Value of Somatostatin Receptor PET/CT in Patients With MEN1 at Various Stages of Their Disease

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Value of somatostatin receptor PET/CT in MEN1 patients at various stages of their disease

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Short Title: ^{68}Ga-DOTATOC in MEN1

Abstract

Context. Despite the growing evidence of the clinical value of somatostatin receptor (SSTR) PET in the evaluation of neuroendocrine tumors/NET, its role remains to be clarified at different time points in the MEN1 patient journey. The rareness of the disease is however a significant impediment to prospective clinical trials.

Objectives. The goals of the study were to assess the indications and value of SSTR PET/CT in MEN1 patients.

Methods. We retrospectively included patients from 7 French expert centres for whom data on SSTR PET/CT and morphological imaging performed at the same period were available. Detection rates of PET study were analysed.

Results. One hundred eight patients were included. SSTR PET/CT was performed at screening (n=33), staging (n=34), restaging (n=37) and for PRRT selection (n=4). PET detected positive pancreatic lesions in 91% of cases at screening, with comparable results to MRI but superiority to CT (P=0.049). Metastases (mostly LN) were present at the screening phase in 28% of cases, possibly due to the suboptimal value of screening morphological imaging in the assessement of nodal metastases and/or a long delay between imaging studies. SSTR PET/CT was considered as superior or complementary to the reference standard in the assessment of LN or distant metastases in the vast majority of cases and regardless of the clinical scenario.

Conclusion: This study shows the potential added value of SSTR PET in the assessment of MEN1-associated NETs and provides a great impetus towards its implementation in the evaluation of MEN1 patients.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an inherited autosomal dominant disease due to germline mutation in the tumor suppressor *MEN1* gene that encodes for menin. The population frequency is approximately 1 in 30,000 individuals. MEN1 predisposes to the development of multiglandular parathyroid disease, pituitary tumors, duodeno-pancreatic neuroendocrine tumors (NETs) as well as other less frequent tumors, such as adrenocortical tumors, bronchial/thymic NETs and lipomas (1).

Until present, MEN1 patients continue to have decreased life expectancy primarily due to the malignant course of NETs, particularly pancreatic and thymic NETs (1-6). It is therefore of major importance to perform an accurate diagnosis at the earliest stage of development and to identify tumors with aggressive behavior that would require a tailored treatment. A personalized approach to each patient is recommended: « The right treatment, for the right patient, at the right time ».

In a large cohort of patients, 23% of patients <21yrs had pancreatic NET (9% non-functional PanNET, 12% insulinomas, and 2% gastrinomas) (7). Due to the suboptimal sensitivity of serum tumor markers (8,9), imaging is the cornerstone of this screening strategy (10). At screening, the existing guidelines recommend to use imaging studies without ionization for depicting duodeno-pancreatic NET, such as MRI and/or EUS (up to yearly) (11). The optimum methods for screening for thymic and bronchial tumors have been less established but mostly rely on MRI or CT.

In recent years, somatostatin receptor (SSTR) PET/CT using [^{68}Ga]-labeled somatostatin analogs has proven to be effective in the diagnostic evaluation of various NETs, and is also mandatory when selecting candidates for targeted radiotherapy (PRRT) in patients with inoperable and progressive metastatic NETs (11). SSTR PET has progressively replaced somatostatin receptor scintigraphy (SRS) due to its many advantages (i.e., greater image

resolution, shorter imaging times, lower radiation exposure, cheaper costs in properly equipped departments). At present, the value of SSTR PET/CT in MEN1-associated NETs has been evaluated in six studies with very promising results in terms of lesion detection and impact on patient management (12-18). Overall, SSTR PET often detects more primary NETs (except thymic carcinoids) and metastases than morphological imaging, with very few false positives. The literature is however hampered by frequent mixing of various clinical scenarios (screening at initial diagnosis, disease staging, restaging or prior to PRRT) and the limited number of cases (19).

