Seminars in ULTRASOUND CT and MRI

The Role of PET/CT in the Imaging of Pancreatic Neoplasms

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Pancreas cancer is a complex disease and its prognosis is related to the origin of the tumor cell as well as the stage of disease at the time of diagnosis. Pancreatic adenocarcinomas derive from the exocrine pancreas and are the fourth leading cause of cancer-related deaths in the United States, while well-differentiated pancreatic neuroendocrine tumors (pNETs) derived from the endocrine part of the pancreas are rare and characterized by a slow growth and good life expectancy. Surgery is the only curative treatment approach, and an accurate assessment of resectability is of paramount importance in order to avoid futile procedures. The role of molecular imaging with positron emission tomography and computed tomography ranges from indispensable for pNETs to controversial for certain scenarios in pancreatic adenocarcinomas. This review article aims to overview molecular pancreatic imaging.
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Introduction

According to the American Cancer Society, the incidence of pancreatic cancer is on the rise, with 56,770 estimated new diagnosed cases and 45,750 estimated deaths for 2019, making it the fourth leading cause of cancer-related deaths, equally for men and women, in the United States.[1] Future projections indicate that before 2030, it will become the second leading cancer-related cause of death.[2] The prognosis is remarkably poor, with a 5-year survival rate of only 9% which is the lowest in any cancer.[1,2] The main reason is that patients are asymptomatic and therefore the majority (80%-85%) are diagnosed at advanced stages; however, even at an early stage, the chance of relapse is high (70%-80%).[3] Early detection is of utmost importance and decreases mortality as patients without or with only small peripancreatic lymph node metastases have a higher 5-year survival rate of 40%-50%.[4] Besides conventional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI), molecular imaging with positron emission tomography and computed tomography (PET/CT) is a powerful tool for detecting and evaluating various cancers. Depending on the cell origin of the pancreatic tumor, different radiotracers are available for functional imaging. They range from high sensitivity and specificity in case of pancreatic neuroendocrine tumors (pNETs) to selectively indicated but increased use more recently in case of pancreatic adenocarcinomas.

This review article will evaluate the current status of molecular imaging for pancreatic neoplasms.

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Pancreatic Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is the most common tumor of the pancreas (95%) and carries a poor prognosis. At the time of diagnosis, patients often present at an advanced stage[3] since the disease is indolent and shows only nonspecific symptoms like abdominal pain or weight loss. The only curative treatment approach is surgery which, due to the anatomical location of the pancreas with its proximity to vital vascular structures and nerves, is only accessible in <20% of the cases[5] and not applicable in a metastatic setting[6,7] Therefore, early and accurate diagnosis is of utmost importance to determine the most effective therapy option and avoid futile surgery.

Molecular imaging for PDAC is mostly performed with the radiotracer ^{18}F fluoro-2-deoxy-D-glucose (FDG) which is based on the principle of increased glucose metabolism of malignant cells.[8]

FDG PET/CT for Initial Diagnosis

The role of imaging in the initial diagnosis is not only to distinguish between benign and malignant tumors but also to

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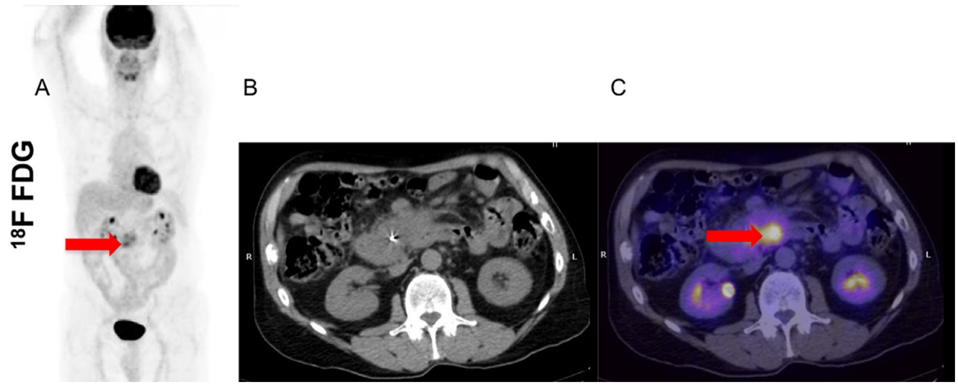

