results. Each pf these areas and the associated controversies are reviewed.

Expert Opinion/Commentary—There have been numerous advances in all aspects of the imaging of panNETs, as well as other NETs, the last few years. The advances are leading to expanded roles of imaging in the management of these patients and the results in panNETs/GI-NETs with these newer aiming approaches, are already being used in more common tumors.

Keywords

neuroendocrine tumor; imaging; MRI; CT scan; somatostatin receptor imaging; gastrinoma; insulinoma; MEN1

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17.Conflicts of Interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

1. Introduction: General

Pancreatic neuroendocrine tumors(panNETs)(also call pancreatic endocrine tumors, islet tumors, islet cell tumors) have a distinctive pathogenesis compared to more common adenocarcinomas [1–3] and are now classified in the general category of Neuroendocrine Tumors(NETs), which also include NETs in other locations, such as carcinoid tumors of the gastrointestinal tract(GI-NETs), as well as those of the respiratory tract[1,2]. This general classification system has allowed a comparison of the biological activity of NETs in different locations which has allowed more general approaches to the development of prognostic factors as well as treatment approaches[1–3]. A number of closely related classification systems have been developed including from WHO, European Neuroendocrine Tumor Network(ENETs) and from the International Union for Cancer Control/American Joint Cancer Committee(UICC/AJCC) that including both TNM staging as well as grading of the tumors. The latter relies on the differentiation of the tumors as well as their proliferative activity assessed by the Ki67 index the mitotic rate index(MI). The grading is divided into three categories including: G1(Ki67<3%, MI<2 per 10HPF), G2(Ki67 3–20%, MI 2–20 per 10HPF) and G3(Ki67 >20, MI>20 per 10HPF)[1–3]. The grading categories GI and G2 are well-differentiated NETs, and recently the G3 NETs were subdivided into well-differentiated(G3-NET) and poorly-differentiated(G3, NEC, [neuroendocrine carcinoma]) because they have different biologic behaviors/prognoses, different pathogenesis and their treatments differ[2]. Both the grading and the TNM stage have important prognostic roles and also are having an effect on the treatment approaches as well as the imaging approaches which are discussed below[1–4] (Fig. 1).

Treatment of patients with PanNETs frequently requires management of two different clinical problems, because a proportion(20–50%) of these patents have a functional syndrome [insulinoma, gastrinoma, glucagonoma, etc.) [F-panNET] due to ectopic release of a biologically active hormone by the tumor[5,6] (Fig. 1). Whereas these both could be treated by curative resection, unfortunately in many patients(30–70%), this is not possible because advanced metastatic disease is present [7–10] (Fig. 1). Because the hormone-excess state can lead to live-threatening effects, and because the panNETs are malignant in 40–90% of cases(except insulinomas which are malignant in 5–15%), treatment must be direct at both the tumor per se and the hormone excess-state, separately in many patient[5–7] (Fig. 1).

2. PanNET management and role of Tumor imaging(Table 1) (Fig. 1)

Management of patients with panNETs requires a number of distinct steps. These include: suspecting the diagnosis(particularly if a F-PanNET); establishing the diagnosis; assessment for a possible accompanying genetic syndrome(MEN1, VHL, etc.); control of the hormone-excess state if a F-panNET is present; imaging to establish the location of the primary and extent of the disease; surgical resection of the tumor if possible; treatment for advanced, metastatic disease and appropriate follow-up[5,9,11–13] (Fig. 1).

As shown in Table 1, tumor imaging is involved in almost every stage of the management of patients with panNETs[8,11,14–21]. Recent studies demonstrate that imaging can be valuable for diagnosis of a pancreatic mass as a likely panNET; for identifying the location

of the primary NET as well as the extent of metastatic disease; to determine the possible resectable; to assess the response to all antitumor therapies including surgical resection; to suggest the approach to use for treatment of advanced disease; and to provide prognostic information (Table 1) (Fig. 1).

Recently there have been a number of advances in panNET tumor imaging, particularly in regard to molecular imaging using radiolabeled somatostatin analogues, but also in other areas. This article will review these advances concentrating on the changes within the last 3 years, but also includes some important points from a review up to 5 years. In some cases, these advances have generated controversy, and these also will be discussed. This review will concentrate primarily on results in panNETs, which in many cases are also applicable to all NETs, however, although some series discussed also contain panNETs with other NETs(carcinoids), series including only GI-NETs(carcinoids) are not included.

3. PanNET imaging: General(Table 2) (Fig. 1).

There are a large number of different modalities that are used to image panNETs. Some are relatively specific to this tumor type and others are widely used in most tumors. In the latter group include the use of cross-sectional imaging modalities including computed tomographic scanning(CT scan), Magnetic Resonance Imaging(MRI) and ultrasonography(US)[19,22] (Fig. 1). Selective angiography was widely used in the past, but now is uncommonly used. More specific modalities for NETs, in general, is the recent widespread use of molecular imaging primarily with radiolabeled somatostatin analogues. These include ^{111}In-pentetreotide using single-photon emission computed tomography(SPECT/CT)(octreoscan)(somatostatin receptor scintigraphy(SRS) which was initially most widely used and now increasingly replaced by ^{68}Ga-DOTA-SSA PET/CT[17,19] (Fig. 1). This approach utilizes the fact 80–100% of well-differentiated panNETs possess and overexpress somatostatin receptors, that bind these somatostatin analogues with high affinity(sst_2>$sst_{5,3}$)[17,19]. Other molecular imaging approaches increasingly include the use of ^{18}F-fluoro-deoxyglucose with PET/CT imaging(FDG PET/CT) which determines glucose uptake by the tumor[17,23–25] (Fig. 1). In the past ^{125}I-MIBG scintigraphy was uncommonly used for panNETs, but widely for other NETs, as is the case now with ^{18}F-DOPA(^{18}F-Dihydroxyphenylalanine) PET/CT, which utilizes the fact that NETs can take up amine precursors, but which is more effective in non-panNET NET tumors[17,21,26,27]. Also, ^{11}C-5-hydroxy-l-tryptophan(^{11}C-5-HTP) functions in a similar manner, but is uncommon used because it is available in only a few centers worldwide[17,26,28]. Selective sampling of hormonal gradients either by portal venous sampling or from hepatic veins after selective injection of secretin(for gastrinomas) or calcium for insulinomas/other F-PanNETs[29–35] is uncommonly used now except in the case of insulinomas which are not localized by other modalities[34,36].

4. Abdominal ultrasonography(US) and contrast enhanced abdominal ultrasonography(CEUS) in panNETs (Table 2) (Fig. 1).

Abdominal ultrasound is still widely used in the localization and staging of panNETs, although, in general it has been replaced by the use of CT scanning and MRI as the main

cross-sectional imaging study. In almost all studies it is less sensitive than CT/MRI scanning and like these other cross-sectional imaging studies, its sensitivity is a function of the panNET size with detection of <20% of small panNETs(<1.5 cm) and >50% of panNETs>2 cm(Table 2). The use of contrast with microbubbles markedly improves the sensitivity of US(CEUS) because the majority of panNETs are hypervascular(63–95%)[37–39]. Because ductal adenocarcinomas of the pancreas are hypoechoic in 73–98%, the use of CEUS has been reported to have a high accuracy(88%) and specificity(85–100%) for distinguishing ductal adenocarcinoma from other lesions, including panNETs[37,39]. The use of CEUS does not involve radiation so for multiple examinations it has this advantage. The results of serial use CEUS of patients with panNETs[40,41] correlate with the CT scan pattern($p<0.0001$), and the Ki-67 index($p<0.0001$), with the hypervascular pattern associated with a low Ki-67, and its results can be used to monitor responses to somatostatin analogues or during PRRT treatment.

5. CT scanning in panNETs(Table 2,3) (Fig. 1).

CT scanning with intravenous contrast is in many centers is the initial imaging study used in patients with panNETs, similar to the investigation of other NETs[11,19,22,42]. A complete CT scanning sequence consists of multiphase imaging which includes pre-contrast views, and arterial/pancreatic/venous phases after contrast administration[19,22,43,44]. The sensitivity of CT scanning, similar to the other cross-sectional imaging studies(MRI, US), depends to a large degree on the size of the tumor mass(Table 2). Whereas it detects most large panNETs >2.5 cm(>70%), it frequently misses small panNETs(<1.5 cm), as well duodenal gastrinomas, which are characteristically small(<1 cm)[45–47](Table 2). The diagnostic value of dynamic CT for panNETs has a sensitivity of 64–81%, in large part due to the fact that a significant proportion of panNETs are not hypervascular on the CT[48,49].

Recently a number of studies have reported the ability of CT scan results to have prognostic value by reporting findings that correlate with pathological tumor grade[50–57]; and by its ability to identify features of panNETs, that have a poor prognosis, including involvement of the pancreatic duct and pancreatic duct dilation[58]. The CT scan specific features that correlated with increased aggressiveness and higher pathological grade were summarized in Table 3A and 3B, and those distinguishing from pancreatic ductal adenocarcinomas(PDAC) were summarized in Table 3C, respectively. Particularly important CT features that correlated with higher pathological grade include: larger tumor size, non-hyperattenuation, presence of distant metastases, CT ratio, ill-defined tumor margins, lower sphericity, heterogeneous enhancing, lower attenuation values, vessel involvement, cystic degeneration, bile duct dilatation and vascular invasion(Table 3).

Recent studies also have reported the ability of CT to differentiate between liver metastases due to a panNETs/GI-NETs from those due to a GI adenocarcinoma[59]; its ability to predict recurrence after resection of panNETs[60]; and its ability to predict which patients will develop pancreatic fistulas post resection of a panNET[61]. A recent study reported that liver metastases from panNETs/GI-NETs can be best distinguished from liver metastases from a GI-adenocarcinomas on CT scanning by assessing the dynamic enhancement pattern($p=0.012$) and the metastases to liver ratios on the hepatic artery phase($p=0.009$)[59].

Both were found to be independent predictors for liver metastases from NETs with the sensitivity and specificity of the combined two predictors being 83% and 91%, respectively[59]. In another recent study[60] the contrast-enhancement ratio(CER) of panNETs calculated from the multiphase enhanced CT scan was determined [CER=CT attenuation of the tumor from the maximum enhancing phase divided by the pre-enhanced phase value] and found to be a useful predictor of disease recurrence post resection of the panNET[60]. In this study[60] the CER was lower in the patients that recurred($p=0.013$) and a CER≤3.2 was significantly associated with disease recurrence[60]. Pancreatic fistulas not infrequently occur after pancreatic resection/enucleation for panNETs, as well as other neoplasms/pathologic processes(mean-22%(range 0–60%, enucleation=25%, resection=20%][61,62], and can be associated with increased morbidity and mortality(5–8%)[61]. Therefore, preoperative prediction of which patients are at increased risk for devoping postoperative pancreatic fistula would be helpful[61]. In a recent study retrospective study[61] of contrast-enhanced CT scans of 119 patients undergoing pancreatic enucleation(n=59) or resection(n=60), the CT finding of decreased preoperative pancreatic density was associated with an increased occurrence of postoperative pancreatic fistula($p<0.01$) in the resected group, but not the patients undergoing enucleation.

The management of small(<1.5–2 cm) NF-panNETs which are asymptomatic in non-familial cases(sporadic)[11,63–65] and in patients with inherited panNET syndromes(MEN1, VHL), as well as the management of small gastrinomas in patients with MEN1 is controversial)[12,16,66,67]. CT scanning plays an important role in patients with these lesions and it is also controversial. This will be discussed in a later section.