The primary aim of the study was to describe the indications and the value of SSTR PET/CT in the setting of a retrospective study that assembles a large cohort of MEN1 patients evaluated in seven reference centres.

Patients and Methods

Study Design

We performed a retrospective, multicentre study conducted in seven reference centres. Each centre provided anonymised data from their MEN1 patients that were obtained as part of their routine management and that were collected from their institutional medical datafiles. Regarding imaging findings, no central reading was performed in the setting of this study, but all images were analyzed on-site by experienced radiologists and nuclear imaging physicians in the setting of institutional multidisciplinary team meetings. The potential added value of SSTR PET compared to other imaging investigations was left to the judgement of the investigators. The precise anatomical location of each lesion within a target organ as well as their size were not collected, making impossible any head-to-head comparison between modalities at each individual level.

Patients

A total of 108 MEN1 patients were included in this study (Nantes University Hospital: 36 patients, Marseille University Hospital: 17 patients, Beaujon University Hospital: 15 patients, Lyon University Hospital: 15 patients, Strasbourg University Hospital: 11 patients Bordeaux University Hospital: 7 patients and Clermont-Ferrand: 7 patients). The diagnosis of MEN1 was defined by the presence of at least two MEN1-related lesions or one MEN1-related lesions and a family history of MEN1, or a positive MEN1 genetic screening test (20). Genetic analysis was performed after obtaining informed consent in one of the TENgen network laboratories (21). All patients underwent SSTR PET/CT (i.e., [^{68}Ga]-Ga-DOTA-TOC PET/CT) at various stages of their disease: screening (No prior-knowledge of any duodeno-

pancreatic or thymic NET), staging (follow-up of untreated NET), restaging (patients treated for NET in ,at least, one anatomic site) and in the selection stage for PRRT.

The study was approved by the Assistance Publique-Hôpitaux de Marseille ethics advisory committee (N°PADS21-159). Waiver of patient consent was granted by the ethics committee, given the retrospective nature of the study.

Imaging techniques

[^{68}Ga]-Ga-DOTA-TOC was used in all centers in accordance with market authorization. PET/CT acquisition protocols were performed according to each institutional guidelines. Images were captured from the vertex to mid thigh at approximately 60 min post-injection. The CT data were used for attenuation correction and fusion imaging. Images were reconstructed in a standard display including transaxial, sagittal and coronal projections. The delay between PET studies and other imaging modalities was less than 3 months. In patients that were evaluated more than once by SSTR PET, the PET study that was temporally closer to the morphological imaging study was selected for analysis. Morphological imaging procotols (CT, MRI and EUS) were also performed according to the institutional guidelines. All examinations were locally interpreted and reviewed by experienced physicians.

Analysis of PET/CT data

PET/CT studies were locally interpreted by experienced nuclear physicians as either positive or negative. A positive PET/CT was defined when at least one focal area of pathologically increased radiotracer uptake was detected, when compared to the surrounding tissue and physiological biodistribution. For regional analysis, the following regions were analysed separately: pancreas, duodenum, stomach, lungs, lymph nodes (LN), liver and bone. A region was considered positive when it contained at least one focal area of pathologically

increased radiotracer uptake, regardless of the number of positive foci. For lesional analysis in the pancreas, the total number of lesions was recorded. If the number of lesions exceeded 5, the count was scored as >5.

Gold Standard

At a patient level, the neuroendocrine nature of the lesions was confirmed by pathological analysis following surgery or biopsy. In non-operated cases, the diagnosis was based in each center by a multidisciplinary consensus that integrated all imaging studies and follow-up data.

Clinical management following SSTR PET study

The clinical management of patients following SSTR PET/CT was described as either: active surveillance, surgery or other therapeutic options (e.g., chemotherapy, somatostatin analogue, targeted therapy or PRRT, liver-directed therapy).

