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^{68}Ga-DOTA-exendin-4 PET/CT detects insulinomas in *MEN-1* patients

^{68}Ga-exendin-4 PET/CT detects insulinomas in patients with endogenous hyperinsulinemic hypoglycemia in MEN-1

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Context: Surgical intervention is advised in patients with multiple endocrine neoplasia type-1 (*MEN-1*) with non-functioning pancreatic neuroendocrine tumors (PanNET) and a size ≥20mm. Functioning PanNET such as patients with endogenous hyperinsulinemic hypoglycemia (EHH) due to (one or multiple) insulinoma(s) should be treated surgically independent of size. Preoperative localization of insulinomas is critical for surgery.
Objective: To evaluate feasibility and sensitivity of ^{68}Ga-DOTA-exendin-4 PET/CT in the detection of clinical-relevant lesions in *MEN-1* patients with EHH in combination with MRI.
Design: Post-hoc subgroup-analysis of a larger prospective imaging study with 52 EHH patients.
Patients: Six of 52 consecutive patients with EHH and genetically proven *MEN-1* mutation were included.
Interventions: All patients received one ^{68}Ga-DOTA-exendin-4 PET/CT and one MRI-scan within 3-4 days. Thereafter, surgery was performed based on all imaging results.
Main Outcome Measures: Lesion-based sensitivity of PET/CT and MRI for detection of clinical-relevant lesions was calculated. Readers were unaware of other results. Reference

standard was surgery with histology and treatment outcome. True positive (=clinical-relevant lesions) was defined as PanNET ≥20mm or insulinoma.
Results: In six patients, 37 PanNET were confirmed by histopathology. Sensitivity (95% confidence interval) in the detection of clinical-relevant lesions for combined PET/CT+MRI, MRI and PET/CT was 92.3% (64%-99.8%), 38.5% (13.9-68.4%) and 84.6% (54.6-98.1%), respectively (P-value=0.014 for the comparison of PET/CT+MRI versus MRI). Post-surgery, EHH resolved in all patients.
Conclusion: ^{68}Ga-DOTA-exendin-4 PET/CT is feasible in *MEN-1* patients with EHH. The combination with MRI is superior to MRI alone in the detection of insulinomas and may guide the surgical strategy.

Evaluating the feasibility and sensitivity of 68Ga-exendin-4 PET/CT in the detection of relevant lesions in MEN-1 patients with hypogylcemia in comparison with magnetic resonance imaging (MRI).

Introduction

Multiple endocrine neoplasia type 1 (*MEN-1*) is an autosomal dominant inherited tumor syndrome caused by heterozygous mutations in the *MEN-1* tumor suppressor gene with an incidence of 1:50,000. More than 80% of these patients develop multifocal functioning (F-PanNET) or non-functioning pancreatic neuroendocrine tumors (NF-PanNET), which are a major cause of premature death due to malignant progression (1,2). The most common F-PanNETs in MEN-1 are duodenal gastrinomas causing Zollinger Ellison Syndrom and pancreatic insulinomas causing endogenous hyperinsulinemic hypoglycemia (EHH)(3). Insulinomas can cause life threatening EHH and surgery is the cornerstone of therapy as current medical treatments remain insufficient, do not provide a permanent cure, and thus should be reserved for the perioperative period or for patients who cannot undergo surgery (4).

Older studies have proposed aggressive resection of every tumor identified by conventional imaging studies in the presence of biochemically proven EHH (5-7). However, pancreatic surgery is associated with significant mortality and long-term morbidity (8,9). NF-PanNET < 20 mm rarely develop metastases (10,11), and current studies have not shown any survival benefit for patients with NF-PanNET ≤ 20 mm who received surgery in comparison to patients who had conservative management, i.e. watchful waiting (12). Consequently, in patients with non-metastatic pancreatic neuroendocrine tumors (PanNET) all international guidelines recommend the resection of symptomatic insulinomas with the aim of eliminating life-threatening endogenous hyperinsulinemic hypoglycemia, but resection of NF-PanNET only above a size ≥20 mm due to the increased risk for malignant progression (12-14). For NF-PanNET <20 mm, the all international guidelines suggest a conservative management strategy (13).