6. MRI scanning in panNETs(Table 2,4) (Fig. 1).

Imaging of panNETs using MRI has the advantage, like US, of not requiring the use of ionizing radiation, which makes it an important procedure for young patients, as well as patients that require multiple follow-up investigations[19,22,44]. A complete MRI examination includes T1(T1W) and T2-weighed(T2W) sequences; before and after the administration of contrast(gadolinium chelates), a dynamic three-dimensional(3D) sequence with venous, arterial and delayed acquisition sequences and diffusion-weighed sequences(DWI)[19,22,44]. Similar to other cross-sectional imaging modalities(US, CT), the sensitivity of MRI for identifying panNETs is markedly affected by panNET size(Table 2). MRI detects most panNETs>2.5 cm in diameter(>70%), but frequently misses small panNETs(<1.5 cm), both in patients with sporadic disease and with inherited panNET syndromes(MEN1, VHL, etc.)(Table 2)[16,19,44,44,66,68].

Similar to reviewed above with CT scanning, with MRI imaging a number of recent studies(Table 4) have investigated its ability of have prognostic value in patients with panNETs. Specifically, these studies report MRI features that correlate with the tumor pathological grading which has proven prognostic significance[56,69–74], as well as correlate with progression-free survival[75]; and MRI features that correlate with aggressive panNET behavior, as well as MRI features seen in panNETs in patients with shortened survival[58,75–77]. Also summarized in Table 4 are recent results of studies reporting the ability of various MRI features to differentiate panNETs from pancreatic

adenocarcinomas[76,78–81]. Important MRI features that correlated with aggressive behavior included: large tumor size(>3 cm), irregular tumor margins, pancreatic duct dilatation, vascular encasement, extrapancreatic tumnor spread, lower ADC ratios, non-bright T2W images and restricted diffusion with the lesion(Table 4). Older studies demonstrate that MRI can frequently miss some liver metastases in patients with metastatic panNETs/other NETs and that it can be up to 50% of those present on pathological examination[82,83]. A number of studies have demonstrated that the use of diffusion-weighted sequences on MRI increases the sensitivity for detection of liver metastases[83,84]. In a recent study[84] adding DWI sequences to the MRI increased the MRI detection of the number of liver metastases in patients with panNETs/GI-NETs in 45% of the patients with 1.78 times more lesions found[84] This resulted in a change in management in 18% of the patients[84].

Similar to CT scanning, MRI is playing an important role in the management of small sporadic panNETs as well as panNETs in inherited panNET syndromes, some of which is controversial. This will be discussed in a separate section later.

7. Molecular imaging in panNETs(Table 2) (Fig. 1).

[Somatostatin receptor imaging(SRI) with ^{111}In-pentetreotide using SPECT/CT (octreoscan (SRS), ^{68}Ga-DOTA-labeled somatostatin analog [^{68}Ga-DOTA-SSA PET/CT]; FDG PET/CT scanning; other molecular tumor localization methods[^{18}F-DOPA(^{18}F-Dihydroxyphenylalanine) PET/CT with or without carbidopa]

7.A. Molecular imaging in panNETs: General.

As discussed above, 80–100% of well-differentiated panNETs possess and overexpress somatostatin receptors, that bind these somatostatin analogues with high affinity(sst_2>$sst_{5,3}$) [17,19,28]. Many studies have established the sensitivity of using radiolabeled somatostatin analogues to image not only panNETs, but GI-NETs and most NETs in other tissues[17,85–87]. Furthermore, because most well-differentiated malignant NETs also overexpress somatostatin receptors, their presence on the tumor is also being used to target cytotoxic radiolabeled somatostatin analogues(^{177}Lu, ^{90}Y) to treat these tumors(Peptide Radio-receptor Therapy)(PRRT)[88]. Imaging for panNETs and other NETs using ^{111}In-pentetreotide and ^{68}Ga-DOTA-SSA PET/CT is approved in the US and most countries. Furthermore, the use of ^{177}Lutetium-labeled somatostatin analogues to treat patients with advanced NETs is starting to be approved in many countries, and likely in the US in the near future, because of the success of a recent Phase 3 study demonstrating its efficacy and safety[89]. This study[89] was a double-blind, Phase 3 study comparing ^{177}Lu-DOTATATE plus octreotide-LAR(30 mg/mo.) to octreotide LAR(60 mg/mo.) in patients with advanced, progressive, somatostatin-receptor positive midgut NETs(midgut carcinoids). ^{177}Lu-DOTATATE treatment resulted in a markedly longer progression-free survival, preliminary evidence of an improved overall survival and an acceptable safety profile[89]. If approved in the future PRRT therapy will require the initial evaluation with either ^{68}Ga-DOTA-SSA PET/CT or ^{111}In-pentetreotide to establish that somatosatin receptors are present on the NET. The assessment of the presence of sst_2 receptors on NETs by SRI has been shown to

be as accurate as determining it by immunohistochemistry of the tumor[90]. Therefore, ^{68}Ga-DOTA-SSA PET/CT or ^{111}In-pentetreotide imaging is currently used for both imaging of the tumor, as well as to confirm the presence of somatostatin receptors on the tumor prior to PRRT anti-tumor therapy.

All current guidelines(ENETs,NANETs) and expert reviews recommend that SRI be performed in most patients with panNETs with exceptions being patients with inherited panNET syndromes and patients with benign insulinomas, which are discussed below.

7.B. Molecular imaging in panNETs with SRS with ^{111}In-pentetreotide(Table 2).

Until recently, SRI in panNETs was almost entirely performed using ^{111}In-pentetreotide with detection by SPECT/CT[87,91]. As is evident from Table 2, ^{111}In-pentetreotide has generally higher sensitivity than cross-sectional imaging for both primary panNETs(non-insulinoma) and has particular value in allowing at one examination a whole-body study and for the detection of both hepatic and distant metastases[85,87,92–94]. Its sensitivity is also affected by tumor size, although less than cross sectional imaging[95] and by tumor somatostatin receptor abundance/presence[28,96,97], which can be affected by tumor grade[98–100]. Its overall sensitivity in is 60–80%[19]. SRS use after cross-sectional imaging resulted in a change in management of 39% of patients(range-16–71%)[85,93]. Of all of the different panNETs, insulinomas were generally thought an exception requiring SRS imaging. In general, the sensitivity of ^{111}In-pentetreotide in benign insulinomas is low(Table 2) and this was attributed to the absence or low levels of sst2,5 in these tumors[44]. Some recent studies with ^{68}Ga-DOTA-SSA PET/CT[36,101] discussed below, suggest this ligand may be useful in imaging insulinomas.

The specificity of ^{111}In-pentetreotide is 92–100%[19], however this is difficult to study because to accurately assess specificity, strict criterion need to be used, long follow-up is required and it must be performed in a blinded, prospective manner[102]. In one prospective study[102] fitting these criteria the false positive rate with ^{111}In-pentetreotide in patients with gastrinomas was 12% and but these altered therapies in only 3%. These are a large number of different non-tumor processes as well as other neoplasms that may overexpress somatostatin receptor and lead to false positives[19,102,103], which in most cases are recognized by experience nuclear medicine physicians[100]. These include[102,104,105] infections, inflammatory processes, hemangiomas, thyroid disease, intrapancreatic or accessory spleen[106,107], arthritis, granulomatous diseases, physiological uptake in the pancreatic uncinate process[108,109](especially with ^{68}Ga-DOTA-SSA PET/CT), breast diseases[110] and numerous other nonendocrine tumors[103].

7.C. Molecular imaging in panNETs with SRI with ^{68}Ga-DOTA-SSA PET/CT(Table 2) (Fig. 1).

7.C.1. ^{68}Ga-DOTA-SSA PET/CT. General—A number of different ^{68}Ga-labeled somatostatin analogues have been used in different studies[16,17,26]. These include primarily ^{68}Ga-DOTATATE(recently approved for use in the US [called Netspot]), ^{68}Ga-DOTATOC, and ^{68}Ga-DOTANOC[16,17,26,111,112]. Although these different ^{68}Ga-labeled somatostatin analogues differ in affinity for the different somatostatin receptor subtypes,

they all have high affinity for sst_2 and in reviews of comparative studies it is concluded that they appear to be little or no major differences in their performances[17,19,44,113–115].

It is now recommended that SRS with ^{111}In-pentetreotide SPECT/CT be replaced by ^{68}Ga-DOTA-SSA PET/CT because of greater sensitivity, diagnostic accuracy and it also has a lower radiation dose[11,14,17,19,21,44,86,115–118]. The use of a ^{68}Ga-labeled peptide over an ^{111}In-labeled peptide has several advantages including; allowing for more rapid scanning because of its shorter half-life [68 min instead of 67.2 hours for ^{111}In-labeled peptides allowing scanning 1–3 hours post-administration instead of 24–48 hours); ^{68}Ga has greater spatial resolution(0.5 vs 1.5 cm); is produced from a generator rather than a cyclotron; its tissue penetration is better and its effective dose is <50% that used with ^{111}In-labeled peptide and the radiolabeled ^{68}Ga-peptide has a higher receptor affinity[17,19,118]. Recently, in order to help physicians decide when to use SRS/SRI, a working group of NET experts published proposed appropriate use criteria[117]. Nine clinical scenarios were proposed as appropriate in NET patients[119]. These included: initial staging after the histological diagnosis; evaluation of an unknown primary; evaluation of a mass suggestive of NET not amenable to endoscopic or percutaneous biopsy; staging prior to planned surgery; monitoring of a NET seen predominantly on SRS/SRI; evaluation of patients with biochemical evidence and symptoms of a NET; evaluation of patients with biochemical evidence of a NET without evidence and symptoms of a NET on conventional imaging or a prior histologic diagnosis; restaging at time of clinical or laboratory progression without progression on conventional imaging; and a new indeterminate lesion on conventional imaging with unclear progression[117].

7.C.2. ^{68}Ga-DOTA-SSA PET/CT. Sensitivity/specificity/accuracy(Table 5)—

With panNETs(except insulinomas), similar to other NETs, ^{68}Ga-DOTA-SSA PET/CT, in various meta-analysis/series has a high sensitivity [mean-92%(range 68–100], high specificity[mean 88(range 50–100)] and high accuracy[mean 93%(range 90–97%) [14,17,19,116,120,120–123]. Table 5 summarizes the sensitivity and specificity of ^{68}Ga-DOTA-SSA PET/CT in a number of recent studies over the last few years(2013–2017) and in most of the studies both the sensitivity and specificity are >90%, usually in the 90–95% range. In a number of recent studies when results with ^{68}Ga-DOTA-SSA PET/CT, were compared with those seen with SRS with ^{111}In-pentetreotide SPECT/CT in the same patients, ^{68}Ga-DOTA-SSA PET/CT in all cases had significantly greater sensitivity, varying from 22% to 46% more sensitive(by ^{68}Ga-DOTA-SSA PET/CT-95–100% vs SRS-45–78%) (Table 5). It is not clear whether the sensitivity of ^{68}Ga-DOTA-SSA PET/CT in noninsulinoma F-panNETs, such as gastrinoma, is the same as that reported in the overall pancreatic series reported in Table 5, which usually contain primarily NF-panNETs, which most frequently present relatively late in their disease course and are frequently larger in size, as well as associated with metastatic disease[5,10,11,124]. In one studies of patients with gastrinoma[125], ^{68}Ga-DOTA-SSA PET/CT had a sensitivity of 68% which is low compared to most panNET series(Table 5). Similarly, in a series of patients with duodeno-pancreatic NETs(5 with ZES)[126] the overall sensitivity of ^{68}Ga-DOTA-SSA PET/CT was 76%, and it frequently missed lesions<10 mm. While it is reported that ^{68}Ga-DOTA-SSA PET/CT will detect smaller lesions with duodeno-pancreatic NETs than ^{111}In-

pentetreotide[127], ^{68}Ga-DOTA-SSA PET/CT still misses significant number of small duodeno-pancreatic NETs in studies(Table 2), and will especially likely miss a significant number of duodenal gastrinomas, which are characteristically <1 cm[45–47,128].