Genotype-phenotype correlation analysis

In order to study the potential relationships between genotype and development of metastases, *MEN1* variants were regrouped into two groups: those with null mutations (i.e. start loss, entire gene or exon deletions, non-sense variants, frameshift variants or variant affecting splicing), and those with non-truncating variations (i.e. synonymous or missense variants). Variants were reclassified according to the guidelines (22) and proposed adjustments for *MEN1* variants (23). Only pathogenic and likely pathogenic variants were considered in the analysis.

Statistical analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Categorical variables are reported as frequencies and percentages. Comparison between PET/CT and CT/MRI findings for the pancreas, duodenum and lymph nodes according to the different groups, were performed using Chi-Square test or Fisher's exact test, as appropriate. Addressing issues of separability and small sample sizes, Firth's penalized likelihood approach was performed in logistic regression models to estimate risk factors associated with PET positivity for PanNET, LN and distant metastases in the screening group according to the age of the patient when performing the PET/CT. Odds-ratios were expressed with 95% confidence intervals. All the tests were two-sided. The association between germline *MEN1* variants and development of metastases was studied using a Fisher's exact test. The statistical significance was defined as $p<0.05$.

Results

Patients

Among the 108 included cases, SSTR PET/CT was performed at various disease stages: 33 at screening, 34 at staging, 37 at re-staging and 4 for PRRT selection. Related cases were younger than index cases at the time of PET study (p=0.098). Primary Hyperparathyroïdism (PHPT), pituitary adenoma, adrenocortical adenoma and lipoma were the most frequent manifestations. At staging and restaging, 5.9% and 16.2% had distant metastases respectively, regardless of the primary NET (**Table 1**).

SSTR PET/CT findings: patient and region-level analysis

On per-patient analysis, SSTR-PET/CT showed NET lesions in 90.9% (30/33) of cases at screening, 100% at staging (34/34), 97.3% at restaging (36/37) and 100% at pre-PRRT evaluation (4/4). The pancreas was the most frequent site for primary NET and was detected by SSTR PET in more than 90% of cases regardless of the context. Two different anatomical regions (including lymph nodes) were positive on PET in 37% of cases. The vast majority (86.8%) of positive LN were abdominal (celiac and superior mesenteric or retroperitoneal). The percentage of patients with liver and bone metastases were 15.7% and 0.9%, respectively (**Table 2**).

Regarding patients found to have PanNET at screening, only 5% harbored simulatenously an extrapancreatic neuroendocrine primary on SSTR PET. LN metastases of duodeno-pancreatic origin were found in 20% and 47% of the screening and staging groups, respectively. Among patients evaluated at the restaging phase, 30% had distant metastases.

On per-organ analysis and regarding pancreatic involvement, PET was positive in 90.9% of cases at screening vs 71.4% for CT (p=0.049) and 92.3% for MRI; it was positive in 97% of cases at staging vs 93.1% for CT and 83.3% for MRI; and 86.5% at restaging vs 54.5% for CT (p=0.003) and 63.6% for MRI (p=0.055). For LN metastasis detection, PET performed better than the other imaging modalities, regardless of the clinical scenario, in particular, at staging, PET was positive in 47.1% of cases vs 13.8% for MRI (p=0.016), and at restaging in 40.5% of cases vs 13.6% for MRI (p=0.03) (**Table 3**). The percentage of regions with SSTR-positive foci on PET/CT imaging is described in Figure 1.

Head-to-head comparison between SSTR PET/CT and morphological imaging at lesion level

Comparison between PET and MRI has been compared for pancreatic lesions and metastases in all cases that have been evaluated by both modalities (72 cases). PET frequently

reported involved regions that were missed by MRI (3.8 to 16.7% depending on the context) while the opposite rarely occurred (0-4.6%) (**Table 4**). When compared to conventional imaging (MRI and CT), tumor multifocality was frequently detected by all modalities (**Figure 2**).