Figure 1 58-year-old man with newly diagnosed PDAC. Focal FDG uptake (arrows) is seen on maximum intensity projection (MIP) PET (A) and transaxial PET (C) corresponding to mass on CT (B).

attempt an accurate assessment of resectability since only 5%-25% of the patients are candidates for curative resection at surgical exploration.[9,10] The overall sensitivity of FDG PET/CT has been reported between 85% and 97% and 96% when PET/CT is done in conjunction with contrast-enhanced CT (ceCT) to 96%.[11-14] The specificity ranges between 64% and 90%[11,13-18] These results are summarized in Table 1. An example is shown in Figure 1.

The detection of peripancreatic lymph nodes may be obscured by the FDG uptake in the primary tumor and thus is reported to have low sensitivity.[19-21] Asagi et al found in 108 patients with PDAC a sensitivity of 42% in FDG PET/CT but nonetheless better when compared to ceCT alone (35%).[22]

Several studies demonstrated the superiority of FDG PET/CT in finding distant metastases.[22-24] Heinrich et al[25] revealed not only a better detection of distant metastases, but suggested that PET changed the disease management in 16% of the patients. Bang et al[13] found similar results, especially in diagnosing liver metastases. Among the 93 patients with histologically proven PDAC, PET changed the treatment plan in 26.9% (25 cases) and resectability in 21.5% (20 cases) due to distant metastases. Diederichs et al[26] reported a sensitivity of 70% for hepatic metastases of all sizes and 93% for hepatic tumors >1 cm. However, the sensitivity is low when it comes to small (<1 cm) liver lesions[26,27]

However, there are some challenges for FDG PET/CT, as summarized below.

- False positive findings: Inflammation, such as any kind of pancreatitis, especially focal pancreatitis, show increased glucose metabolism leading to false positive results and decreasing specificity.[19,28]
- False negative findings: Glucose intolerance is often seen in patients with pancreatic disease. Hyperglycemia is known to decrease FDG uptake and can result in false negative findings.[19,26]
- Small tumors (T1, T2) can be missed by FDG PET/CT.[25,29,30]
- In regards of the aggressiveness of the tumor, several studies showed that a higher baseline standard uptake value (SUV) correlates with poorer outcome as well as more advanced disease.[21,31-33]

FDG PET/CT for Detection of Recurrent Disease

Patients with PDAC have a high relapse rate within a year after surgery.[34] Conventional imaging with ceCT has difficulties in differentiating between benign processes (eg, post-treatment changes, tumor necrosis, or fibrosis) and malignancy. Molecular imaging plays a key role for detecting recurrent disease. In one study, FDG PET was able to detect 96% of locoregional recurrences as opposed to CT/MRI that detected 39%. For

Table 1 A Summary of Studies Evaluating FDG PET/CT for Initial Diagnosis of PDAC

First Author (Reference)	Year	Number of Patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Zhang et al[11]	2015	70	92	65	87	77
			96*	90*	96*	90*
Santhosh et al[17]	2013	87	93	90	95	87
Buchs et al[12]	2011	45	96	67	92	80
Kauhanen et al[20]	2009	38	85	94	94	85
Bang et al[13]	2006	102	97	78	98	70
Lemke et al[16]	2004	104	89	64	81	76
Rose et al[15]	1999	81	92	85	96	73

PDAC, pancreatic ductal adenocarcinoma.
*PET/ceCT.