7.C.3. ^{68}Ga-DOTA-SSA PET/CT. Change clinical management of patients(Table 5)—

One of the most important assessment of any new imaging modality is whether its use changes clinical management[129–131]. In various meta-analyses, ^{68}Ga-DOTA-SSA PET/CT changes management in 37%−81% of NET patients[85,121,132]. The results of two studies[129,131] that dealt entirely with this question, provide some additional insights. Two questionnaires were sent to physicians referring 100 consecutive patients for ^{68}Ga-DOTA-SSA PET/CT[129], one pre-PET/CT and the other post/PET-CT to determine the impact of ^{68}Ga-DOTA-SSA PET/CT on the patient's management. Intended management changes were reported in 60% of the patients[129], with the largest changes occurring in patients considered for chemotherapy(23%) or as a result of a change in suspicion for metastatic disease(24%). A follow-up study[131] was recently published with a similar design but including a 6-month follow-up questionnaire which included results from 130 patients referred for a ^{68}Ga-DOTA-SSA PET/CT. In this report[131] ^{68}Ga-DOTA-SSA PET/CT resulted in an intended change in management of 50%, and these changes were fully implemented in 75%, confirming that ^{68}Ga-DOTA-SSA PET/CT was having a marked effect on the management of NET patients.

7.C.4. ^{68}Ga-DOTA-SSA PET/CT. Prognostic/therapeutic value(Table 5)—

Similar to the CT scan and MRI, the ^{68}Ga-DOTA-SSA PET/CT results have a prognostic effect in a number of ways as summarized in Table 5. First, ^{68}Ga-DOTA-SSA PET/CT has a very high sensitivity for assessing the extent and location of metastatic disease and the presence of metastases in each of these sites has been shown to have important prognostic significance(Table 5). Second, the ^{68}Ga-DOTA-SSA PET/CT SUV/max correlates with PFS, Ki-67, tumor grade/progression in a number of studies(Table 5). Third, Determination of tumor volume inversely correlated with PFS and overall survival(Table 5).

With PRRT the Krenning score comparing the uptake by the NET of ^{177}Lu-DOTA-octreotate to that by the liver is predictive of response[133]. In recent studies ^{68}Ga-DOTA-SSA PET/CT SUV was predictive of tumor absorbed doses on subsequent PRRT[134] and for predicting responding lesions to PRRT[135](Table 5).

7.D. Molecular imaging in panNETs with 18F-^{18}F-FDG PET/CT(Fig. 1).

7.D.1. ^{18}F-Fluorodeoxyglucose positron emission tomography(^{18}F-FDG PET/CT). General.—

^{18}F-FDG PET/CT assesses tumor metabolic activity by determining the glucose uptake and therefore measures a different tumor parameter than SRI which is assessing somatostatin receptor expression. Although ^{18}F-FDG PET/CT is widely used in oncology, until recently, it was generally not thought helpful in patients with panNETs/GI-NETs[17,44]. However, numerous recent studies report high uptake by a proportion of NETs[19,23,136,137]. In a number of studies the high uptake/SUV of ^{18}F-FDG PET/CT was reported to be associated with higher Ki67 values, and was a predictor of overall survival as well as PFS[17,19,138]. Lately there have been an increasing number of papers

advocating either the use of FDG either alone or combined in dual imaging with ^{68}Ga-DOTA-SSA PET/CT[23,24,136,137,139–141].

7.D.2. ^{18}F-FDG PET/CT. Sensitivity alone and compared to ^{68}Ga-DOTA-SSA PET/CT in panNETs and collective NET series(Table 6).—Data from recent studies(2013–2017) assessing the sensitivity of ^{18}F-FDG PET/CT in imaging either panNETs or in combined series with other NETs are summarized in Table 6. ^{18}F-FDG PET/CT has a mean sensitivity of 65% for identifying panNETs(range58–73%) which is similar to the result from recent combined series of panNETs and other NETs (range-37–72%)(Table 6). In series reporting both the results with ^{18}F-FDG PET/CT and 68Ga-DOTA-SSA PET/CT in the same patients with either panNETs only or with combined NET series, in each case ^{68}Ga-DOTA-SSA PET/CT has a significantly better sensitivity(91–100%) compared to 42–73% for ^{18}F-FDG PET/CT(Table 6).

7.D.3. ^{18}F-FDG PET/CT. Sensitivity related to tumor grade—One of the likely reasons that ^{18}F-FDG PET/CT was originally thought not useful in panNETs/NETs is because many series contained primarily well-differentiated Grade G1 tumors and they have the lowest glucose uptake rates and are frequently negative on ^{18}F-FDG PET/CT scanning(Table 6). In recent data(2013–2017) in G1 panNETs ^{18}F-FDG PET/CT had a mean positivity of 31%(range-20–45%) and in combined NET series the positivity it was <20% (Table 6). In contrast, the ^{18}F-FDG PET/CT positivity in G2 panNETs was 45% and in combined series 51%(range-25–86%) and in G3 panNETs it was 81%(range-75–88%) and in combined series of G3 NETs it was 72%(range-51–100%)(Table 6).

7.D.4. ^{18}F-FDG PET/CT. correlation with prognosis differentiation/grade/survival(Table 6).—Numerous recent studies provided additional support for the conclusion that ^{18}F-FDG PET/CT positivity, assessment of its SUVmax or tumor metabolic parameters such as metabolic tumor volume or total lesion glycolysis have prognostic value(Table 6). In numerous studies a number of these results from ^{18}F-FDG PET/CT have been shown to correlate with Ki-67, with the tumor grade, with the presence or development of progressive disease(Table 6). These ^{18}F-FDG PET/CT parameters also correlate with PFS, OS and in one study had a sensitivity and specificity for differentiating G1/G2 tumors form G3 of 100% and 62%, respectively(Table 6). A number of studies have concluded that the results of ^{18}F-FDG PET/CT and ^{68}Ga-DOTA-SSA PET/CT provide complementary information that is clinical relevant[24,136,142–145]. Recent studies[139,140] have extended this principal of the complementariness of these to nuclear medicine imaging studies to recommend a NETPET score be assigned to NETs based on the result of these two studies that could have important prognostic value and help select better therapeutic options.

7.D.5. ^{18}F-FDG PET/CT: correlation with therapeutic response and ability to alter patient management(Table 6).—^{18}F-FDG PET/CT positivity is reported to have therapeutic value in correlating to occurrence of refractoriness to treatment with PRRT with ^{177}Lu DOTATATE[146]. It also correlates with shorter PFS after PRRT[147] and with shorter postoperative disease-free survival after resection of the NET[148](Table 6). Each of these correlations could be clinically relevant, because they potentially allow stratification of

patients to tailor follow-up as well as to earlier detect progression and allow new therapies to be instituted earlier. The use of ^{177}Lu DOTATATE[146] alone is reported to change patient management in 22% of cases and in combination with ^{68}Ga-DOTA-SSA PET/CT to change management in 59% of patients[24](Table 6).

7.E. Molecular imaging in panNETs with other modalities [^{18}F-DOPA PET/CT,^{11}C-5-HTP, radiolabeled GLP-1R receptor ligands, radiolabeled somatostatin antagonists for SRI] (Fig. 1).

^{18}F-DOPA PET/CT and ^{11}C-5-HTP [^{11}C-5-hydroxy-L-tryptophan PET/CT] are two other molecular probes which have been used to image panNETs and other NETs[17,19,21,26,44,87,149,150]. Each of these molecular probes has a different basis of action than ^{18}F-FDG PET/CT or SRI with ^{68}Ga-DOTA-SSA PET/CT or with ^{111}In-pentetreotide with SPECT/CT(Octreoscan). ^{18}F-DOPA PET/CT and ^{11}C-5-HTP are taken up by NETs which decarboxylate amine precursors[17,19,21,26,44,87,149,150]. Although ^{11}C-5-HTP is a sensitive method to image panNETs and other NETs[151,152],^{11}C-5-HTP will not be discussed further because only a few centers have ^{11}C-5-HTP available and thus it is rarely used. ^{18}F-DOPA PET/CT has been widely used in imaging various NETs[17,26,27]. While ^{18}F-DOPA PET/CT is reported to be a particularly good imaging modality for medullary thyroid cancer, investigating hyperinsulinemic states and in staging of some carcinoid tumors, it has less sensitivity than SRI with ^{68}Ga-DOTA-SSA PET/CT or ^{111}In-pentetreotide using SPECT/CT (octreoscan) for imaging panNETs[17,26,27]. Recently carbidopa [a peripheral aromatic amino acid decarboxylase inhibitor] administration during the ^{18}F-DOPA PET/CT study has been reported to increase its sensitivity for panNETs[153,154]. Specifically, the use of carbidopa increased the sensitivity of ^{18}F-DOPA PET/CT for imaging insulinomas to 70%[153] and for NF-panNETs[154] to 90%, which was superior to the 68% sensitivity seen with ^{111}In-pentetreotide using SPECT/CT (octreoscan). This will be discussed in more detail in a later section on insulinomas.

With SRI using ^{68}Ga-DOTA-SSA PET/CT or ^{111}In-pentetreotide using SPECT/CT (octreoscan), the SSA peptides included were only somatostatin receptor (sst) agonists, primarily because the general opinion was agonists would be the most desirable for imaging because they were internalized, whereas somatostatin receptor antagonists were not[17,91,155]. Recently it has been discovered that radiolabeled SSST antagonists give superior imaging compared to radiolabeled SST agonists[155–157]. In an in vitro study on a sst_3 antagonist, the sst_3 antagonist identified 76-fold more binding sites than the sst_3 agonist[157]. Subsequently, a limited number of studies including small number of patients with NETs (both panNETs and GI-NETs included) show that radiolabeled sst_2 antagonists [^{111}In-DOTA-BASS; ^{68}Ga-OPS202 [^{68}Ga-NODAGA-JR11] demonstrate superior tumor imaging compared to radiolabeled agonists and high sensitivity[155,156,158–160]. These results have been extended to the possibility of using ^{177}Lu-radiolabeled sst_2 antagonists for PRRT rather than ^{177}Lu-radiolabeled sst_2 agonists, as is now the case[161]. In a preclinical study[161] in sst_2 positive cells and an in vivo study in tumor bearing mice, 5 times greater uptake by the tumor was seen with the radiolabeled sst_2 antagonist, ^{177}Lu-DOTA-JR11, than with the sst_2 radiolabeled agonist, ^{177}Lu-DOTA-octreotate and this resulted in a longer growth delay. When studies with these two sst2 radiolabeled agents were extended to 4

patients with advanced NETs[156], the ^{177}Lu-DOTA-JR11 delivered 1.7–10.6-fold higher tumor doses than the agonist, ^{177}Lu-DOTA-octreotate, and caused a partial remission in 50% of the patients. These results demonstrate that radiolabeled sst_2 antagonists show promise as an improved agent over radiolabeled sst_2 agonists for panNET/NET imaging as well as for delivery of cytotoxic radiotherapy, specifically PRRT. At present no sst2 radiolabeled antagonist are approved for either imaging or PRRT, but that could change in the future because of the studies reviewed above.

Recent studies demonstrate that insulinomas overexpress receptors for GLP-1 (Glucagon-like Peptide 1) and that radiolabeled GLP-1R agonists have high sensitivity for localizing these panNETs, which are frequently small in size and a fraction are not localized by other imaging modalities[162,163]. This will be dealt with in a subsequent specific section dealing with insulinomas.

Although limited evidence is available[19], a recent study reports higher sensitivity of ^{68}Ga-DOTA-SSA PET/MRI in detecting NET lesions, specifically liver metastases, compared to ^{68}Ga-DOTA-SSA PET/CT[164].