Clinical management following SSTR PET study

Overall, SSTR PET/CT was considered by investigators as superior to conventional imaging (MRI and/or CT) in terms of lesion detection in 51.5% of cases (17/33) at screening, 44.1% (15/34) at staging and 56.1% (23/41) at restaging+pre-PRRT stage. In the same scenarios, PET was considered as either equal and/or complementary to conventional imaging in respectively 39.4% (13/33), 38.2% (13/34) and 36.6% (15/41). In the remaining cases, PET was considered as inferior to conventional imaging (9%, 17.6% and 7.3%, respectively).

Surgical treatment was performed after PET in 39.4% (13/33), 26.8% (9/34) and 8.1% (3/37) in the screening, staging and restaging subgroups, respectively. Active surveillance was decided in 51.5%, 58.8% and 64.9% across the same subgroups. In the remaining cases, patients were treated medically with the use of SSA in respectively 6%, 14.7% and 10,8% in the same respective subgroups. Three out of the 4 cases were eligible for PRRT and subsequently treated.

Clinical and genetic factors affecting the value of SSTR PET

At the screening phase, multivariate analysis taking into account age at the time of PET study, sex, time interval between initial diagnosis and PET, index vs non-index status; only age at the time of PET was found to be weakly positively associated with positive PET findings for pancreatic NET, although non significantly (OR, 1.13;95% CI, 0.99-1.29; p=0.071). Importantly, there was no statistical difference across decades regarding PET

positivity for PanNET. Finally, at screening, no statistical difference was observed between age at the time of PET and PET positivity for lymph nodes (OR, 0.22, 95% CI 0.002-21.906; p=0.520) and distant metastases (OR, 0.02, 95% CI 0.001-8.712; p=0.212) as well as between index vs non-index status and PET positivity for lymph nodes (OR, 0.40, 95% CI 0.17-0.95; p=0.390) and distant metastases (OR, 0.68, 95% CI 0.30-1.53; p=0.353), as well as between index vs non-index status and PET positivity for lymph nodes (OR, 0.40, 95% CI 0.17-0.95; p=0.390) and distant metastases (OR, 0.68, 95% CI 0.30-1.53; p=0.353).

All but 3 patients carried a germline variant in the *MEN1* gene (**Supplemental Table 1,** https://figshare.com/articles/online_resource/MENNETREY_Supplemental_Tables_docx/16644070) (24). Variants were available for 97 patients and corresponded to frameshift deletion, insertion or insertion-deletion in 34 cases (35%), non-sense mutations in 10 cases (10%), missense variants in 26 cases (27%), large deletion of the gene in 5 cases (5%), start loss in 3 cases (3%), in frame deletion or duplication in 2 cases (2%), variants affected splice junction in the latter 17 cases (18%). Among the variants identified in the 97 patients, 2 variants were classified as uncertain significance.

Twelve new variants have been identified. No significant statistical association was observed between genotype (null *vs* non-truncating variants) and the presence of metastatic lymph nodes (OR, 2, 95% CI 0.77-5.05; p=0.24), distant metastases (OR, 1.47, 95% CI 0.48-3.98; p=0.6) or both (OR, 1.4, 95% IC 0.43-4.13; p=0.77) (**Supplemental Table 2,** https://figshare.com/articles/online_resource/MENNETREY_Supplemental_Tables_docx/16644070)(24). Although not statistically significant, there was a trend towards decreased risk for nodal or distant metastasis in patients with non-truncating variants (OR, 0.47, 95% CI 0.18-1.7; p=0.17).

Discussion

To the best of our knowledge, this is the largest study that evaluates SSTR PET/CT in the real life settting of patients with MEN1 at various stages of their disease (screening, staging, restaging and pre-PRRT). Although the present non-interventional study is limited by important biaises, it provides some important insights regarding the utilization of SSTR PET in MEN1 patients. The principal conclusions that can be drawn from this study include: Firstly, most of MEN1 patients in our cohort harbor SSTR positive pancreatic NETs. Secondly, NETs metastases can be detected in a large proportion of cases by SSTR PET. Thirdly, SSTR can be considered as superior or complementary to conventional imaging in the vast majority of cases, regardless of the disease stage.