In clinical routine different imaging modalities are used for the localization of insulinomas: contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI) (which is more sensitive than CT for this indication (15,16)), endoscopic ultrasound (EUS) and somatostatin receptor imaging (Octreoscan® or ^{68}Ga-DOTATOC/^{68}Ga-DOTATATE/^{68}Ga-DOTANOC PET/CT). Especially in the context of *MEN-1*, when multiple other PanNET are detected, these investigations remain insufficient due to mainly two reasons. First, the small size of insulinomas (usually < 20 mm at presentation (15,17)) makes them susceptible to motion artefacts, such as respiratory motion, cardiac pulsation and bowel peristalsis, and thus limits their detectability (18). Secondly morphological imaging as well as somatostatin receptor imaging is not able to differentiate insulinomas from NF-PanNETs. To regionalize an insulinoma calcium stimulations test is recommended to avoid "blind" pancreatic resections (19,20).

In general, gastroenteropancreatic neuroendocrine neoplasms are known to overexpress the somatostatin receptor subtype 2 at a high density in 70%-100% of the cases, except in benign insulinomas where the expression is lower. Glucagon-like peptide-1 receptors (GLP-1R), on the other hand are expressed at high density in sporadic insulinomas (21). Exendin-4 is a synthetic US Food U.S.Food and Drug Administration (FDA) approved glucagon-like peptide-1 (GLP-1) analog primarily established for the treatment of type 2 diabetes mellitus targeting GLP-1R. The GLP-1 pathway is important in islet regeneration (22,23) by regulating inhibition of β-cell apoptosis (24) and stimulation of β-cell proliferation and insulin secretion. Previous studies have shown that GLP-1R imaging can be used as a very sensitive, non-invasive method to localize benign sporadic insulinomas using radiolabeled exendin-4 SPECT/CT or PET/CT (25-31), where GLP-1R PET/CT performs significantly better than SPECT/CT (28). Nonetheless, as opposed to benign insulinomas, malignant insulinomas often lack the GLP-1 receptors and conversely often overexpress the somatostatin type 2 receptor (32).

In the context of *MEN-1*, the biological characteristics (benign or malignant) of insulin-secreting neuroendocrine tumors (NET) is not well explored. A recent study with GLP-1R imaging using ^{68}Ga-DOTA-exendin-4 PET/CT in heterozygous *MEN-1* knockout mice demonstrated its potential for lesion detection in the *MEN-1* pancreas(33). This was related to increased GLP-1R expression in early tumorigenesis. However, in humans with *MEN-1* and EHH, *in vivo* or *in vitro* GLP-1R expression has not been examined as yet. In view of the always multiple PanNETs visualized on conventional imaging in the context of *MEN-1* patients, the exact localization of the insulin-secreting PanNET is critical for the surgical strategy in order to avoid unnecessary morbidity due to extensive surgery.

In this retrospective analysis, combination of ^{68}Ga-DOTA-exendin-4 ([Nle^{14},Lys^{40}(Ahx-DOTA-^{68}Ga)NH$_2$]exendin-4) PET/CT and MRI was analyzed to evaluate its potential role in patients with *MEN-1* mutations and confirmed EHH. We hypothesized that GLP-1R imaging in the context of *MEN-1* is feasible and may be able to guide surgical strategy in patients with PanNETs in the context of EHH and multiple pancreatic lesions.

Materials and Methods

Study design and patients

Between January 2014 until March 2017, 52 patients with biochemically-proven EHH highly suspicious for an insulinoma were prospectively recruited from different centers in Europe and the United States of America (ClinicalTrials.gov, NCT02127541). Six of the 52 patients (female: 4; male: 2 patients, median age 34.5 [interquartile range 18.8-46] years) were identified to have a genetically-proven germline mutation in the MEN1 gene and were included in this post-hoc analysis.

The patients fulfilled the inclusion criteria, which were age ≥18 years, biochemically-proven EHH with neuroglycopenic symptoms, a positive Whipple triad and negative results on sulfonylurea screening. Exclusion criteria were evidence of a malignant insulinoma on conventional imaging, pregnancy or breastfeeding women, and renal insufficiency (serum creatinine >140 µmol/L). None of the patients had bariatric surgery or other known causes for EHH (34).

The study was approved by the Regional Scientific Ethics Committee and patients provided written consent in accordance with provisions of the Declaration of Helsinki prior to study participation.

Procedures

All patients received one ^{68}Ga-DOTA-exendin-4 PET/CT and a standardized contrast-enhanced MRI scan within 3-4 days. The reference standard was successful surgery with

histopathological and immunohistochemical confirmation of PanNETs including insulinoma and normalization of blood glucose levels after surgery.