8. Endoscopic ultrasound(EUS) in panNETs (Fig. 1).

EUS has a number of special features that make it particularly valuable in the assessment of panNETs and distinguishing them from other pancreatic lesions. First, it is generally accepted as the most sensitive modality for imaging small panNETs[16,44,48,165,166]. EUS has the ability to identify panNETs as small as 0.5 cm in diameter and detects most lesions >1.5 cm[16,167]. In a recent study, CT scanning failed to detect 65% of panNETs identified by EUS of ≤10mm, and another 15% of lesions 1–2cm detected by EUS[168]. Furthermore, in a recent systematic study, EUS detected a panNET preoperatively in 25% of patients in which cross-sectional imaging studies were negative[166]. In meta-analyses[166,169], EUS had pooled sensitivity of 87–97% for detecting a panNET and a specificity of 98%. It also allows for assessment of lesion depth, invasiveness, and presence of lymphadenopathy[170]. Furthermore, EUS allows for the evaluation of cystic panNETs which will be briefly discussed later in this article[48]. Second, it allows serial measurements to be made of small lesions that are being followed to determine changes in size. This later point is particularly important in patients with inherited panNET syndromes (MEN1, VHL, etc.), as well as in patients with small sporadic NF-panNETs, who are being followed, each of which will be discussed in more detail below. Fourth, it allows EUS-directed cytology or biopsies to be performed, which can confirm the histology of the lesion as well as provide grading of the NET[48,170]. Lastly, it can have a therapeutic option in patients with functional NETs such as insulinomas, where surgery is not considered, by allowing EUS-administered cytotoxic agents such as ethanol, which can control the hormone-excess state[6,171]. Unfortunate, EUS is an invasive procedure, in some settings requires general anesthesia, and is frequently available only in specialty center.

EUS-FNA is the main tissue sampling technique for pancreatic neoplasms, with a sensitivity of 80–90%, and specificity of 96%, with a sampling adequacy rate of 83–93%[48]. For panNETs not only is the establishment of the diagnosis of primary importance, also the

determination of tumor grade has important prognostic value as well as can affect therapeutic approaches as discussed above[48,172]. There are numerous studies which have compared EUS-FNA results or to those found at surgery, with discordance in some cases, particularly with EUS-FNA[48,173,174]. In general, with EUS-FNA the concordance rate with surgical specimens for grade determination is 69–82%[48,174,175], and for establishing the tumor as a panNET is 98%[48]. In a meta-analysis, the pooled sensitivity and specificity for EUS-FNA in panNETs in distinguishing the various NET grades was 64% and 87%, respectively for differentiating G2, G3 lesions from G1 lesions[176].

In recent studies EUS has high sensitivity for diagnosing panNETs(87–99%)[169,177,178] which was significantly greater than for CT Scanning, MRI or transabdominal US[177]. On EUS higher grade panNETs were more likely to be large≥20mm), heterogeneous and have obstruction of the pancreatic duct[174,177]. In recent studies the sensitivity of EUS-FA for diagnosing panNETs is reported to be 84–90%[170,173,179], specificity(99%)[179] and the concordance between the WHO tumor grade between surgical and EUS-FA specimens was 64–88%%[172–175,177,180,181]. The concordance rate on EUS-FNA samples compared to surgical samples varied with panNET size being 88–95%% for panNETs<20 mm, but only 7–57% for panNETs≥20mm[174,177] and also was more accurate when larger number of cells(>2000) were counted[174,175,181]. Discrepancies between EUS-FNA and surgical specimens occurred especially in Grade G2 panNETs, which in one series reported 71% of the histological G2 surgical specimens were classified as G1 on EUS-FNA, which was attributed to tumor heterogeneity[173]. PanNET location within the pancreas can also affect the diagnostic accuracy of EUS-FNA for establishing a panNET with the accuracy being 94% in the pancreatic body/tail but reduced to 70%(p=0.02) in the pancreatic head[179]. This difference was attributed to lower sample adequacy rates in the pancreatic head[179]. In a study of the number of needle passes at EUS-FNA that are optimum to establish whether a pancreatic lesion is a panNET, it was found that at least two passes were required when an on-site cytologist was not present[182]

Contrast enhanced EUS(CE-EUS) is reported to have a high sensitivity(95%) in identifying panNETs compared to CT(81%) or transabdominal US(45%) and also to identify a heterogeneous tumor texture which was a significant factor for malignancy(OR=53)[183]. Contrast enhanced Harmonic EUS(CEH-EUS) compared to EUS had a higher sensitivity for identifying a pancreatic lesion as panNET(91% vs 81%) or pancreatic adenocarcinoma(88% vs 82%)[184].

9. Measurement of hormonal gradients to localize F-panNETs

Selective sampling for hormonal gradients in patients with F-panNETs (primarily in patients with insulinomas or gastrinomas, rarely glucagonomas) was used frequently in the past when other imaging methods did not localize the F-panNET [29–36,185]. At present, it is rarely used for gastrinomas or other F-panNETs, but is still, not infrequently used, for patients with insulinomas [29–35,185]. Hormone gradients can be assessed either by portal venous sampling (which is rarely used today) or by sampling from hepatic veins after selective injection of secretin (for gastrinomas) or calcium for insulinomas/insulinomas/ other F-PanNETs gradients [29–34,34,35,185]. This methodology has high sensitivity

because the detection of a hormone gradient is not influenced by tumor size to the degree seen with other imaging studies(Table 2). However, it is an invasive method and is generally only available in a few highly specialized centers, and therefore is uncommonly used today. This will be discussed in more detail in the specific sections on insulinomas and gastrinomas later in this paper.

10. Intraoperative methods to localize panNETs

During the operation, there are a number of procedures that are frequently used to localize the panNET which include the use of intraoperative ultrasound (IOUS) [186] in the case of gastrinomas, which are frequently in the duodenum, the use of duodenotomy and transillumination of the duodenum, as well as mobilization of the duodenum [45,128,187]; and in some cases, radio-guided-surgery [188,189]. IOUS is particularly useful for intrapancreatic lesions allowing detection of small lesions (as small as 2 mm), defining their relationship to the pancreatic duct, also allows detection of hepatic metastases [186,190], however IOUS is not as sensitive for duodenal NETs such as duodenal gastrinomas. Duodenal gastrinomas in patients with ZES (60–90% of all patients) are frequently small, many be multiple (especially in MEN1/ZES) and difficult to find, thus requiring a duodenotomy with or without transillumination of the duodenum to find them [16,45,47,187,191]. The use of duodenotomy has been shown to increase the cure rate [45].

Radioguided surgery in a number of patients with panNETs and other NETs has been reported in a few studies, generally involving small number of patients [186,188,189,192–194]. These include primarily the use of various hand-held detectors after the prior administration of radiolabeled somatostatin analogues, which in some cases identified lesions not otherwise evident. [186,188,189,192–194]. This approach has been used successful after 18F-DOPA in patients with medullary thyroid cancer to find additional metastases [195]. However, one of the problems with the abdomen is the high background levels of the isotope particularly in the upper abdomen which have made this approach difficult [194], and likely contribute to its very limited use for panNETs and other GI-NETs.

11. Imaging in specific panNETs with special features.

11.1. Imaging in specific panNETs with special features: General points

A few specific panNETs present special problems in imaging and these will briefly be considered in the following few paragraphs. These include: insulinomas, gastrinomas, cystic panNETs and panNETs in hereditary panNET syndromes, particular patients with MEN1 and VHL. Each of these present some specifically features/aspects that complicate the imaging.

11.2. Imaging in specific panNETs with special features: Insulinomas (Fig. 1).

Insulinomas present special problems for imaging/localization because they are frequently small (up to 40% <1cm in some series), the hypoglycemic symptoms can be severe and they are not always easily controlled with medical therapy, and insulinomas are the exception to other panNETs, because 90–95% are benign and if localized the patient can be cured [9,11,124,196]. As discussed earlier, this small size decreases the sensitivity of cross-

sectional imaging (CT, MRI, US) for localizing insulinomas (Table 2). Greater than 99% of insulinomas are pancreatic in location, and EUS has excellent sensitivity for localizing these tumors, however it does miss a small percentage (6–29%) (Table 2). Therefore, there is a need for additional aiming studies in some patients.

Molecular imaging using ^{111}In-pentetreotide with SPECT/CT (octreoscan) has proven disappointing in localizing insulinoma being positive in 33–60% of patients (Table 2), likely do to the low number/absence of the somatostatin receptor subtype, sst_2 in insulinomas in a significant number of patients[197,198]. Molecular imaging using ^{68}Ga-DOTA-SSA PET/CT has given conflicting results. In one study [199] ^{68}Ga-DOTA-SSA PET/CT had a sensitivity of only 32% whereas in another study [36] ^{68}Ga-DOTA-SSA PET/CT had a sensitivity of 90% compared to only 55% for CT,61% for MRI and 21% for abdominal US. In a third study [101] ^{68}Ga-DOTA-SSA PET/CT was positive in 75% of patients with benign insulinomas. ^{18}F-DOPA PET/CT has proven useful for distinguishing focal from diffuse congenital hyperinsulinemia in infants, thus helping to select those infants for surgery and also by shortening the intervention by guiding surgery[27,200]. ^{18}F-DOPA PET/CT has a relatively low sensitivity for detecting insulinomas in most studies (25–50%) [201,202]. However, a recent studies reports that performing ^{18}F-DOPA PET/CT with carbidopa increases the sensitivity to 73%[202]. A newer molecular method which shows promise for imaging insulinomas is the use of radiolabeled agonists of the GLP1receptor(GLP1R) which are overexpressed by insulinomas[162,163,203,204]. A number of different radiolabel GLP1R agonists have been used (^{68}Ga NOTA exendin-4[176], ^{111}In-DTPA-exendin-4[162], ^{99M}Tc-GLP1[204] PET/CT) and each have similar sensitivity. In various studies this method has a sensitivity of 95–100% [162,163,204] which exceed that with cross-sectional imaging (47–74%) and even that with EUS (84–88% [162,163,204].

Assessment of insulin gradients continues to be used in a number of centers for patients with insulinomas with negative imaging by other modalities [30,32–35]. At present this is performed in almost all cases by the selective intra-arterial injection of calcium with sampling for insulin concentrations from hepatic veins [30,32–35]. This method has high sensitivity varying from 72–100%, with most studies reporting a sentivity of 88–100% [29,32–34]. In the diagnosis of endogenous hyperinsulinemic hypoglycemia it is important to differentiate insulinoma from the noninsulinoma pancreatogenous hypoglycemia syndrome(NIPHS), which is due to nesidioblastosis, as they are treated differently[35,196,205]. Unfortunately, the cross-sectional imaging may be negative in both, ^{68}Ga-DOTA-SSA PET/CT can give a false positive result in NIPHS suggesting insulinoma, and the selective calcium infusion with insulin gradients can be positive in both[35,205,206]. In a recent study [35] the results of the selective arterial calcium study with hepatic venous sampling for insulin(SACST) was reported to differentiate these two conditions using two criteria[a maximum increase in hepatic venous insulin concentration >91.5 or >263.5 ulU/mL] with 95% and 100% specificity, respectively.

11.3. Imaging in specific panNETs with special features: Gastrinomas (Fig. 1).

Gastrinomas present some unique problems in imaging and tumor localization which have some differences from the problems faced in patients with insulinomas. In contrast to

insulinomas in which the hypoglycemia can be difficult in some patients to control medically, the hormone-excess state in ZES (hypergastrinemia resulting in acid hypersecretion), can be well controlled medically (i.e. using PPIs or less frequently histamine H_2 receptor antagonists), both acutely and long-term with no side-effects except for vitamin B_{12} deficiency in some patients [5,207–212]. Therefore, the urgency to localize and resect the panNET in patients with ZES is not a great as in insulinomas. However, a similar problem to insulinomas exist with difficulty in imaging of the primary tumor, in that gastrinomas are often small in size (<1 cm), particularly those in the duodenum, which is the cause of the ZES in 60–95% of patients in different series [5,45,210]. In addition to localizing the primary gastrinoma, another important imaging challenge in ZES is to localize the extent of the disease, because in contrast to insulinomas, gastrinomas are malignant in 60–90% of cases and frequently metastasize to adjacent lymph nodes, the liver, end less frequently to distant sites such as bone, which can all affect the management[7,11,94,210,213,214]. Furthermore, patients with MEN1/ZES present a number of specific imaging problems and controversies and will be discussed in a specific section below.