abdominal spread, PET showed positivity in 7/7 patients and found 2 additional extraabdominal metastases whereas CT/MRI failed to identify disease in all these cases. However, CT/MR was superior in diagnosing liver metastases in 11/12 patients (96%) compared to 5/12 (42%) with PET.[35] Similar results were reported by Sperti et al.[33] FDG PET was able to detect postsurgical relapse in 84.7% (61/72 patients) compared to CT in 48.6% (35/72 patients) and changed treatment course in 44% (32/72 patients); again, it missed hepatic lesions, especially subcentimeter lesions, in 2 patients with disease identified on ceCT. Another group compared PET/CT and PET/ceCT in 45 patients with suspected relapse of PDAC[36] and found a sensitivity of 83% and specificity of 91% for PET/CT vs 92% and 95%, respectively, for PET/ceCT. A recent meta-analysis[37] comprising of 7 studies with a total of 333 patients found a sensitivity of 88% and a specificity of 89% for FDG PET/CT compared to ceCT alone with 70% and 80%, respectively. PET/ceCT had the highest sensitivity and specificity with 95% and 81%. Table 2 summarizes these publications.

A limitation are false positive findings due to post-therapeutic changes like postsurgical or postradiation therapy inflammation. Therefore, some authors recommend performing FDG PET/CT 6 weeks after treatment.[35,38]

FDG PET/CT for Evaluation of Treatment Response

The main difference between molecular imaging and conventional imaging modalities is that FDG PET is able to assess metabolic changes to treatment that occur earlier than morphologic changes in tumor size.[39] In comparison with ceCT, FDG PET/CT has reported superiority in assessing response to therapy and moreover serves as a good outcome predictor based on changes in standardized uptake value (SUV).[40,41] In a small cohort of 15 patients, PET/CT was able to reveal 5 responders who on follow-up had a longer time to progression.[13] In a larger population of 40 patients receiving preoperative chemoradiotherapy, 21 patients were histologically identified as responders and 19 patients as nonresponders. A higher baseline SUV was found in 71% of the responders vs 32% of the nonresponders; in addition, SUV measurements decreased more in responders vs nonresponders.[42] Similar results were seen in a study with 32 patients receiving concurrent chemoradiotherapy: a significantly higher overall survival (OS) (17 vs 9.8 months) and progression-free survival (8.4 vs 3.8 months) was seen in patients with a greater decrease in SUV compared to those with a lesser decline.[43] A recent publication on therapy assessment in 42 patients with locally advanced PDAC receiving chemotherapy alone or chemoradiotherapy found that FDG PET/CT changed treatment management in 52.4% of cases.[44]

Other Radiopharmaceuticals

Personalized precision medicine and targeted treatment approaches lead to the search for novel radiotracers to improve imaging of PDAC. A possible pathway might be imaging tumor cell proliferation; this has been proposed as a predictor of prognosis and outcome.[45,46] ^{18}F-fluorothymidine (FLT) reflects the rate of proliferation in cancer cells. Herrman et al[47] demonstrated in a study with 31 patients with pancreatic tumors that FLT is able to stratify between malignant and benign lesions with a specificity of 100% and a sensitivity of 71.4%. In a subsequent study, the same group compared FLT to FDG in a cohort of 42 patients and found a sensitivity of 70% and specificity of 75% for FLT compared to 92% and 50% for FDG, respectively. Challapalli et al[48] evaluated the response to chemotherapy with FLT PET/CT. A higher baseline SUV was correlated with a poorer outcome. Figure 2 shows a comparison of FDG and FLT in a patient with suspected recurrence of PDAC.

Recently, (4S)-4-(3-^{18}F-Fluoropropyl)-L-glutamate (FSPG) has evolved from preclinical to clinical studies in various cancers.[49-51] It is a glutamate analog which reflects the xC-transporter activity, a mediator of the redox state in the cell. Cheng et al[52] presented first results of FSPG in 23 patients with PDAC. FSPG detected more metastases with a sensitivity of 95%, specificity of 100%, and accuracy of 95.7% vs FDG with 90%, 66.7%, and 90%, respectively.