PET/CT was performed on different scanners in supine position: PET/16-detector CT scanner (Discovery ST; GE Healthcare), PET/64-detector CT scanner (Discovery ST; GE Healthcare), PET/128-detector CT scanner (Biograph mCT-X RT Pro Edition). Calibration of PET scanners and their cross calibration was performed. One bed position of the upper abdomen was acquired during 8 min, 2.5 h after the intravenous injection of ^{68}Ga-DOTA-exendin-4. PET images were reconstructed using an ordered-subsets expectation maximization (OSEM) algorithm with 3 iterations and 25 subsets. Low-dose CT (120 kVp, 30–100 mAs) was used in all patients for attenuation correction and to provide an anatomic reference.

Abdominal MRI acquisition was performed on a commercially available 3T system (Magnetom Prisma, Siemens Healthcare, Erlangen, Germany) in supine position using a multichannel body surface coil. The protocol aimed for a high spatial resolution and robustness with regard to breathing and motion artefacts. The body surface coil was placed firmly across the abdomen and patients were asked to breathe calm and shallow to avoid excessive abdominal excursion during breathing.

The protocol included standard sequences: a) coronal half fourier acquisition single shot turbo spin echo (HASTE) localizer b) coronal breath hold T2 weighted HASTE c) transverse breath hold T2 weighted HASTE d) transverse, fat suppressed T2 weighted turbo spin echo (TSE) images in breath hold e) Breath hold in- and out-of-phase T1-weighted gradient-echo sequence f) free breathing echo planar diffusion weighted images in the transverse plane using five b values (0, 50, 200, 400, and 800) g) transverse, free breathing (respiratory-triggered, navigator-echo technique) h) fat suppressed, T2 weighted spin echo sequences images using periodically rotated overlapping parallel lines with enhanced reconstruction (BLADE).

Detailed acquisition parameters for non-contrast-enhanced PET/CT and standardized contrast-enhanced MRI have been described elsewhere (28).

Evaluation

Only the pancreas was regarded as potential tumor site. In order to localize tumors in the pancreas in a standardized manner, the pancreas was categorized into three regions, namely, head, body, and tail, with the portal vein and the superior mesenteric artery serving as anatomic landmarks (Figure 1).

PET/CT, and MRI scans were independently assessed in a random order, by three board-certified nuclear medicine physicians for PET/CT scans and three different board-certified radiologists for MRI, each with >10 years of experience in PET/CT or MRI reading. All readers were unaware of the patients' identity, other imaging results, or the patient's clinical history. The number of lesions that could be clearly identified as a single focus was determined for each patient through majority reading.

A dual-accredited radiologist/nuclear medicine physician correlated lesions from blinded reading of ^{68}Ga-DOTA-exendin-4 PET/CT and standardized contrast enhanced MRI, which was used for the sensitivity analysis of combined ^{68}Ga-DOTA-exendin-4 PET/CT and MRI in the detection of clinical-relevant lesions.

A ^{68}Ga-DOTA-exendin-4 PET positive lesion was defined as insulinoma. On contrast-enhanced MRI a lesion with a clear tumor-to-background ratio visualized in at least 2 sequences was defined as PanNET (Figure 2).

The reference standard for tumor size was from the surgical specimens and from MRI imaging.

^{68}Ga-DOTA-exendin-4 uptake was quantified using maximum standardized uptake values (SUVmax).

Histopathologic diagnosis was made at the local referring institution where surgery was performed. In case of controversial findings, central histological reading was available at the tertiary institution (Institute of Pathology, University Bern).

Statistical analysis

Diagnostic performance in the detection of clinical-relevant lesion was quantified on a per-lesion basis as sensitivity, specificity and diagnostic accuracy. The reference standard was the histopathological diagnosis of surgical-removed tissue. Data were assessed according to ENETS recommendation, namely, to resect clinical-relevant lesions, that is insulinomas independent of size and (if possible) only NF-PanNET ≥ 20 mm with the aim of a pancreas preserving surgery approach (13). Findings were defined as follows:

For MRI which can measure tumor size but not discriminate between NF-PanNET and insulinomas (Figure 3):

True positive (TP): detected NF-PanNET and Insulinomas ≥ 20 mm

True negative (TN): all NF-PanNET < 20 mm (defined as clinical not relevant lesion)

False negative (FN): not detected NF-PanNET and insulinomas ≥ 20 mm; all Insulinomas < 20 mm

False positive (FP): all detected lesions ≥ 20 mm, which were not confirmed by surgery/histology.