Cross-sectional imaging studies miss most small duodenal gastrinomas, while they detect most pancreatic gastrinomas, which are generally larger in size[16,68,215]. EUS identifies most pancreatic gastrinomas, but misses most primary duodenal gastrinomas[16,216]. SRI with ^{111}In-pentetreotide with detection by SPECT/CT (octreoscan) is more sensitive than cross-sectional imaging in ZES localizing 30–70% of the primary tumors in different series and >90% of patients with metastases, however it misses the majority of duodenal gastrinomas (Table 2), instead generally detected the adjacent positive lymph nodes[16,45,92,217]. ^{68}Ga-DOTA-SSA PET/CT is currently overall the most sensitive modality available for staging patients with ZES, however it can miss a significant number of small duodenal gastrinomas, although at present the exact percentage is unclear[125,126].

Because of the difficulty in localizing small gastrinomas, particularly those in the duodenum, by imaging studies, at surgery the intra-operative localizations studies (IOUS, IOE, mobilization of duodenum, routine resection of lymph nodes), play a major role in localizing the gastrinoma at surgery and increasing the probability of cure [5,45,187,218,219]. Surgical exploration is recommended in ZES patients without MEN1/ZES, unresectable metastatic disease or with medical contraindications, because studies show it increase survival, decreases the devopment of liver metastases, which are one of the main prognostic factors for decreased survival[7,215,220,221]. Therefore, once the diagnosis is established by assessing fasting serum gastrin levels and simultaneous gastric acidity and in some patient’s secretin provocative testing [5,210,222], and the patient is established as a surgical candidate, surgery needs to be considered. Even if the imaging studies are negative, surgery has been shown to be of value and is recommended [9,11,218]. In a proportion of these imaging negative patients, the duodenal gastrinomas will only be detected by the intra-surgical localization methods[45,128,187,216].

In contrast to patients with insulinomas, most patients with ZES are not cured long-term(70–90%-sporadic ZES, 100% MEN1/ZES without aggressive resection) [5,136,216,223]. Even in the sporadic group who undergo possible curative resection(<50% all ZES patients), 50–

60% are cured immediately post resection, and 35–40% long-term[5,136,216,223,224]. Therefore, almost all ZES patients require continued follow-up and repeated imaging studies in addition to hormonal evaluation with fasting serum gastrin and secretin test for patients possibly cured[11,210,216,224,225].

11.4. Imaging in specific panNETs with special features: Patients with inherited panNET syndromes (MEN1,VHL) (Fig. 1).

Both patients with MEN1 and VHL can development panNETs with a number of unusual features that makes both their imaging, and the management of the findings controversial, particular with MEN1.

MEN1 patients characteristically develop NETs of the parathyroid (95–100%)[resulting in hyperparathyroidism], pituitary(54–65%) and pancreas/duodenum(95–100%), and generally, but not always, present with hyperparathyroidism[12,66,226,227]. In recent studies they also develop adrenal adenomas, carcinoids(thymic, lung, gastric), and nonendocrine tumors(leiomyomas(sarcomas), CNS tumors, and skin tumors)[12,16,66,228,229]. In 80–100% of MEN1 patients NF-panNETs are found, however most are small(microscopic), multiple and in only 0–12% do they become symptomatic[12,16,66]. F-panNET also occur in MEN1 patients with a relative frequency of gastrinomas 54%[range 20–61%]>insulinomas 18%[range 7–31%]>other F-panNETs (3% [range, 1–5%]) [12,16,66,230]. In MEN1/ZES patients, similar to patients with sporadic ZES, the gastrinomas occur primarily in the duodenum(85–100%), and are usually small in size, but in contrast to sporadic ZES in MEN1/ZES patients, the duodenal gastrinomas are invariably multiple[12,47,66,231]. The result of the multiplicity of the NF-panNETs and the duodenal gastrinomas in MEN1 patients is that they cannot be cured without aggressive surgical procedures (Whipple resection, total pancreatectomy), whereas patients with other F-panNETs, such as glucagonomas and insulinomas, are generally curable without extensive resections [12,66,232]. This has resulted in controversy on not only what imaging studies to performed initially in MEN1 patients, but also with follow-up, as well as the treatment of both that NF-panNETs and the MEN1/ZES patient’s gastrinomas [16,66,67,136]. This controversy is not only fueled by the fact that the panNETs/duodenal gastrinomas in MEN1 patients are multiple; not cured by simple enucleation/resection; small in size, not predicted by changes in tumor markers and missed by most imaging studies; but also, by the fact that these small lesions(<1.5–2cm) have an excellent prognosis in most cases without surgery and are frequently diagnosed in younger patients (presenting at least 10 years earlier than sporadic cases) [12,66,227,233]. Nevertheless, recent studies demonstrate that MEN1 patients still have shortened life expectancy (mean age death-55 yr.) and that malignant NETs including especially panNETs and thymic carcinoids, are one of the main determinants of this earlier death [12,66,230]. The result of these conflicting points is that, at present, there is controversy in patients with small NF-panNETs/duodenal gastrinomas (<1.5–2 cm) in MEN1 patients, on whether to perform surgery or whether to observe the patient and if so what serial imaging studies to perform [16,66,67,136]. Guidelines from ENETs, NANETs and the Endocrine Society recommend a conservative approach to these patients with panNETs<1–2 cm[9,11,13,66]. All recommend that if this approach is taken the patients need to be carefully followed with serial panNET imaging studies. Numerous

studies demonstrate that EUS is the most sensitive imaging modality identifying panNETs and allows serial imaging studies [16,165], however it requires general anesthesia in some centers, is only available in highly specialized centers, is operator dependent, and a recent study reports it may overestimate the size of panNETs [234]. MRI has been advocated in some studies [16,235] and has the advantage that it does not involve radiation (which evidence suggests may more easily damage MEN1-gene defective cells), however it frequently misses small lesions, as does CT scanning(<1.5–2cm)[16,235]. SRI with ^{68}Ga-DOTA-SSA PET/CT is highly sensitive in MEN1 patients [16,66,236–238], but is controversial, because these patients have many other NETs including gastric, adrenal, etc. which can confuse the identification of panNETs, and also the additional identification of small panNETs (<1.5–2 cm) will not change management if existing guidelines are being followed [16,66,239]. A recent study [25] reports the usefulness of ^{18}F-FDG PET/CT as an effective screening modality in MEN1 patients to identify panNETs of increasing malignant potential and surgical resection was recommended for ^{18}F-FDG PET/CT positive lesions. In this study [25] 51% of patients with MEN1 who had a panNET localized by standard imaging, 25% of these patients (5/49) had ^{18}F-FDG PET/CT positive lesions identified in addition to two other patients, and at surgery 75% of the patients with ^{18}F-FDG PET/CT positive lesions, had aggressive or metastatic panNETs[25]. As discussed above, cross sectional imaging or SRI will not identify the functionality of the panNET localized, so that in a patient with MEN1 and insulinoma, both the insulinoma and other NF-panNETs may be visualized. In this case scanning with radiolabeled GLP1R analogues or measurement of hormonal insulin gradients may be of value.

Von Hippel Lindau Disease(VHL) is an inherited, autosomal dominant disorder in which 35–87% of patients have pancreatic lesions, in addition to the usual features of this disease [hemangioblastomas of retina and CNS; endolymphatic sac tumors, renal cell carcinomas/cysts; pheochromocytomas; epididymal cystadenomas] [12,240,240,241]. The pancreatic lesions are primarily cysts [simple cyst-(mean-47%, range-7–72%), serous cystadenomas(mean-11%, range-7–19%)] and the primary pancreatic tumors are cystadenomas, hemangioblastomas, adenocarcinomas and panNETs [12,240,242]. In older studies 10–17% of patients had panNETs [12], however in more recent studies with enhanced imaging such as EUS or SRI with ^{68}Ga-DOTA-SSA PET/CT or SRS with ^{111}In-pentetreotide SPECT/CT, VHL patients are reported to have panNETs in 31–79% [241,243–245]. Almost all the panNETs are NF-panNETs, although in rare patients a F-panNET has been reported[12]. The NF-panNETs in VHL differ from MEN1 in that 67–70% have a single panNET, which in 20%-mean(range-2–50%) is malignant with a mean size of 2.6–5.3 in different series[12,242,243]. In most VHL patients the smaller panNETs are asymptomatic and do not progress, with the result that it is uncommon for a VHL patient to die of the panNET (2–7% and is very uncommom if the panNET is<3cm[12]. Therefore, at present it is currently recommended that only panNETs≥3 cm be resected, although not all series agree with this criterion [12]. There is not complete agreement on which imaging procedures should be routinely performed in VHL patients for detection of panNETs and if detected how to image on follow-up [12,240]. The National Cancer Network (NCCN) guidelines recommend triphasic CT or MRI for the diagnosis of panNETs [246,247]. The frequent multiple cystic lesions in VHL patients possess a challenge in diagnosing panNETs

on MRI or CT[243,245,248]. CT scanning is reported to have sensitivity of 29–94% for detecting panNETs in VHL patients [240] and in one comparative study CT scanning had twice as great a sensitivity for detecting panNETs than MRI[245]. EUS has been shown to be more sensitive than CT/MRI alone or with SRS at detecting solid pancreatic lesions in VHL patients [244]. In VHL patients ^{68} Ga-DOTA-SSA PET/CT has been shown to be more sensitivity for the detection of panNETs than cross-sectional imaging with CT scans[243] and shows a high frequency of multiple lesions(36%)[243]. The cerebellar and spinal hemangiobastomas, as well as a number of other VHL non-panNET lesions can be positive on SRI[243]. During follow-up, panNETs in patients with VHL demonstrate a nonlinear growth pattern with some showing no growth or even a decrease in size using serial CT/MRI assessments [249]. The growth patterns are variable, no associated with grade or malignancy, and assessment of tumor density (>200) showed a 75% specificity for identifying malignant panNETs [249]. In general studies show there is a very low to no role for, ^{18}F-DOPA PET/CT, and ^{11}C-5-HTP PET in diagnosing VHL panNETs, [244,245,245]. The role of ^{18}F-FDG PET/CT in diagnosis/therapy of panNETs in VHL patients is unclear with some stating there is little or no role[243], whereas other studies support a role[250–252]. In a recent study [250] volumetric parameters on ^{18}F-FDG PET/CT in VHL patients with panNETs were useful in detecting higher grade tumors with higher malignant potential. In a prospective study ^{18}F-FDG PET/CT identified 87% of the panNETs in VHL patients seen on CT scan; the SUV max on ^{18}F-FDG PET/CT correlated with tumor size; and identified 93% of patients with lesions requiring surgery including 3 patients with metastatic foci not seen on CT scan[251]. (p=0.0062).

11.5. Imaging in specific panNETs with special features: Cystic panNETs

Cystic panNETs are reported to represent 9–11.5% of all panNETs[253]and they have both similarities and differences from solid panNETs[253–255]. They differ from the solid panNETs[253] in that they are less frequently found in the pancreatic head/uncinate(28 vs 46%)[253](20 vs 42%)[255]; larger in size [254]; less frequently a F-PanNET[253–255]; less likely associated with MEN1[254]; more likely benign/uncertain rather than malignant(90 vs 66%)[253]; more likely to be a G1 grade(82 vs 53%, p<0.001) [253]; less likely to have lymph node metastases(11 vs 29%)[253], and in a met-analysis to have a similar 5 yr. OS or DFS[253,255].