PET/MRI

Imaging with simultaneous PET/MRI combines the high soft tissue contrast of MRI with the benefits of molecular imaging. In a prospective study[53] of 37 PDAC patients at initial diagnosis, FDG PET/MRI was compared to FDG PET/CT plus ceCT. The authors showed similar results and no significant differences between the modalities, making PET/MRI a good alternative to PET/CT with less radiation exposure. Currently, most of the literature found on imaging with PET/MRI in PDAC is based on retrospective fusion of PET and MRI; however, it can be assumed that simultaneously acquired PET/MRI images would provide the same or even better results. Nagamachi et al[54] looked into 119 patients with malignant and benign pancreatic tumors. Retrospectively fused PET/MRI had a better accuracy in differentiating PDAC compared to PET/CT (96.6% vs 86.6%). Furthermore, T2-weighted images were

Table 2 A Summary of Studies Evaluating FDG PET/CT for Recurrent PDAC

First Author (Reference)	Year	Number of Patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Daamen et al[37]	2018	333	88 95*	89 81*		
Kitajima et al[36]	2010	45	83	91	83	87
Sperti et al[33]	2010	72	98	90	98	89

PDAC, pancreatic ductal adenocarcinoma.
*PET/ceCT.

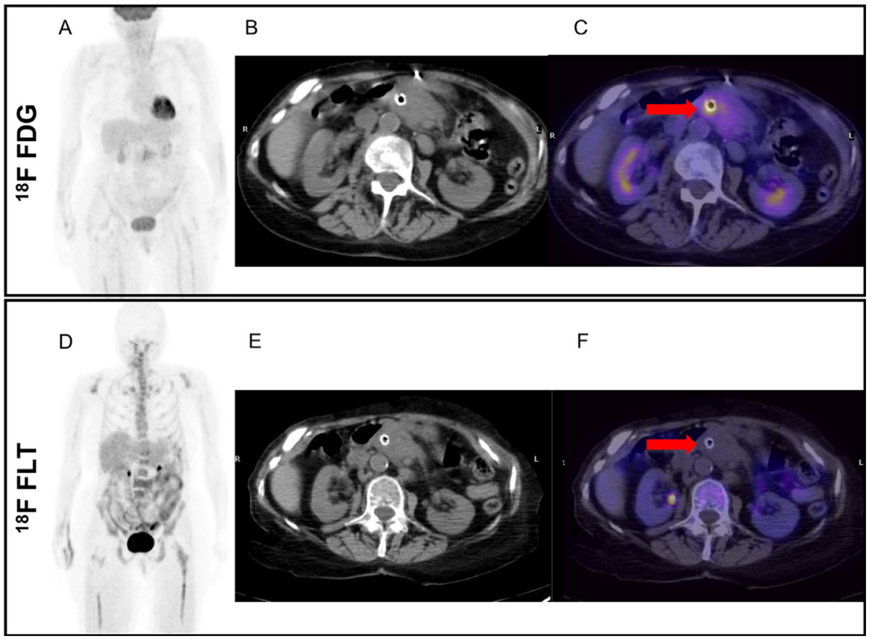

Figure 2 63-year-old woman with suspected recurrence of PDAC. FDG PET shows diffuse low-grade uptake along metallic stent (A, C), axial CT (B, E), and FLT PET (D), while FLT PET shows no uptake in the same area (F). Therefore, this was interpreted as inflammation rather than recurrent PDAC.

Table 3 A Summary of Studies Evaluating FDG PET/MRI for Pancreatic Adenocarcinoma

First Author [Reference]	Year	Number of Patients	Main Results
Joo et al[53]	2017	37	Comparison of PET/MRI, PET/CT plus ceCT had similar results in TNM staging
Nagamachi et al[54]	2013	119	Retrospective fusion of PET and MRI improved diagnostic accuracy vs PET/CT: 96.6% vs 86.6%
Tatsumi et al[55]	2011	47	Retrospective fusion of PET and MRI showed better diagnostic accuracy: PET/T1-w 93%, PET/T2-w 90.7%, PET/CT: 88.4%

T1-w, T1-weighted; T2-w, T2-weighted.

able to provide a better distinction of cystic lesions. Tatsumi et al[55] found that fusing T1- or T2-weighted images with PET had a higher diagnostic accuracy than PET/CT. Table 3 gives an overview of the most important publications.