For ^{68}Ga-DOTA-exendin PET/CT which cannot measure tumor size but can likely discriminate between NF-PanNET and Insulinomas (Figure 3):

TP: detected Insulinoma of any size and detected NF-PanNET ≥ 20 mm

TN: not detected NF-PanNET < 20 mm

FN: not detected NF-PanNET ≥ 20 mm and not detected Insulinoma of any size

FP: detected NF-PanNET < 20 mm

In case of discordant findings for combined ^{68}Ga-DOTA-exendin-4 PET/CT and MRI i.e. TP with one imaging method and FN with the other, the combined finding is rated as TP.

All analyses were conducted using the statistical software package R (R Core Team, 2018), Version 3.5.0, using two-sided statistical tests. Confidence intervals are calculated at a 1-α level of 95%. P values should be interpreted as a continuous measure of evidence against the corresponding null-hypothesis (i.e. no difference between imaging methods) and not as confirmatory (“significant” vs. “non-significant”).

Sensitivity, specificity and overall diagnostic accuracy for each imaging method in the detection of clinical-relevant lesions were calculated with exact binomial 95 % confidence interval using the R package epiR. The imaging methods were tested for a difference in the respective measure using mixed-effects logistic regression models (GLMM).

The models included the respective outcome as binary endpoint (e.g. for sensitivity the outcome was TP, 0/1), patient as random effect, and the imaging method as main predictor. For the objective of identification of all clinical-relevant tumor findings ^{68}Ga-DOTA-exendin-4 PET/CT and MRI were compared to both methods combined. P-values for the comparisons are reported. No adjustment for multiple testing was made. Cross tabulations of the findings based on the imaging methods and the results of histopathology are given.

Results

Surgery and histopathological evaluation

All 6 patients received surgery based on all available imaging results and following the recommendations of current international guidelines. Table 1 summarizes the individual surgical procedures.

In six patients a total of 37 PanNETs were confirmed by histopathology with a median number of lesions per patient of 7.5 and interquartile range (IQR) of 2.5-8.5 (see Table 1). This included 11 (30%) insulinomas with a median size of 11 mm (range 1-20 mm), 26 (70%) NF-PanNETs with a median size of 4 mm (range 0.5-25 mm). The tumor grade was determined histologically using mitotic rates and Ki-67 indices (European Neuroendocrine Tumor Society proposal for grading GEP- NETs) (35) and was available in 25 lesions: 19 Lesions were classified as G1 tumors and six lesions were classified as G2 tumors. No G3 tumors were identified. Twenty-two lesions were not detected by the imaging procedures. Median tumor size of all lesions was 6 mm (range 0.5-25 mm).

Table 2 summarizes the diagnostic performance of ^{68}Ga-DOTA-exendin-4 PET/CT and MRI for detection of all clinical-relevant tumor findings.

Comparison of MRI with histopathology

MRI reading is based on majority reading by 3 radiologists. In the detection of clinical-relevant lesions, defined as PanNET ≥ 20mm, MRI showed 5 true positive, 24 true negative, 8 false negative and 0 false positive findings. MRI did not detect 22 tumors, which had a median size of 2.1 mm (range 0.5-17 mm).

Comparison of ^{68}Ga-DOTA-exendin-4 PET/CT with histopathology

Lesion detection on ^{68}Ga-DOTA-exendin-4 PET/CT is based on majority reading by 3 nuclear medicine physicians. SUVmax was determined for all detected insulinomas and ranged from 4.3-43 with a median SUVmax (IQR) of 22.4 (9.1-34.9).

^{68}Ga-DOTA-exendin-4 PET/CT identified 11/37 (30%) tumors with a median size of 14 mm (range 4-21 mm) of which 10/11 (91%) were insulinomas and 1/11 (9%) was a NF-PanNET with a diameter of 21 mm. ^{68}Ga-DOTA-exendin-4 PET/CT did not detect 26 tumors, median size of 4 mm (range 0.5-25 mm). This included 1/26 (4%) insulinoma (tumor size 1mm), 2/26 (8%) and 25/26 (88%) NF-PanNETs (median tumor size 4 mm, range 0.5-25 mm).