Cystic pancreatic neoplasms such as pancreatic serous cystic neoplasms can be hypervascular and difficult to distinguish from panNETs[256]. Unenhanced CT and MRI features including differences in MRI T2 weighted images and ADC maps have been described which help distinguish these two tumor groups[256]. Cystic panNETs are often misdiagnosed by cross-sectional imaging, with a misdiagnosis of up to 43% in some studies[257–259]. EUS-FNA had a high accuracy for identifying malignancy in cystic panNETs, as it did for solid panNETs (89% and 90%, respectively)[254,260]. Furthermore, the use of EUS-FNA with cytology made a diagnosis of a cystic panNET in 71% of cases in one study, compared to a correct diagnosis in only 38% with EUS alone[261]. In another study EUS-FNA had a sensitivity of 63% and when compared to patients with mucinous cysts, the patients with cystic panNETs had cystic fluid with a lower CEA concentration, thicker cyst walls were seen, and the diagnostic cytology was more frequently positive [261].

In a recent meta-analysis[262] including 431 patients with cystic panNETs: cytology had a sensitivity of 78%: 85% were in NF-panNETs; in the 15% with a F-panNETS that were cystic, they were primarily insulinomas; 88% were ENETs stage 1–11b which is limited to the pancreas and the 5 yr. DFS was 92% for stages 1–111.

12. Controversial aspects of Imaging of panNETs (Table 7)

There remain a number of controversies in imaging of panNETs, with a number of the most important ones listed in Table 7. In the preceding paragraphs a number of these have been discussed and will only be briefly dealt with here.

The introduction of molecular imaging particular SRI with ^{111}In-pentetreotide with detection by SPECT/CT (octreoscan) and later ^{68} Ga-DOTA-SSA PET/CT, has not only greatly enhanced our sensitivity for detecting most panNETs[17,19,26], it also has generated a number of areas of that are unclear and, in some cases, controversial.

In the inherited panNET syndromes (MEN1, VHL) small panNETs (<1.5–2 cm in MEN1, <3 cm in VHL) are generally observed, which is in keeping with the ENETs and NANETs guidelines [9,11,13], as discussed previously. Recently a number studies discussed in an earlier section, have recommended that routine use of ^{68} Ga-DOTA-SSA PET/CT in these patients. In is certainly clear from these studies that ^{68} Ga-DOTA-SSA PET/CT detects more panNETs and other NETs in MEN1 patients, but it is not clear that this changes management in many patients, if the existing treatment guidelines are being followed [16,239]. While most would agree that if a patient is going to undo abdominal surgical exploration that ^{68} Ga-DOTA-SSA PET/CT would be indicated, as well in patients with advanced disease, but in the routine patient with only a small NF-panNET, it remains unclear when or how frequently ^{68} Ga-DOTA-SSA PET/CT is indicated (Table 7). A similar situation exists in patients with VHL(Table 7). Cross-sectional imaging studies identify most panNETs ≥3cm, which is the recommended size for surgical removal in patients with VHL, and it is not established that the detection of additional lesions by ^{68} Ga-DOTA-SSA PET/CT less that this size will change management. The controversy over the management of these patients extends to the general question of how they should be managed with imaging studies. It is unclear whether EUS-FNA should be routinely used in MEN1/VHL patients, or only in a selected group such as those with lesions changing in size, as well as what criteria of change should be used to recommend surgical exploration (Table 7). Recent studies [25,240,245,250,251] raises the possibility that ^{18}F-FDG PET/CT, which is preferentially taken up by more aggressive, proliferative tumors, can be used to identify those who will require earlier intervention. At present it is unclear who subgroup of MEN1/VHL patients should be investigated with ^{18}F-FDG PET/CT and how often it should be repeated (Table 7).

Recently a similar watch and wait approach to the management of small, NF-panNETs (<1.5–2 cm) in patients with sporadic disease is being advocated [63–65,263–265], similar to patients with MEN1/VHL. Similar questions about the use of EUS alone or with EUS-FNA, the roles of molecular imaging with ^{18}F-FDG PET/CT or with ^{68} Ga-DOTA-SSA PET/CT can be raised about the management of these patients and the role of different

imagine modalities, as was raise in the preceding paragraph with the inherited panNET syndromes.

Recently a number of derived parameters from various imagining modalities have been proposed as correlating with tumor grading, survival, recurrence or aggressive tumor behavior such as SUVmax of molecular imaging modalities (^{18}F-FDG PET/CT, ^{68} Ga-DOTA-SSA PET/CT)(Table 5,6), ADC and other diffusion constants with MRI (Table 4) and various CT ratios (Table 3). The exact role of these in the routine management of panNET patients is unclear.

Gastrinomas and insulinomas have a number of unclear areas related to imaging and in some cases they are controversial. The exact role of ^{68} Ga-DOTA-SSA PET/CT in mangemnt of insulinomas is unclear with one study reporting very low sensitivity and another excellent sensitivity. This is an important issue because in a percentage of these patients the insulinomas are not imaged with existing techniques, and because the medical management is not always satisfactory, this complicates the ability to cure the patient surgically. In gastrinomas, the principal imaging problem is the inability to localize duodenal gastrinomas, which are frequently <1 cm in diameter. The reports on the sensitivity of ^{68} Ga-DOTA-SSA PET/CT in ZES are limited and not correlated with the surgical result, so it is unclear how useful ^{68} Ga-DOTA-SSA PET/CT will be for these small lesions. The role of hormonal sampling for both of these F-panNETs is unclear. Whether it will be replaced by ^{68} Ga-DOTA-SSA PETS/CT is unclear. Furthermore, the development of radiolabeled GLP1 receptor ligands promises to be a very sensitive imaging method for insulinomas, however it is unclear whether it will become more generally available and replace other commonly used imaging techniques[162,163,176,204].

13. Conclusions

There are a number of new imaging modalities for panNETs as well as NETs in other locations, that are proving to have excellent sensitivity and specificity and are being increasingly used in their localization. Both with these new modalities, which include a number of forms of molecular imaging, as well as with refinements of older imaging modalities, there is an enhanced ability not only to localize panNETs, but to provide important prognostic information both for treatment and for survival. In addition to enhancing the management of patients with panNETs, in a number of cases there are unanswered questions, as well as controversy. In this article each of these areas are reviewed in detail.

14. Expert Commentary

PanNETs as well as GI-NETs(carcinoids) have long fascinated physicians because of the florid and distinctive clinical syndromes that can be associated with those that over secrete biologically active peptide/amines (insulinomas, glucagonomas, carcinoid syndrome). The NETs themselves have generally been thought as quite uncommon, generally pursuing an indolent course, and not generally a major cancer type, because of their relatively low death

rate. In general, there were few new treatments, few advances in their imaging, no Phase 3 randomized trials, and their treatment had little impact on other aspects of oncology.

In general, all of this has changed. It is now clear that panNETs, as well as NETs in other locations are increasing in frequency, whether because of increased detection or increased occurrence, is not clear[266]. Also, there have been large strides in the pathology of NETs, with the development of classification/grading systems that have prognostic value and can influence patient management[1,2]. Insights from these pathologic studies have begun to have an impact on therapeutic approaches in other more frequent, aggressive tumors such as prostate cancer[267–269]. From the pathological studies of panNETs and other NETs it has become clear that they frequently over-express G-protein coupled receptors from a number of families(especially somatostatin, GLP1, bombesin) and from that, arose the concept that these could be used to localize these tumors, as well as later, to treat them[91]. From this developed the use of radiolabeled somatostatin analogues to imagine the tumors, which is now the most sensitive localization method available[17,91]. Furthermore, using other radiolabeled somatostatin analogues it has been possible to treat these tumors, because almost all, overexpress somatostatin receptors, if well differentiated[88,91]. This latter point has been shown in a recent Phase 3 study[89]. This methodology is now being investigated for both the diagnosis, imaging and treatment of prostate cancer using radiolabeled bombesin receptor analogues[267,268]. Furthermore, it is now realized that a significant proportion of panNETs and NETs in other locations pursue an aggressive course, and can cause considerable morbidity[1–3]. This has led to a number of double-blind Phase 3 studies of antitumor treatment for malignant panNETs and/or patients with other NETs in other locations with advanced diseases[270–273]. These include studies demonstrating the antiproliferative efficacy of somatostatin analogues; the mTOR inhibitor, everolimus and the tyrosine kinase inhibitor, sunitinib[270–273].

Each of the above advances and recent changes have impacted the imaging of panNETs, as well as NETs in other locations (Figure 1), either directly or indirectly as discussed in detail in this paper. Briefly, the increased frequency of panNETs/NETs have presented an increased number of patients with these tumors, particularly patients with earlier disease and smaller panNETs/GI-NETs. The controversy over the treatment of these patients with an increasing tendency for watch and waiting in NF-small(<1.5–2cm) panNETs has led to queries of how best to image these tumors serially, the role of EUS, and the need for more sensitive imaging. The establishment of a classification system that has prognostic value has had a direct impact on the attempt to develop parameters from imaging modalities that correlate with the tumor classification as well as long-term prognosis. The increased insights from pathology identifying increased G-protein receptor expression in these tumors has led to the development molecular imaging with somatostatin and GLP1 receptor analogues, as well as PRRT for treatment of the advanced, progressive disease in patients. The ascendency of PRRT is leading to changes in the use of imaging modalities, both in the need to establish the presence of somatostatin receptors on the tumor prior to considering PRRT, as well as to develop imaging parameters predicative of its outcome. The increased understanding of the natural history of syndromes with inherited panNETs and the proper imaging approaches that should be used, is being directly affected by the controversies in their treatment.

Therefore, as should be apparent from the above discussions, imaging of panNETs as well as other NETs, is undergoing a number of rapid changes, is involved in numerous areas of controversy, and some of these will extend to the use of many of these imaging modalities in other cancer's management, as these approaches are increasingly used in oncology.

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•of interest

••of considerable interest

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15.

Key Issues

- There have been advances in many aspects of the imaging of panNETs/other NETs over the last few years.
- New tumor pathology classification and grading systems with prognostic value have been established which are affecting the approach/use of imaging in panNET patients
- The discovery of over-expression of various G-protein coupled receptors by panNETs/other NETs has led to the development somatostatin receptor imaging(SRI)
- Recent studies are defining the roles of SRI and other forms of newer molecular imaging in panNETs
- Recent studies of both cross-sectional imaging modalities (CT,MRI, ultrasound) as well as molecular imaging studies, are increasingly describing imaging parameters that correlate with tumor grade/survival/recurrence.
- Increasing understanding of the natural history of small NF-PanNETs in both sporadic and inherited panNETs syndromes is having a marked effect on the imaging approaches used in their management.
- These advances have generated a number of controversies and new unanswered questions.