Despite the potential added value of SSTR PET in MEN1, there is still a concern from physicians and patients regarding diagnostic radiation exposure that can be illustrated by the relatively advanced age of patients at the time of PET study in the screening group. This strong reservation to use ionizing radiation also exists for other patients with an underlying genetic susceptibility syndrome towards certain cancers. This is even more valid in MEN1 patients because fundamental studies demonstrate that menin is involved in DNA repair and mutated cells are more sensitive to injury from radiation, however, this merits further studies (25). The psychological impact, acceptability of repeated imaging studies, their availability and cost are also important factors to consider. Overall, these controversies exist and are important but the under-use of SSTR PET/CT or PET/MR must be balanced against the potential risk of delayed diagnosis of NET (25). Our study shows that more that 90% of patients belonging to this group harbor SSTR-positive pancreatic NET with an important trend towards multifocality within the pancreatic gland. The identification that 91% of patients with MEN1 in the screening group have a pancreatic NET is important and consistent with the data from pathological studies (26,27). These studies report that more than 90% of pancreases from MEN1 patients had neuroendocrine microtumors and/or NET. We

acknowledge that it is somewhat surprising that these patients were considered as negative on previous imaging investigations but this may illustrate some possible drawbacks or limits of the current imaging strategy or possible practical difficulties in the implementation of guidelines. Nevertheless, MRI and CT performed at the same period of the SSTR PET were found to accurately depict duodeno-pancreatic NETs. Of note, it is widely accepted that the highly elevated tumor-to-background uptake greatly facilitates their detection on SSTR PET/CT. Our study was not designed to provide any recommendation regarding the use of SSTR PET/CT in the screening of duodeno-pancreatic NET in MEN1 patients. We also support the use of imaging studies without ionization such as MRI in the first two decades of patients' lives but strongly encourage paying more attention to SSTR PET and discussing the optimal time frame for offering it to patients in the future guidelines. Furthermore, newer PET technology can dramatically decrease patients' exposure to radiation.

The diagnosis of metastases (mainly LN) remains a critical problem for morphological imaging due to its limited sensitivity and specificity, especially in the diagnosis of tiny nodes. We found a high proportion of patients with regional and distant metastases that were considered as occult on CT, while the opposite situation was rarely observed. In particular, for disease staging and restaging, the added value provided by SSTR PET/CT clearly promotes its use prior any surgical intervention. Our results are in accordance with other studies that found a very good sensitivity of SSTR PET in the staging/restaging of duodeno-pancreatic NETs, which can be higher than that of the recommended imaging modalities. We also show that SSTR provides complementary information to conventional imaging in the vast majority of cases, regardless of the disease stage that could significantly impact the management of patients. At present, the value of SSTR PET/CT in MEN1-associated NETs has been evaluated in the setting of five studies which showed very promising results. Froeling *et al.*, pioneered the evaluation of the impact of [^{68}Ga]-Ga-DOTA-TOC PET/CT in the diagnosis