In the detection of clinical-relevant lesions, ^{68}Ga-DOTA-exendin-4 PET/CT was true positive in 11/37 (30%), true negative in 24/37 (65%) and false negative in 2/37 (5%) and false positive in 0/37 (0%).

Surgical strategy and outcome

Surgical planning was based on all available imaging results and performed in all six patients. Symptoms of EHH ceased in all patients after surgery with no recurrence within a follow-up period of 3 months. Median time between study imaging and surgery were 3.5 months (IQR 2.8–9) months.

Side effects

Nausea and sporadic vomiting are known side effects of ^{68}Ga-DOTA-exendin-4 and have been described elsewhere (28). All patients received an exogenous glucose (1,000 mL, 10%) infusion for 5 h starting just before injection of the radiotracer and a flow adapted as needed.

Discussion

To our knowledge, this is the first study investigating the potential role of GLP-1R imaging in patients with EHH and a known *MEN-1* germline mutation. The main findings of this study can be summarized as follows: 1) Overexpression of GLP-1R is present in insulinomas in patients with EHH in the context of *MEN-1* syndrome and, therefore, GLP-1R imaging is feasible and helpful in this context to guide selective and pancreas-sparing surgery. 2) Conventional imaging alone may be insufficient as it detects less than half of the pancreatic lesions in *MEN-1* patients. Combination of ^{68}Ga-DOTA-exendin-4 PET/CT and MRI is highly beneficial to detect clinical-relevant lesions in MEN-1 patients as morphological

imaging alone cannot differentiate between insulin-secreting between insulin-secreting and non-insulin-secreting PanNETs.

Our data confirm that preoperative GLP-1R PET/CT in the context of a *MEN-1* mutation is useful. This finding is further substantiated by the fact that *in vivo* assessment of GLP-1R density using SUVmax measurements yielded similar results in *MEN-1* insulinomas as seen in sporadic benign insulinoma cases, median SUVmax (IQR): 22.4 (9.1-34.9) versus 20 (12.5-35.3) (28) indicating that insulinomas in the context of *MEN-1* show a similar GLP-1R overexpression. So far this feature has only been proven in conventional heterozygous knockout mouse model of Men1 (33). These *MEN-1* mice exhibited an overexpression of GLP-1R in microadenomas, consistent with our findings in humans and suggesting that ^{68}Ga-DOTA-exendin-4 has a potential role for the detection of insulinomas in patients with *MEN-1* and EHH.

On histopathological examination 37 PanNETs were diagnosed in six patients consistent with previous histopathological studies (36). Amongst them, 22 lesions were not detected by MRI or GLP-1R imaging, mainly because there were not insulinoma or with a size below imaging resolution. The small size of the undetected lesions, the limited spatial resolution of MRI as well as the susceptibility to motion artefacts and bowel peristaltic movement, could be an explanation as to why the lesions were missed in MRI. However, for the detected tumors $\geq$ 20mm in which according to ENETs guidelines resection due to increased malignancy potential is recommended (13), MRI had a sensitivity of 100%.

Insulin secreting NET in the context of *MEN-1* are typically smaller lesions within multiple PanNET (36). It is, therefore, highly relevant that, GLP-1R imaging detected insulinomas up to a minimal size of 4 mm (Table 1), corroborating the high sensitivity of this investigation. In addition, the fact that all six patients were cured of their hypoglycemia following surgery suggests that the clinical-relevant insulin-secreting NET were successfully treated by GLP-1R imaging guided surgery.

Morphological assessment of PanNET (i.e. size) in patients with *MEN-1* is critical to determine the potential for a malignant course of the disease (12). However conventional morphological imaging is not able to distinguish between functional and non-functional tumors, thus the only criteria justifying resection of a tumor is based on its size. Since insulinomas in the context of *MEN-1* are often small (36), MRI produces a high number of false negative findings (8 lesions) and a low number of true positive findings (5 lesions) in comparison to GLP-1R PET/CT, which showed only 2 false negative findings and a higher number of true positive findings (11 lesions) . The combination of both imaging modalities reduces the high rate of false negative findings to 1 lesion and increases the rate of true positive findings to 12 resulting in a sensitivity of 92.3%. Consequently, in clinical routine practice the combination of both modalities is advocated in patients with *MEN-1* and EHH. Identification of PanNET < 20 mm with native low dose CT was inferior compared to MRI (results not shown). However, contrast-enhanced CT in combination with GLP-1R imaging as a one stop shot PET/CT procedure is likely to perform as good as MRI plus GLP-1R PET because contrast medium enhanced CT is able to detect and pancreatic neighborhood and the lesion threshold size of $\geq$ 20 mm should be above the detection limit of contrast-enhanced CT. Another alternative is the use of an integrated PET/MRI scanner.