Conclusion

For initial diagnosis, FDG PET/ceCT plays a key role not only in distinguishing malignant from benign processes but also as a decision maker in assessment of distant metastases. It shows lower sensitivity in detecting peripancreatic spread. In these cases, a multimodality approach including special ceCT protocols and endoscopic ultrasound is needed.

Treatment response is generally evaluated using the response evaluation criteria in solid tumors. Metabolic response to therapy, however, can be detected earlier than morphologic tumor shrinkage making FDG PET/CT a good prognosis predictor. An early and accurate evaluation of therapy response benefits clinical treatment decision-making and more importantly, spares the patient ineffective therapies.

Imaging with FDG PET/MRI appears similar to PET/CT.

Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (pNETs) account for 5% of all pancreatic tumors. They are rare but their incidence is on the rise.[56,57] This is most likely due to more awareness and incidental findings, as well as rapidly developing diagnostic methods. pNETs can occur sporadically or as part of a hereditary syndrome like multiple endocrine neoplasia type 1 (MEN-I), von Hippel-Lindau syndrome, neurofibromatosis type 1 (NF 1).[58,59] The prognosis is very much dependent on the differentiation and grade of the tumor. Grading of pNETs is based on the rate of proliferation given by the mitotic count

Table 4 Grading of Pancreatic Neuroendocrine Tumors

Grade	Ki67-Index	WHO Classification
G1	<2%	Neuroendocrine tumor G1: well-differentiated
G2	3%-20%	Neuroendocrine tumor G2: well-differentiated
G3	>20%	Neuroendocrine carcinoma

and Ki67 index (Table 4). Well-differentiated pNETs, G1 and G2, are characterized by a slow growth and good life expectancy even with liver metastases present,[60] whereas poorly differentiated pNETs, G3, show poor survival.[56] pNETs are categorized in functioning and nonfunctioning tumors. Functioning tumors are diagnosed earlier due to hormone-related symptoms and are usually small in size. Nonfunctioning tumors are more frequent, indolent and therefore diagnosed often at an advanced stage with synchronous metastases.

Functional Imaging

What makes well-differentiated NETs suitable for targeted radionuclide imaging is the overexpression of somatostatin receptors (SSR) on their cell surface.[61,62] Different subtypes of human SSRs have been identified: 1, 2A, 2B, 3, 4, and 5. The majority of pNETs show overexpression of subtype 2A.[63] Poorly differentiated NET, also known as neuroendocrine carcinoma, usually lose their expression of SSR.

The most available and used imaging was planar and single photon emission computed tomography (SPECT) with gamma cameras using Indium-111 (^{111}In) labeled octreotide. However, this has been largely replaced by PET radiopharmaceuticals with better imaging characteristics.

Currently, there are 3 well-established somatostatin analogs that are conjugated to DOTA and labeled with Gallium-68 (^{68}Ga): ^{68}Ga DOTATATE (DOTA,Tyr(3)-octreotate), ^{68}Ga DOTANOC (DOTA,1-Nal(3)-octreotide) and ^{68}Ga DOTATOC (DOTA, D-Phe1, Tyr (3)-octreotide). DOTATATE has a 10-fold higher and selected affinity to SSR2 receptor followed by DOTATOC which also binds to SSR5, whereas DOTANOC is selective towards SSR2, SSR3, and SSR5.[64] Although ^{68}Ga DOTATOC, ^{68}Ga DOTANOC, and ^{68}Ga DOTATATE have different affinity to the various SSR, they all show high affinity to SSR 2 and are equally powerful in their diagnostic accuracy.[65,66]

A meta-analysis comprising of 416 patients comparing ^{68}Ga DOTATOC and ^{68}Ga DOTATATE revealed a pooled sensitivity of 93% and 96% and a pooled specificity of 85% and 100%.[67]

SSR PET/CT for Initial Diagnosis

pNETs are solid and hypervascular tumors that may have calcifications in 20% of the cases.[68,69] At the time of initial diagnosis, synchronous liver metastases are found in 59%-80% of the cases.[70,71] Hepatic metastases are mostly hypervascular and show central necrosis.[72]