and management of MEN1 patients (12). This retrospective, single-centre study included a series of 19 MEN1 patients. A total of 78 lesions were detected with a sensitivity and specificity of [^{68}Ga]-Ga-DOTA-TOC PET/CT of 91.7% and 93.5% respectively, regardless of tumor origin. PET performed better than CT alone (43.3% sensitivity and 61.3% specificity), especially in the diagnosis of LN metastases. A change in patient management was observed in 50% cases, most of which related to indications for pancreatic surgery. Sadowski *et al.,* have prospectively evaluated 26 MEN1 patients with [^{68}Ga]-Ga-DOTA-TATE PET/CT, SRS and CT (13). A total of 107, 33 and 48 lesions were detected by [^{68}Ga]-Ga-DOTA-TATE, SRS and CT, respectively. All the lesions observed by SRS and CT scan were found on [^{68}Ga]-Ga-DOTA-TATE. A change in therapeutic management was induced by PET in 31% of cases (8/26), mostly due to surgical indications. Lastoria *et al.,* have prospectively evaluated 18 *MEN1* patients with [^{68}Ga]-Ga-DOTA-TATE PET/CT (14). A pathological gold standard was obtained in 9 cases. Sensitivity and specificity of [^{68}Ga]-Ga-DOTA-TATE were both 100% for PanNET. Morgat *et al.*, has prospectively compared [^{68}Ga]-Ga-DOTA-TOC, SRS and CECT in the detection of duodeno-pancreatic NET in a series of 19 *MEN1* patients (15). [^{68}Ga]-Ga-DOTA-TOC was found to perform better than SRS and CECT (detection rates 76%, 20% and 60%, respectively $p<0.0001$), as well as have a higher specificity. [^{68}Ga]-Ga-DOTA-TOC detected 15 of 25 subcentimetric duodenopancreatic lesions that were not visualised by CECT. Finally, Patil *et al.*, have reported their experience from a retrospective analysis of 34 MEN1 patients evaluated by either [^{68}Ga]-Ga-DOTA-TATE or NOC and CT (16). PET was found to detect more lesions than CT (per-lesion: 74.1% vs 63.7%, $p=0.23$ and per-patient: 89.2% vs 71.4%, $p=0.09$), with a PPV of 100% for both modalities. The combination of the two imaging modalities provided the highest detection rates. [^{68}Ga]-Ga-DOTA-TATE or NOC PET/CT was particularly superior to CECT in the detection of gastrinoma (90% vs 10%, $p=0.0003$) and metastases (85% vs 47.5%, $p<0.00001$), especially

small LN metastases. [^{68}Ga]-Ga-DOTA-TATE was inferior to CT for thymic carcinoids (85.7% vs. 100%). We could not evaluate this latter finding in our study since none of our patients harbored a thymic NET at the time of the study. Cuthbertson *et al.,* have assessed the value of SSTR PET/CT in a series of 183 cases with PanNET (36 MEN1, 141 sporadic, 6 other). Overall, PET provided additional informations to other imaging findings in 54% of patients and influenced management in 39% of cases (18).

The identification of predictors of tumor aggressiveness is of main importance in order to guide physicians towards a more personalized risk-stratified follow-up. In our study, we failed to identify a relationship between the nature of the variants (i.e. null variants: non-sense variants, frameshift variants, entire gene or exon deletions, variants affecting start codon or splicing *vs* non-truncating variants: missense or synonymous) and LN and/or distant metastases. Missense variants were slightly associated with a less aggressive clinical phenotype but more patients would be necessary to achieve a statistical significance. Nevertheless, in our analysis, patients' age was not considered due to the lack of reliable information regarding the age of onset of metastatic disease.

We acknowledge several important limitations of the present study: its retrospective nature, the limited sample size per-subgroup, and the absence of pathologically proof for all SSTR positive foci. The latter point is often lacking in imaging studies because of ethical and practical reasons, it is often not possible to obtain pathological confirmation of each lesion. Of note, there are limited false positive findings in the evaluation of duodeno-pancreatic NETs and experienced nuclear physicians are aware of potential variants, caveats, and pitfalls that are commonly encountered on SSTR PET imaging (28).

In conclusion, our retrospective study of 108 MEN1 patients shows that SSTR-based imaging is superior and complementary to conventional imaging in the vast majority of cases in the assessment of LN or distant metastases, regardless of the disease stage. This study gives

new evidence-based data illustrating the steadily growing role of SSTR PET in the evaluation of adult patients with MEN1. Its role warrants to be clarified in the upcoming future clinical practice guidelines for MEN1.