^{68}Ga-DOTA-exendin-4 PET/CT was positive in one NF-PanNET (patient Nr. 5/tumor Nr. 22) with high ^{68}Ga-DOTA-exendin-4 uptake (SUVmax of 34.9). The diameter of this tumor was 21 mm and MRI detected it as well.

This is an intriguing finding. It suggests that NF-PanNET can sometimes express the GLP-1R at a high density consistent with previous findings in the literature (21). However, well differentiated NETs, such as gastrinomas and PPomas were not detected by GLP-1R

imaging in this study confirming previous findings, that the GLP-1R receptor is mainly overexpressed in insulinomas (21).

This study has limitations:

1) It was a retrospective analysis of prospectively collected data. As in all retrospective studies, they are prone to possible bias. In particular, there was not always enough reliable data on the intraoperative tumor localization. 2) Histological assessment was not *a priori* centralized and proliferative activity of the tumors could have an influence on the overexpression of the GLP-1R (32); this was not evaluated in all tumors. Furthermore, an additional limit maybe that positivity for insulin staining is not mandatory associated with significant EHH, especially in patients with *MEN-1*. However, the fact that all patients were cured of hypoglycemia following the surgical intervention suggests that the clinical-relevant lesions were surgically removed. 3) Low-dose native CT scan is not per se a diagnostic procedure, because it is unable to document clearly the size of lesions as well as important anatomical structures (e.g. main pancreatic duct) which is important for planning the surgical strategy. In an ideal setting contrast-enhanced PET/CT or contrast enhanced PET/MRI should be used.

In conclusion, GLP-1R PET/CT is a useful and reliable imaging technique to selectively identify insulinomas within the multiple pancreatic NET in patients with MEN-1. The careful interpretation of a morphological modality (MRI) in combination with a functional imaging technique (GLP-1R PET/CT) may guide the surgical procedure and avoid unnecessary pancreatic resections. “Blind” pancreatic resections should be history.

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The authors have nothing to disclose.

Data Availability

All data generated or analyzed during this study are included in this published article or in the data repositories listed in References

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FIG 1. Schema of the pancreas which was used for standardized reading by blinded board-certified nuclear medicine physicians and board certified radiologists.

FIG. 2. Patient 4 with EHH and 3 suspicious lesions in MRI. (A) Transaxial contrast enhanced T1 weighted MRI shows a 20 mm measuring hypointense lesion in the uncinate process of the pancreatic head. (B) Transaxial PET/CT 2.5 h after injection of ^{68}Ga-DOTA-exendin-4 shows an intensive focal uptake in the same lesion. (C) Transaxial diffusion weighted MRI shows a 4 mm measuring hyperintense lesion in the pancreatic body which is ^{68}Ga-DOTA-exendin-4 positive (D). (E)Transaxial T2 weighted MRI shows a 25 mm measuring lesion in the pancreatic tail without ^{68}Ga-DOTA-exendin-4 uptake (F). Histological evaluation revealed one insulinoma in the uncinated process and pancreatic body (both ^{68}Ga-DOTA-exendin-4 PET positive) and a NF-PanNET of 25 mm in the pancreatic tail. All other tumors were no insulinomas and smaller than 20 mm and therefore not clinical-relevant. EHH resolved after surgery.

FIG. 3. Flowchart with MRI (A) and ^{68}Ga-DOTA-exendin-4 PET/CT (B) reading results. According to ENETS guidelines true positive was defined as PanNET ≥20mm or insulinoma (=clincal-relevant lesions). Abbreviation: TP = true positive, TN = true negative, FP = false positive, FN = false negative, NF-PanNET = non-functioning pancreatic neuroendocrine tumor. [a]MRI is not able to distinguish between functional and non-functional tumors, thus the only criteria justifiying resection of tumor in the pancreas is a size of ≥ 20

mm. As a result insulinoma < 20 mm are classified as false negative in MRI reading.
[b]Diameter measured with MRI