A meta-analysis including 2105 patients from 22 studies evaluating ^{68}Ga DOTA-peptide PET/CT for NET showed a pooled sensitivity of 93% and specificity of 96%.[73]

Kumar et al[74] showed in a cohort of 141 patients with pNETs an overall sensitivity of 85.7% and a specificity of 79.1%. When stratified for diagnosis and staging, a sensitivity of 73% and a specificity of 50% were found, while for restaging a sensitivity of 98.6% and a specificity of 100% were reported. The discrepancy between diagnosis and restaging is due to the higher number of patients with an insulinoma in the diagnosis group, a NET known to express less SSR.

When it comes to detecting NET of unknown origin, SSR PET/CT has been demonstrated to be superior to CT alone[75]: PET/CT was able to localize the primary tumor in 35/59 (59%) cases of which 16 patients had pNETs. In a retrospective analysis, CT alone was only able to detect 8/16 (50%) pNETs.

Compared to MRI alone, SSR PET/CT was reported to have a higher sensitivity as well. Schmid-Tannwald et al[76] reported in a study with 18 pNET patients a PET/CT detectability rate of 100%, whereas T2-weighted images showed a detectability rate of 39.1%, which improved when combined with DWI to 65.2%. In a prospective study[77] comprising of 19 heterogenous NET patients and comparing SSR PET/CT, SSR SPECT/CT, and MR, SSR PET/CT had a sensitivity of 96% and a specificity of 97% compared to SSR SPECT/CT 60% and 99% and DW MRI 72% and 100, respectively. Table 5 summarizes studies evaluating SSR PET/CT for pancreatic neuroendocrine tumors.

SSR PET/CT for Recurrent Disease

Haug et al[78] showed a high sensitivity of 90% and specificity of 82% for ^{68}Ga DOTATATE PET/CT. In a subgroup analysis of gastroenteropancreatic NETs, the sensitivity rose to 94% and the specificity to 85%. The negative predictive value was 90% indicating that a negative scan rules out relapse of disease.

Other Radiopharmaceuticals

Recently, the widely used somatostatin analog DOTATATE has been labeled with another positron emitter, Copper-64 (^{64}Cu). In a comparison with ^{68}Ga DOTATOC, it had better performance for detecting true positive lesions.[79] This was probably due to the shorter positron range leading to better detectability, but it might also be related to the different somatostatin analog. Further studies comparing of ^{64}Cu DOTATATE and ^{68}Ga DOTATATE are needed.

PET/MRI

MRI has a high soft tissue contrast which benefits the detection of liver metastases.[80] Functional information from DWI has been demonstrated to have high sensitivity for detecting hepatic metastases derived from NETs.[81] Compared to PET/CT, the overall sensitivity of PET/MR for soft tissue tumors is higher, especially with specific MRI techniques like DWI and hepatobiliary phase.[82-85] However, one group showed that PET/MR was not better in pancreatic, small bowel lesions, and lymph node metastases.[84] An example of ^{68}Ga DOTATATE PET/CT and PET/MRI in the same patient is shown in Figure 3.

^{18}F FDG PET/CT

Well-differentiated pNETs do not show high glucose metabolism resulting in low sensitivity for FDG PET/CT. Poorly differentiated pNETs, on the other hand, show low expression of SSR and high glucose metabolism. They are suitable for imaging with FDG.[86-88] A Ki67 index of at least 10% has been proposed for stratification for ^{18}F FDG imaging.[89] pNETs which show glycolytic activity are associated with an aggressive tumor and poorer survival.[90,91]

Table 5 A Summary of Studies Evaluating SSR PET/CT for Pancreatic Neuroendocrine Tumors