Data Availability Statement

Supplemental date can be uploaded using the following link:

https://figshare.com/articles/online_resource/MENNETREY_Supplemental_Tables_docx/16644070

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Tables and Figures' legends

Table 1. Patients and tumors' characteristics at the time of SSTR PET/CT study

(*) percentage metastatic at the time of PET study.

Abreviations :

PET : positron emission tomography

SSTR : somatostatin receptor

PRRT : peptide receptor targeted radiotherapy

NET : neuroendocrine tumours

MEN 1 : multiple endocrine neoplasia type 1

Table 2. Positive results on SSTR PET/CT on per Patient and per Region analysis across disease stage subgroups

*Previous history of pancreatectomy for duodeno-pancreatic NET

Table 3. Imaging positivity on SSTR PET/CT, CT, MRI and EUS (per-region analysis)

Abreviations:

NET : neuroendocrine tumours

SSTR : somatostatin receptor

PET : positron emission tomography

CT : CT scan

MRI : magnetic resonance imaging

EUS : endoscopic ultrasound

Table 4. Head-to-head comparison between SSTR PET/CT and MRI or CT for detection of pancreatic NET and metastases (LN and distant met)

Figure 1. Percentage of regions with SSTR-positive foci on PET/CT imaging

Figure 2. Number of pancreatic NET on SSTR PET/CT and conventional imaging-CI (CT or MRI)

Number of patients in ordinate

Tables and Figures

Table 1.

	Screening	Staging	Restaging	Pre PRRT
N	33	34	37	4
Index Case in the MEN1 family (%)	45.5	41.2	32.4	75
Male/female sex (%)	54.5/45.5	41.2/58.8	43.2/56.8	50/50
Average age at the time of PET study (min-max). median (IQR)				
Index Cases	54 (18-77)	55.5 (22-69)	56 (37-78)	56 (49-66)
Related cases	38.5 (22-72)	49.5 (20-77)	50 (22-71)	42 (42-42)
Positive genetic test (%)	96.9	97	100	75
Primary hyperparathyroidism (%)	90.9	97	97.2	50
Pituitary Adenoma (%) (Secreting %)	45.4 (60)	50 (58.8)	62.1 (60.8)	50 (100)
Adrenocortical adenoma (%)	15.1	52.9	48.6	25
Lipoma (%)	21.2	26.4	21.6	50
Previous personal history of NET				
Duodenum (%)	0	20.6	18.9	50
Pancreas (%)	0	76.4	86.4	50
Thymus (%)	0	0	16.2	0
Lung (%)	0	11.8	10.8	25
Delay between SSTR PET and diagnosis of MEN1 (Years), median (IQR)	1	4	11	7
Metastatic disease of NET at the time of PET study (regardless of the primary): % regional/% distant	0	5.9/5.9	35.1/16.2	25/100

Table 2.

	Screening	Staging	Restaging	Pre-PRRT
N	33	34	37	4
Per Patient	30/33 (90.9%)	34/34 (100%)	36/37 (97.3%)	4/4 (100%)
Per organ (primary tumor)				
Pancreas	30/33 (90.9%)	33/34 (97.0%)	32/37 (86.5%)	3/4* (75%)
Duodenum	1/33 (3.0%)	3/34 (8.8%)	4/37 (10.8%)	0/4
Stomach	0/33	2/34 (5.9%)	3/37 (8.1%)	0/4
Lung	0/33	2/34 (5.9%)	1/37 (2.7%)	0/4
Per organ (metastases)				
Lymph Node	7/33 (21.2%)	16/34 (47.0%)	15/37 (40.5%)	0/4
Lung	1/33 (3.0%)	2/34 (5.9%)	4/37 (10.8%)	0/4
Liver	2/33 (6.0%)	5/34 (14.7%)	6/37 (16.2%)	4/4 (100%)
Bone	0/33	0/34	1/37 (2.7%)	0/4

Table 3.