TABLE 1. Summary of lesion characteristics

Pat	Tumor No.	MRI[a]	MRI[b]	GLP-1R PET/CT[a]	GLP-1R PET/CT[b]	Localization	Surgery type	Tumor size (mm)	Histological diagnosis / Immunohistochemistry	Grading	Blood glucose
Pat. 1	1	Positive	TP	Positive	TP	Body	Enucleation	20	Insulinoma / Insulin	G2 / Ki67= 5%	Normalization
Pat. 2	2	Positive	FN	Positive	TP	Tail	Extended left resection	14	Insulinoma / Insulin	G1 / Ki67 < 2%	Normalization
	3	Positive	FN	Positive	TP	Tail		11	Insulinoma / Insulin	G1 / Ki67 < 2%	
	4	Positive	FN	Positive	TP	Tail		6	Insulinoma / Insulin	G1 / Ki67 < 2%	
	5	Positive	TN	Negative	TN	Body		9	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	
	6	Negative	FN	Negative	FN	Body-Tail		1	Insulinoma / Insulin	G1 / Ki67 < 2%	
	7	Negative	TN	Negative	TN	Body-Tail		4	NF-PanNET/ ChA/Syn	NA	
	8	Negative	TN	Negative	TN	Body-Tail		5	NF-PanNET/ ChA/Syn	NA	
Pat. 3	9	Positive	FN	Positive	TP	Head	Completion Pancreatectomy	17	Insulinoma / Insulin	G1	Normalization
	10	Negative	TN	Negative	TN	Head		10	NF-PanNET/ ChA/Syn	NA	
	11	Negative	TN	Negative	TN	Head		9	NF-PanNET/ ChA/Syn	NA	
Pat. 4	12	Positive	TP	Negative	FN	Tail	Left resection / uncus enucleation	25	NF-PanNET/ ChA/Syn	G2 / Ki67= 3%	Normalization
	13	Negative	TN	Negative	TN	Head		17	NF-PanNET/ Gastrin	G1 / Ki67 < 2%	
	14	Positive	TP	Positive	TP	Uncus		20	Insulinoma / Insulin	G1 / Ki67 < 2%	
	15	Positive	FN	Positive	TP	Body		4	Insulinoma / Insulin	G1 / Ki67 < 2%	
	16	Negative	TN	Negative	TN	Tail		1	NF-PanNET/ ChA/Syn	NA	
	17	Negative	TN	Negative	TN	Tail		1	NF-PanNET/ ChA/Syn	NA	
	18	Negative	TN	Negative	TN	Tail		1	NF-PanNET/ ChA/Syn	NA	
	19	Negative	TN	Negative	TN	Tail		1	NF-PanNET/ ChA/Syn	NA	
	20	Negative	TN	Negative	TN	Tail		1	NF-PanNET/ ChA/Syn	NA	
	21	Neg	T	Neg	TN	Tail		1	NF-PanNET/ ChA/Syn	NA	

		ativ e	N	ative							
Pa t. 5	22	Posi tive	TP	Posi tive	TP	Body	Exended left resection	21	NF-PanNET/ ChA/Syn	G2 / Ki67= 3%	Norma lizatio n
	23	Posi tive	F N	Posi tive	TP	Tail		7	Insulinoma / Insulin	G1 / Ki67 < 2%	
	24	Posi tive	F N	Posi tive	TP	Tail		11	Insulinoma / Insulin	G2 / Ki67= 3%	
	25	Posi tive	T N	Neg ative	TN	Tail		19	NF-PanNET/ ChA/Syn	G2 / Ki67= 3,5%	
	26	Neg ativ e	T N	Neg ative	TN	Body-Tail		7	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	
	27	Neg ativ e	T N	Neg ative	TN	Body-Tail		3	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	
	28	Neg ativ e	T N	Neg ative	TN	Body-Tail		5	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	
	29	Neg ativ e	T N	Neg ative	TN	Body-Tail		4	NF-PanNET/ ChA/Syn	NA	
Pa t. 6	30	Posi tive	TP	Posi tive	TP	Body	Exended left resection	20	Insulinoma / Insulin	G2 / Ki67= 2-5%	Norma lizatio n
	31	Neg ativ e	T N	Neg ative	TN	Body		5	NF-PanNET / Gastrin	G1 / Ki67 < 2%	
	32	Posi tive	T N	Neg ative	TN	Tail		15	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	
	33	Neg ativ e	T N	Neg ative	TN	Tail		9	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	
	34	Neg ativ e	T N	Neg ative	TN	Tail		0.8	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	
	35	Neg ativ e	T N	Neg ative	TN	Tail		1	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	
	36	Neg ativ e	T N	Neg ative	TN	Tail		1.1	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	
	37	Neg ativ e	T N	Neg ative	TN	Tail		0.5	NF-PanNET/ ChA/Syn	G1 / Ki67 < 2%	