First Author (Reference)	Year	Radiotracer	Number of Patients	Sensitivity	Specificity	Main Results
Johnbeck et al[79]	2017	^{64}Cu DOTATATE vs ^{68}Ga DOTATOC	59	^{64}Cu DOTATATE: 100% ^{68}Ga DOTATOC: 100%	^{64}Cu DOTATATE: 90% ^{68}Ga DOTATOC: 90%	More lesions detected by ^{64}Cu DOTATATE
Yang et al[67]	2014	^{68}Ga DOTATATE vs ^{68}Ga DOTATOC	416	^{68}Ga DOTATATE: 96% ^{68}Ga DOTATOC: 93%	^{68}Ga DOTATATE: 100% ^{68}Ga DOTATOC: 85%	
Etchebehere et al[77]	2014	^{68}Ga DOTATATE vs ^{99m}Tc HYNIC-octreotide vs. DW MRI	18	^{68}Ga DOTATATE: 96% ^{99m}Tc HYNIC-octreotide: 60% DW MRI: 72%	^{68}Ga DOTATATE: 97% ^{99m}Tc HYNIC-octreotide: 99% DW MRI: 100%	^{68}Ga DOTATATE more sensitive in detecting bone metastases and unknown primary lesions
Wild et al[66]	2013	^{68}Ga DOTANOC vs ^{68}Ga DOTATATE	18	^{68}Ga DOTANOC: 94% ^{68}Ga DOTATATE: 86%	-	^{68}Ga DOTANOC superior in detecting hepatic metastases
Geijer et al[73]	2013	SSR PET/CT vs SSR scintigraphy	2105	-	-	Better performance of SSR PET/CT
Schmid-Tannwald et al[76]	2013	^{68}Ga DOTATATE vs ce MRI vs DW MRI	18	-	-	Higher sensitivity of ^{68}Ga DOTATATE, added value of DW MRI
Kumar et al[74]	2011	^{68}Ga DOTATOC vs ^{18}F FDG vs ceCT	20	^{68}Ga DOTATOC: 100% ^{8}F FDG: 25% ceCT: 83%	-	Superiority of ^{68}Ga DOTATOC in diagnosing and staging of pNETs

ce, contrast enhanced; CT, computed tomography; DW, diffusion weighted; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; pNETs, pancreatic neuroendocrine tumors; SSR, somatostatin receptor.

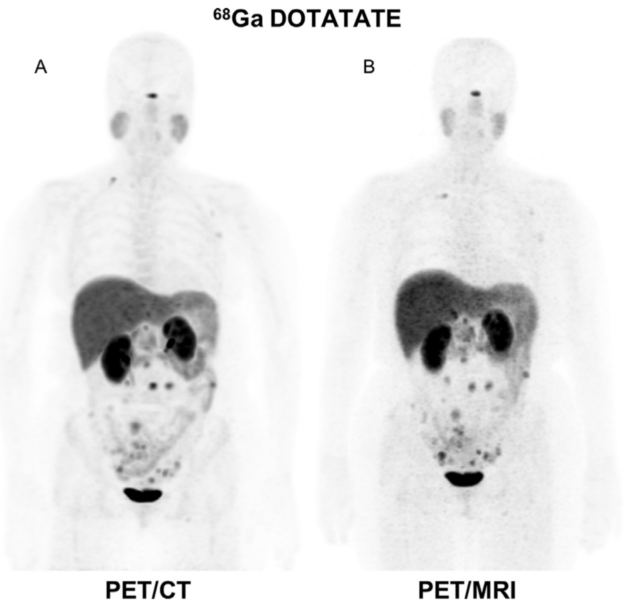

Figure 3 65-year-old woman with metastatic PNET. MIP from ^{68}Ga DOTATATE PET/CT (A) and PET/MRI (B) acquired on same day are shown.

Conclusion

Functional imaging with PET/CT with ^{68}Ga labeled DOTA chelated somatostatin analogs emerged as gold standard in the diagnosis, follow-up as well as in the stratification for further therapy. SSR PET/CT is also used to evaluate the resectability of the primary tumor and the eligibility for peptide receptor radionuclide therapy with Lutetium-177 (^{177}Lu) or Yttrium-90 (^{90}Y) labeled DOTATATE.[92]

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