	Screening				Staging				Restaging				Pre-PRRT			
	PET	**CT**	**MRI**	**EUS**	**PET**	**CT**	**MRI**	**EUS**	**PET**	**CT**	**MRI**	**EUS**	**PET**	**CT**	**MRI**	**EUS**
N	33	28	26	15	34	29	24	15	37	33	22	10	4	3	3	
Primary NET																
Pancreas	30 (90.9%)	20 (71.4%)	24 (92.3%)	11 (73%)	33 (97.0%)	27 (93.1%)	20 (83.3%)	15 (100%)	32 (86.5%)	18 (54.5%)	14 (63.6%)	10 (100%)	3 (75%)	2 (66.7)	1 (33.3%)	
Duodenum	1 (3.0%)	0 (0%)	1 (3.8%)	0 (0%)	3 (8.8%)	2 (6.9%)	2 (8.3%)	0 (0%)	4 (10.8%)	1 (3.0%)	1 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Stomach	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.9%)	1 (3.4%)	1 (3.4%)	0 (0%)	3 (8.1%)	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Lungs	0 (0%)	0 (0%)			2 (5.9%)	2 (6.9%)			1 (2.7%)	1 (3.0%)			0 (0%)	0 (0%)		
Thymus	0 (0%)	0 (0%)			0 (0%)	0 (0%)			0 (0%)	0 (0%)			0 (0%)	0 (0%)		
NET metastases																
Lymph Node	7 (21.2%)	4 (14.3%)	4 (15.4%)	0 (0%)	16 (47.1%)	8 (27.6%)	4 (13.8%)	1 (6.7%)	15 (40.5%)	10 (30.3%)	3 (13.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Lung	1 (3.0%)	1 (3.6%)			2 (5.9%)	3 (10.3%)			4 (10.8%)	3 (9.0%)			0 (0%)	0 (0%)		
Liver	2 (6.0%)	0 (0%)	1 (3.8%)	0 (0%)	5 (14.7%)	4 (13.7%)	3 (10.3%)	0 (0%)	6 (16.2%)	6 (18.1%)	3 (13.6%)	0 (0%)	4 (100%)	3 (100%)	3 (100%)	
Bone	0 (0%)	0 (0%)			0 (0%)	0 (0%)			1 (2.7%)	1 (3.0%)			0 (0%)	0 (0%)		

Table 4.

	Screening		Staging		Restaging	
Patients (N)	26		24		22	
Pancreatic NET	MRI +	MRI -	MRI +	MRI -	MRI +	MRI -
PET + PET -	24 (92.3) 0	**1 (3.8)** 1 (3.8)	20 (83.3) 0	**4 (16.7)** 0	13 (59) 1 (4.6)	**3 (13.7)** 5 (22.7)
Patients (N)	15		15		9	
Pancreatic NET	EUS +	EUS -	EUS +	EUS -	EUS +	EUS -
PET + PET -	11 (73.3) 0	**3 (20)** 1 (6.7)	15 (100) 0	0 0	7 (77.8) 2 (22.2)	0 0
Patients (N)	28		29		33	
Lymph Node	CT +	CT -	CT +	CT -	CT +	CT -
PET + PET -	3 (10.8) 1 (3.5)	**4 (14.3)** 20 (71.4)	7 (24.1) 1 (3.5)	**7 (24.1)** 14 (48.3)	10 (30.3) 0	**4 (12.1)** 19 (57.6)
Distant metastases	CT +	CT -	CT +	CT -	CT +	CT -
PET + PET -	1 (3.5) 0	**2 (7.2)** 25 (89.3)	5 (17.2) 1 (3.5)	**2 (6.9)** 21 (72.4)	8 (24.2) 0	**2 (6.1)** 23 (69.7)