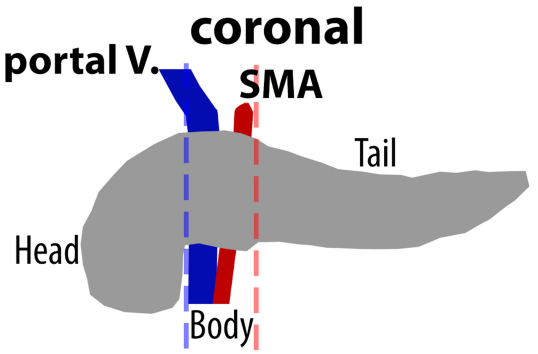
[a]Results of scan reading. Readers were unaware of other results when reading the scans. [b]Evaluation according to ENETS recommendation with true positive results in case of symptomatic insulinomas and NF-PanNET ≥ 20 mm. Abbreviation: TP = true positive, TN = true negative, FN = false negative, NF-PanNET = non-functioning pancreatic neuroendocrine tumor; NA = not available, ChA = Chromgranin A, Syn= Synaptophysin.

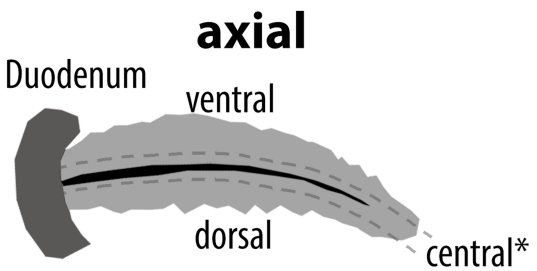
TABLE 2. Comparison of combined ^{68}Ga-DOTA-exendin-4 PET/CT + MRI, ^{68}Ga -exendin-4 PET/CT and MRI alone in the detection of clinical-relevant PanNET(defined as NF-PanNET ≥20 mm or insulinomas) in *MEN-1* patients with endogenous hyperinsulinemia hypoglycemia + neuroglycopenia and multiple pancreatic tumors

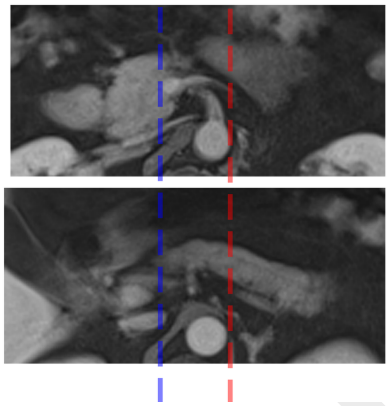
	^{68}Ga-DOTA-exendin-4 PET/CT + MRI	**^{68}Ga-DOTA-exendin-4 PET/CT**	**Test for superiority[a]**	**MRI**	**Test for superiority[b]**
Clinical-relevant lesion Sensitivity	92.3% [64.0-99.8]	84.6% [54.6-98.1]	0.537	38.5% [13.9-68.4]	0.014
Clinical-relevant lesion	100% [85.8-100]	100% [85.8-100]	1.000	100% [85.8-100]	1.000

Specificity					
Clinical-relevant lesion Accuracy	97.3% [85.8-99.9]	94.6% [81.8-99.3]	0.802	78.4% [61.8-90.2]	0.059

Diagnostic performance as majority reading [95% confidence interval]] of three independent readers. [a] P-values for comparison of combined ^{68}Ga-DOTA-exendin-4 PET/CT + MRI and ^{68}Ga-DOTA-exendin-4 PET/CT alone. [b] P-Values for comparison of combined ^{68}Ga-DOTA-exendin-4 PET/CT + MRI and MRI alone.







* Corridor parallel and centered around pancreatic duct.
If contact to duct and small = central lesion

If large or unclear then use i.e. ventral-central
Please indicate lesion on axial and coronal depiction with x^1, x^2 etc.