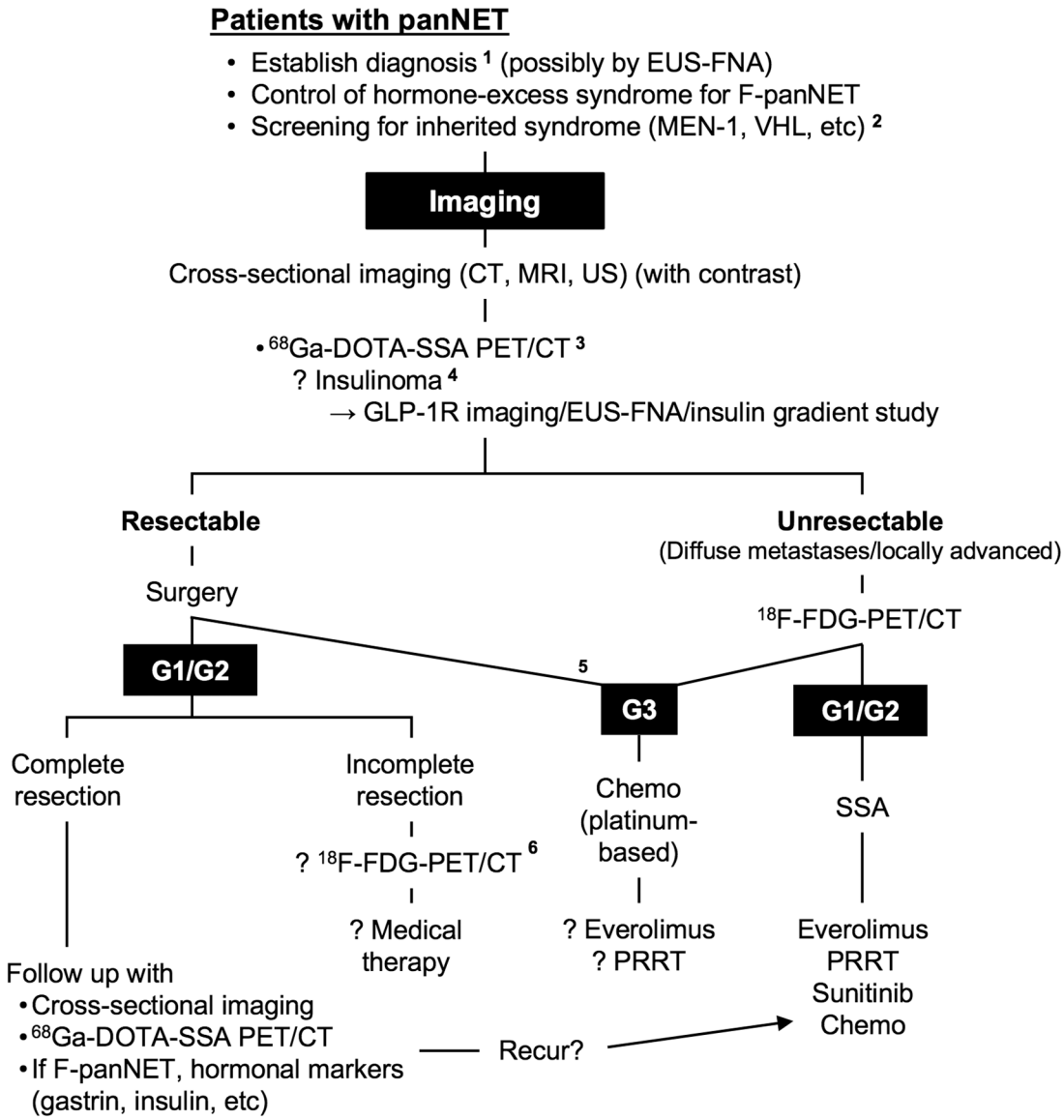

Figure 1.

Algorithm of imaging for the management/treatment of panNET

1 Diagnosis based on histopathological findings in NF-panNET, and hormone function tests in F-panNET (see section 2).

2 Sporadic or inherited panNETs frequently managed differently (see section 1).

3 ^{68}Ga PET/CT allows whole body assessment of disease extent and is more sensitive than cross-sectional imaging (see section 7.C).

4 Sensitivity of ^{68}Ga-DOTA-SSA PET/CT in insulinomas may be low, due to the low expression/absence of somatostatin receptor subtype 2. In MEN1, neither somatostatin receptor imaging nor cross-sectional imaging identify which imaged NET is functional. Therefore, GLP-1R, EUS-FNA or insulin gradient may be helpful (see section 11).

5 If resected panNET is cured but is G3, which is uncommon, then follow as G1/G2 category.

6 ^{18}F-FDG PET/CT can identify aggressive NETs (see section 7.D).

CT, computed tomography; EUS-FNA, endoscopic ultrasound with fine needle aspiration; F, functioning; FDG, fluorodeoxyglucose; G1/2/3, grade 1/2/3 (according to the WHO classification system); GI, gastrointestinal; GLP-1R, Glucagon-like Peptide 1 receptor; MEN1, multiple endocrine neoplasia-type 1; MRI, magnetic resonance imaging; NF, non-functioning; panNET, pancreatic neuroendocrine tumor; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; US, ultrasonography; VHL, Von Hippel Lindau Disease.

Table 1:

Roles for tumor imaging in the management of panNETs [8,11,14–21].

1	Molecular imaging with radiolabeled somatostatin analogues [^{111}In-Pentetreotide (octreoscan)/^{68}Ga-DOTATOC PET/CT/etc.] is increasingly used for suspecting and the diagnosis of panNET in patients with a pancreatic mass [14,132].
2	Imaging is used to establish the location of the primary panNET.
3	Imaging is used to establish the extent of the tumor burden and determine whether surgical excision should be attempted[8,11,14,132,210].
4	Imaging is used to allowing staging of the disease and thus determination of prognosis[7,8,14,19].
5	Imaging results may alter treatment approaches to advanced disease[7,94].
6	Rate of growth of the tumor determined by previous imaging results or during follow-up has important prognostic value [274–276].
7	Imaging results have important prognostic value[8,24,94,137,140,141]
8	Serial imaging is essential to determine response to all antitumor treatments in patients with advanced disease[8,14].
9	Serial imaging is essential to determine recurrence post-surgical resection, particularly patients with NF-panNETs [11,224].
10	In patients with inherited panNET syndromes (MEN1, VHL, etc) imaging studies are essential in localizing the panNETs which are usually nonfunctional, localizing duodenal gastrinomas in MEN1 patients and NETs in other locations in MEN1 patients [12,16,236,243].

Table 2:

Sensitivity of various imaging modalities for panNETs and their hepatic metastases

	Sensitivity (%)				
Imaging	**Duodenal**	**Pancreatic**			**Liver Mets**
Modality	**Gastrinoma**	**Insulinoma**	**PanNET <1.5 cm**	**PanNET >2.5 cm**	
CT scan	5–47	20–63	34	50–94	75–100
MRI	10–44	10–85	34	60–95	67–100
US	0–21	26–50	11–33	30–76	15–77
Angiography	15–51	50–60	30–60	60–90	33–86
EUS	40–63	71–94	40–90	82–100	N/A
SRS[Octreoscan]	30–32	33–60	29–30	52–96	90–100
^{68}GaDOTATAC PET/CT	68–100	31–90	60–80	68–100	95–100
Hormonal sampling					
PVS	50–76	80	N/A	N/A	
Stimulated with hepatic venous sampling	67–92	72–100	N/A	N/A	40

References: CT[19,21,36,45,217] :MRI[19,21,36,45,68,217]; US[19,36,45,217]; Angiography[45,213,217];EUS[19,21,168]; SRS[19,21,217]; ^{68}GaDOTATAC PET/CT [19,21,36,115,125,199,277]; Hormonal sampling-insulinomas[34,36]; gastrinoma [45,191,213]

Table 3:

CT scan proposed criteria for identifying aggressive panNETs (Part A), correlating with tumor grade/ differentiating High grade G3 from G1/G2 panNETs (Part B) or differentiation of panNETs from adenocarcinomas (Part C)

A. CT scan findings favoring aggressive over non-aggressive panNETs [(1)]	
1	Presence of pancreatic ductal dilation(p=0.014) [54]; (p<0.05)[49]
2	Increased tumor size(p=0.003)[54]; p<0,0001 [56]
3	Presence of vascular involvement (p=0.003)[54]
4	Presence of lymphadenopathy p=0.002) [54]
5	The texture parameter entropy (p=0.003)[54]
6	Tumor shape with less round, more lobulated in advanced grades[56]
7	On multivariate analysis, size>3cm, (p=0.006); portal enhancement ratio (≤1.1) (p=0.001); hepatic metastases(p=0.003) predicted worse recurrence-free survival [278]
8	The contrast enhancement pattern of panNETs correlates with the histological classification [279]. None of benign panNETs had early contrast enhancement with rapid wash-out, while panNETs of uncertain behavior or that were NET carcinomas frequent have either even or only late contrast enhancement[279]
B. CT scan findings correlating with grade or distinguishing PanNETs with G3 over G1/G2	
1	G2 over G1 was favored by larger tumor size(p=0.029); tumor conspicuity [non-hyperattenuation compared to pancreatic parenchyma during the portal venous phases] (p=0.016), presence of distant metastases. In a panNET≥2cm, M grade(M1), tumor conspicuity accuracy of a G2 diagnosis was 71%, 61%,71% and all together=825[50]
2	Presence of iso/hypo-attenuation (43% of panNETs) correlated with higher grading [51].
3	The CT ratio (proportion of the quantification value in tumor versus parenchyma in arterial phase) predicted G3 grades in panNETs with a sensitivity-100%. specificity-94% and correlated with microvessel density(p<0.001) [52]
4	Increased tumor grade correlated with increasing tumor size [52,54]; with ill-defined tumor margins[49,53]; lower sphericity, higher skewness of arterial 2D analysis [53]; heterogeneous enhancing[49,56]; hypervascularity[49]
5	G2 favored over G1 by a lower attenuation value, and ROC analysis showed this had sensitivity of 83%, specificity=92%with AUC=853[55]. G2 was also favored by irregular tumor margins, vessel involvement, cystic degeneration/necrosis, but less that tumor size or CT attenuation[55]
6	Grade 3 favored over G1/G2 by: portal enhancement ratio (<1) [sensit=92%, specif=81%]; poorly defined margin, tumor size>3cm. bile duct dilation and vascular invasion. When at least 2 of 5 criteria present sensit=92% and specif=88% for G3[57]
C. CT scan findings favoring panNETs over pancreatic ductal adenocarcinomas	
1	Well circumscribed, homogeneously enhancing and hypervascular appearance favor pNETs[49]
2	Pancreatic duct dilation more frequent in pancreatic cancer[49]
3	The uncommon features on CT in a panNET of ill-defined, heterogeneously enhancing and hypovascular appearance with duct dilatation could be differentiated from PDAC with 0.76–81 diagnostic performance [49]

Table 4:

MRI/MDCP proposed criteria for identifying aggressive panNETs (Part A), correlating with tumor grade/ differentiating High grade G3 from G1/G2 panNETs (Part B) or differentiation of panNETs from adenocarcinomas (Part C)

A. MRI findings favoring: aggressive over non-aggressive panNETs[(1)]	
1	A maximum diameter of ≥30 mm with irregular margins (p<0.001) [76][(1)]; panNET>2cm(p=0.002) [75]
2	Absence of a cleavage plane with the main pancreatic duct (p=0.002) [76][(1)]; presence of pancreatic duct dilation(p=0.021) [77] or pancreatic duct involvement(p=0.024) [58]
3	Presence of vascular encasement (p<0.001) [76][(1)]
4	Presence of extrapancreatic spread (p=0.006) [76][(1)]
5	Presence of abdominal metastases (p<0.001) [76][(1)]
6	In [76] using the presence of criteria 3,4, and 3 in a sequential algorithm, MRI had a sensitivity of 93% and a specificity of 77% for identifying malignant NF-pan-NETs [76]
7	Lower ADC values/ratios occurred in aggressive panNETs(p<0.01) [77]
8	Presence of a non-rounded or ovoid shape and increased vascularity in arterial phase (p<0.05) [77]
9	Presence of a non-bright T2W image(p=0.008) [75] or restricted diffusion within the lesion(p=0.014) [75].
B. MRI findings correlating with grade or distinguishing PanNETs with G3 over G1/G2.	
1	With MRI with diffusion weighted imaging (DWI), lower apparent (ADC) and true (D) diffusion coefficients occurred in G3 panNETs, with optimal cut-offs of 1.19 10^{-3} mm^2/s for ADC (sensit-100%, Specif-92%) and for D, 1.04 10^{-3} mm^2/s (sensit-82%, specif-92%) [69]
2	On univariate analysis tumor diameter (p<0.0001), shape(p<0.0001), enhancement pattern (p<0.0001), cystic portion (p0.012, and ADC value (p=0.012) all differed between G1,G2,G3[56]. On multi-variate analysis only the ADC value was significant(p=0.002) [56]
3	Ill-defined boundaries, larger size, necrosis, low-moderate enhancement, pancreatic duct dilatation, metastases and high diffusion-weighted imaging intensity were more common in panNEC(G3) than G1/2[71]
4	In a large number of different tumors, the ADC mean correlated significantly and inversely with the Ki-67 index and including in NETs (panNETs/other NETs) (r=−0.52) [70]
5	A cut-off value of ADC of 0.94×10^{-3} mm^2/s differentiated G3 from G1/G2 with a sensitivity of 72% and specificity of 92% [71]. G3 had lower ADC than G1/G2[72]
6	G2 was favored over G1 panNETs by the presence of marked hyperintensity(p=0.01), the ADC value negative correlated with grade and was lower in G2, with a cut-off value of 0.93×10–3 mm2/sec identifying G2 with a sensitivity of 82% and specificity of 80% [73]
7	High grade panNETs had low to intermediate T2W signals, ill-defined border, their liver metastases had a cystic component in 80% and wash out in 70%(0% of lower grades) [74]
8	G3 have lower mean ADC than G1, but not G2; greater skewness, kurtosis than G1; and greater tumor size than G1[280]
C. MRI findings favoring panNETs over pancreatic ductal adenocarcinomas (PDAC	
1	Hyperintensity on T2-weighed images (82% of NF-panNETs) instead of hypointensity [76][(1)]; High T2 signal, homogeneous enhancement on arterial phase, hypervascular liver metastases, absence of duct obstruction or vascular encasement [79]
2	Hyperintensity/Isointensity during the arterial/pancreatic phase of the dynamic study(36–76%NF-panNETs) instead of hypodensity as seen in 89% of adenocarcinomas [76,80,281][(1)]
3	The intravoxel incoherent motion-derived flowing blood volume f and microvessel density are significantly lower in ductal adenocarcinomas than panNETs [78].
4	Enhancement degree at the arterial and portal phases and the ADC values had a sensitivity of 92–97% and specificity of 77–92% for differentiating PDAC from panNETs [80]
5	On MRI with univariate analysis nonhypervascular panNETs compared to PDAC showed higher frequency of well-defined margins, portal hyper/iso-enhancement, and maximal upstream parenchymal thickness(MUPT) of ≥10 mm, lower frequency of

ductal dilation, vascular invasion, peri-pancreatic infiltration. On multivariate analysis well-defined margin, portal hyper/iso-enhancement were significant and resulted in as sensitivity of 64% and specificity of 99% to distinguish panNETs from PDAC [81].

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(1) Differentiation of biologic behavior was defined as differentiating G1 from G2 or TNM stage I/II vs stage III/IV using univariate analysis. Studies were in NP-panNETs [76]

Table 5:

Recent results (2013–2017) with ^{68}Ga-DOTA-SSA PET/CT : Sensitivity, specificity with panNETs only and all NETs (Part A); comparison with ^{111}In-Penetreotide SPECT/CT (Part B) and prognostic value for tumor grade/differentiation or survival (Part C).

A. Recent results ^{68}Ga-DOTA-SSA PET/CT: Sensitivity, specificity with panNETs only and all NETs	
1	Sensitivity with panNETs only : **2017**[(95%)[282],(88%)[283],; **2016**[(92)[126],(88%); **2014**[(84%)[284],(98%)[285], (100%)[123]; **2013**[(100%)[286],(68%)[125]
2	Sensitivity with series containing various GI-NETs including panNETs: **2017**[(82%)[113],(92%)[126], (92%)[19]; **2016**[(99.9%)[287],(96%)[288],(97%)[120], (95%)[289], (100%)[141]; **2015**[(100%)[290]; **2014**[(94%)[291],(95%)[24],(91%)[136],(96%)[123]; **2013**[(98%)[292],(86%)[111]
3	Specificity with panNETs only: 2017[(100%)[126]; 2016[(83%)[126]; 2014[(100) [123]
4	Specificity with series containing various GI-NETs including panNETs: **2017**[(100%)[113],(88%)[19]; **2016**[(93%)[288],(97%)[120]; **2014**[(95%)[291],(50%)[136], (97%)[123]; **2013**[(100%)[292]
B. Recent results ^{68}Ga-DOTA-SSA PET/CT: Compared to ^{111}In-Penetreotide SPECT/CT	
1	Sensitivity with series containing various GI-NETs including panNETs: **2017**[(100% vs 78%) [14], **2016**[(99.9% vs 60%)[287], (96% vs 72%)[288], (95% vs 45%)[289]; **2015**[(100% vs 54%)[290]
2	Specificity with series containing various GI-NETs including panNETs: **2016**[(93% vs 93%)[288]
C. Recent results ^{68}Ga-DOTA-SSA PET/CT: ability of the addition of ^{68}Ga-DOTA-SSA PET/CT to change patient management (% of patients)	
1	**2017** (50%) [131], (51%) [14], (39%) [85], (73%) [122], (50%) [143]; **2016** (36%) [288], (40%) [120],(33%) [289]; **2014** (75%)[121]; **2013** (59%) [292],(17%) [111]
D. ^{68}Ga-DOTA-SSA PET/CT findings correlating with prognosis: grade/differentiation/survival	
1	^{68}Ga-DOTA-SSA PET/CT has high sensitivity for detection of metastatic disease both in lymph nodes and liver, as well as distant metastases (bone, etc.), all of which have a major impact on treatment, prognosis and survival [1,5,7,10,94,122,124,292]
2	Determination of ^{68}Ga-DOTA-SSA PET/CT-avid tumor volume (TV) inversely correlated with PFS(p=0.001) and overall disease related survival(OS)(P=0.002)[293].
3	In various studies [111,137,143,294,295] ^{68}Ga-DOTA-SSA PET/CT's tumor standardized uptake value(SUV) correlate with PFS, Ki-67, tumor grade/differentiation or tumor progression, whereas in others [114,283]no correlation with Ki-67, grade or sst receptor density
4	The degree of ^{68}Ga-DOTA-SSA PET/CT uptake by the NET correlates with sst2 expression determine by immunohistochemistry which was an independent predictor of OS (p=0.037)[28]
E. ^{68}Ga-DOTA-SSA PET/CT findings correlating with response to PRRT	
1	^{68}Ga-DOTA-SSA PET/CT SUV correlated with the degree of uptake of radioligand on PRRT [134] and a SUV/max cutoff of 16.4 was predictive of responding lesions with sensitivity of 95% and specificity of 60%[135]

Table 6:

Recent results (2013–2017) with ^{18}F-FDG PET/CT : Sensitivity with panNETs only and all NETs (Part A); comparison with ^{111}In-Penetreotide SPECT/CT (Part B); effect of grading on FDG positivity(Part C); prognostic value for tumor grade/differentiation or survival (Part D); and effect of FDG on treatment(Part E) or patient management (Part F)

A. Recent results ^{68}Ga-DOTA-SSA PET/CT: Sensitivity, specificity with panNETs only and all NETs	
1	Sensitivity with panNETs only : **2017**[(68%%)[23],(58%)[147],(60%)[282]; **2016**[(65%)[296]; **2014**[(73%)[285]
2	Sensitivity with series containing various GI-NETs including panNETs: **2017**[(67%)[23]; **2016**[(49%)[297],(58%)[141]; **2015**[(72%)[298]; **2014**[(56%)[137],(37%)[24]
B. Recent results comparing sensitivity of ^{68}Ga-DOTA-SSA PET/CT to ^{18}F-FDG PET/CT	
1	Sensitivity with panNETs only : **2017**(94% vs 60%)[282]; **2014**[(98% vs 73%)[285];
2	Sensitivity with series containing various GI-NETs including panNETs: **2014**[(100% vs 56%)[137],(95% vs 37%)[24],(91% vs 42%%)[136]
3	Specificity with series containing various GI-NETs including panNETs: **2014**[(50% vs 100%)[136]
C. Recent results ^{18}F-FDG PET/CT : Affect of tumor grade on positivity	
1	**Sensitivity with panNETs only** : **G1** (28%) [296], (20%) [282], (45%) [285]; **G2** (83%) [296], (33%) [285],(76%) [282]; **G3** (75%) [121],(88%) [285]
2	Sensitivity with series containing various GI-NETs including panNETs: **G1** (17%) [24], (10%) [299]; **G2** (43%) [24], (25%) [299],(86%) [298]; **G3** (51%) [24],(65%) [299], (100%) [298];
D. ^{18}F-FDG PET/CT correlating with prognosis: grade/differentiation/survival	
1	On univariate analysis in patients with panNETs, the metabolic tumor volume(MTV)(p=0.003) and total lesion glycolysis (TLG) (p=0.027) computed from^{18}F-FDG PET/CT were significant predictors of OS[300]. MTV and TLG correlated with a higher Ki-67[142]
2	^{18}F-FDG PET/CT positivity predicted progressive disease in NETs(sensitivity-91%, specificity-86%)[23]; and/or postoperative DFS(p=0.0463)[148].
3	^{18}F-FDG PET/CT positivity or SUVmax correlated with increased tumor grade (p=0.01)[280], p=0.018[24,143,148,282,285,301]; increased Ki-67[296]; increased tumor size (p=0.01)[296], [282], metastatic lymph nodes[282]
4	^{18}F-FDG PET/CT positivity had a sensitivity of 100% and specificity of 62% in differentiating G1/G2 form G3 panNETs[148]
5	^{18F}-FDG PET/CT positivity or SUVmax correlated with shorter PFS[137,297,301], overall survival[297,299,301]
E. ^{18}F-FDG PET/CT correlating with treatment responses	
1	FDG positivity correlated with treatment refractoriness with PRRT with ^{177}Lu DOTATATE[146]; a shorter PFS after PRRT (21 vs 69 mos)[147]
F. ^{18}F-FDG PET/CT results altered patient management	
1	The ^{18}F-FDG PET/CT result changed management in 22% of NET patients, whereas the ^{68}Ga-DOTA-SSA PET/CT result changed management in 50% of patients in one study[143]

Table 7:

Controversial areas of imaging of panNETs

1. In patients with MEN1:

1.A. What is the role of molecular imaging particularly SRI with ^{68}Ga-DOTA-SSA PET/CT[16,239]

1.B. What is the role of imaging with ^{18}F-FDG PET/CT in MEN1 patients? [25] Should it be done routinely: When repeated?

1.C. What is the role of EUS and/or EUS-FNA initially and in follow-up of patients with MEN1?

1.D. In patients with NF-panNETs <1.5–2cm, what should be the follow-up imaging modalities and how often should they be repeated?

1.E. In patients with NF-panNETs <1.5–2cm who are observed, what are the criteria for change on imaging that should recommend surgical removal?

1.F. Are assessments of hormonal gradients particularly in MEN1/insulinoma patients, still of value to the localize functional panNET in a patient with multiple panNETs?

2. In patients with VHL:

2.A. What is the role of molecular imaging particularly SRI with ^{68}Ga-DOTA-SSA PET/CT[243].

2.B. What is the role of imaging with ^{18}F-FDG PET/CT in VHL patients? [245,250–252] Should it be done routinely: When repeated?

2.C. What is the role of EUS and/or EUS-FNA initially and in follow-up of patients with MEN1?[244]

2.D. In patients with VHL with NF-panNETs <3cm, what should be the follow-up imaging modalities and how often should they be repeated?

3. In which patients should dual imaging with ^{68}Ga-DOTA-SSA PET/CT and ^{18}F-FDG PET/CT be performed?

4. Should SUV/Max values for molecular imaging be more widely used for prognostic value?

5. With MRI or CT what parameters should be used for prognosis and when should it be?

6. What imaging parameters have the best predictive value for the response to medical anti-tumor treatment? To PRRT?

7. What is the role of molecular imaging particularly SRI with ^{68}Ga-DOTA-SSA PET/CT in patients with insulinomas?[36,101,199]

8. Does insulin hormonal sampling from hepatic veins after arterial calcium infusion still have a role in patients with insulinomas? [36,101,199].

9. In patients with small, sporadic NF-panNETs (<1.5–2 cm) who are being observed[63–65,263–265], **what is the role of molecular imaging with ^{18}F-FDG PET/CT or EUS-FNA?**

10. In patients with insulinomas, will the use of radiolabeled GLP1 receptor ligands be more generally used [162,163,176,204] **and replace some of the existing imaging studies now widely used in insulinoma patients?**