

Title: Qualitative and Quantitative Analyses of Noninvasive Diagnosis of Insulinoma
Using [¹⁸F]FB(ePEG12)12-exendin-4 PET/CT

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48 **Key Words**

49 Insulinoma, β -cell imaging, glucagon-like peptide-1 receptor, positron emission
50 tomography

51

Abstract

Background: This study represents the first interim report from a Phase II clinical trial. Accurate localization of insulinomas remains a clinical challenge despite the availability of various imaging modalities. The current study aimed to evaluate the efficacy of positron emission tomography/computed tomography (PET/CT) using [^{18}F]FB(ePEG12)12-exendin-4 (^{18}F -exendin-4), a novel ^{18}F -labeled PEGylated GLP-1 receptor-targeted imaging probe, for the noninvasive detection of insulinomas.

Methods: This prospective single-center study enrolled patients with biochemically confirmed hyperinsulinemic hypoglycemia suggestive of insulinoma. All patients underwent ^{18}F -exendin-4 PET/CT, with scans performed at 60 and 120 min after injection. The findings of ^{18}F -exendin-4 PET/CT were then compared with those of conventional imaging modalities performed before and after ^{18}F -exendin-4 PET/CT in actual clinical settings, with all findings being verified through surgical and pathological findings.

Results: ^{18}F -exendin-4 PET/CT successfully identified insulinomas in all 12 patients (100% sensitivity), showing significantly higher uptake in tumor tissues than in the surrounding pancreatic tissues and organs. The detection rate of ^{18}F -exendin-4 PET/CT exceeded that of the conventional imaging modalities (CT, 83%; magnetic resonance imaging, 63%; endoscopic ultrasonography, 90%; selective arterial calcium stimulation, 89%). All identified lesions were surgically confirmed to be insulinomas, with complete clinical resolution of hypoglycemia after resection.

Conclusions: ^{18}F -exendin-4 PET/CT demonstrated effective sensitivity for non-invasive insulinoma detection, offering a reliable and practical diagnostic alternative to invasive procedures for precise and prompt preoperative localization with functional evaluation. This novel imaging approach may therefore improve the management of patients with

76 suspected insulinomas.

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80 tomography

Introduction

Insulinomas, with an annual incidence rate of 1–4 cases per million, are rare neuroendocrine neoplasms (NENs), a broader category that includes neuroendocrine tumors (NETs), and cause hypoglycemia due to insulin overproduction (1-3). Although most cases are sporadic, some have been associated with multiple endocrine neoplasia type 1 (4). Despite being the most frequent among the functional neuroendocrine tumors, insulinomas present a significant clinical challenge due to localization difficulties and potentially fatal neurological symptoms caused by hypoglycemia.

Although surgical treatment has remained the major curative approach, it requires precise tumor localization for reliable cure and minimization of the surgical invasiveness and risk of postoperative complications (5). However, conventional methods of tumor localization have shown limited reliability particularly for small lesions in size, which constitute the majority of insulinomas. Most insulinomas are <2 cm, making detection more challenging (6). It has raised the clinical issue that there are cases where surgery has not been performed due to the difficulties in the diagnostic procedure (7, 8), especially in preoperative tumor localization. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) have shown moderate sensitivity (44%–74% and 56%–90%, respectively) (9) and do not directly reflect the endocrine characteristics of the tumor. Although endoscopic ultrasound (EUS) and selective arterial calcium infusion testing (SACST) offer improved sensitivity (75%–86% and 84%–100%, respectively), such procedures are invasive (5, 10-13). Despite the clinical availability of these methods, preoperative localization fails in 10%–27% of cases, necessitating reoperation in up to 13% of cases (14, 15). Failed localization also complicates the differentiation between insulinomas and noninsulinoma pancreatogenous hypoglycemia syndrome, although

SACST may allow clinical differential diagnosis (16). However, the need for the operator's skill, limited facilities and invasiveness remains clinical issues.

In the 2000s, molecular imaging had emerged as an effective imaging approach for NETs. Somatostatin receptors are used as target molecules for diagnosing NETs. However, in the case of insulinomas, they are less effective for functional diagnosis because insulinomas express somatostatin receptor type 2 (SSTR2) at lower levels compared to other NETs. (9, 17). Recently, glucagon-like peptide-1 receptor (GLP-1R) has shown promise for the localization of insulinomas (18-22). GLP-1R is specifically expressed in pancreatic beta cells and shows a six-fold higher expression in insulinomas than in normal beta cells (23, 24).

We had previously developed a positron emission tomography (PET) probe, namely [^{18}F]FB(ePEG12)12-exendin-4, using fluorine-18 for high spatial resolution, with PEGylation applied to enhance tumor accumulation (25), and confirmed its safety and utility for the noninvasive diagnosis of insulinomas (7, 26-28). Accordingly, the current study reports on the qualitative and quantitative analyses of [^{18}F]FB(ePEG12)12-exendin-4 PET/CT for noninvasive diagnosis of insulinoma in patients with biochemically confirmed hyperinsulinemic hypoglycemia.

Materials and Methods

Study Design and Participants

This prospective single-center study was conducted at Kyoto University Hospital from March 2022 to June 2024. We enrolled patients aged ≥ 16 years with biochemically suspected hyperinsulinemic hypoglycemia suggestive of insulinoma and the other noninsulinoma-related hypoglycemia such as non-insulinoma pancreatogenous hypoglycemia syndrome and post-gastric bypass hypoglycemia. The exclusion criteria included severe hepatic or renal dysfunction, current use of GLP-1-related medications, alcohol intolerance, and pregnancy or lactation. The study protocol was approved by The Kyoto University Certified Review Board approved (Y0074) and was conducted in accordance with the provisions of the Declaration of Helsinki. All participants provided written informed consent.

Clinical Assessment

Comprehensive baseline characteristics, including demographics, clinical history, and physical examination findings, were collected. Endocrinological evaluation included fasting plasma glucose, HbA1c, serum insulin, C-peptide, and anti-insulin antibodies. All patients underwent conventional imaging evaluation (CT, MRI, and/or EUS) and SACST in accordance with standard clinical practice. In cases wherein a tumor was confirmed via EUS, the maximum diameter of the tumor was measured using ultrasound. Fajans index was defined as the immunoreactive insulin / plasma glucose confirmed during the prolonged fasting test (29).

GLP-1R PET/CT Protocol

[¹⁸F]FB(ePEG12)12-exendin-4 (¹⁸F-exendin-4) was synthesized according to previously published methods (25, 26). Patients received 37.0–53.3 MBq of ¹⁸F-exendin-4 intravenously for over 5 min and underwent fasting during the scans. PET/CT scans were performed at 60 and 120 min after injection using an integrated PET/CT scanner (Discovery IQ; GE Healthcare) with a bismuth germinate (BGO) scintillator (Figure 1). Safety monitoring included blood glucose measurements at 10, 30, 60, and 120 min after injection, along with continuous monitoring of vital signs and symptoms. A 5–10% glucose solution was administered intravenously as needed for hypoglycemia management. Severe hypoglycemia was defined as a change in the level of consciousness, which prompted intravenous administration of 50% glucose solution.

Image Analysis

PET/CT images were analyzed both qualitatively and quantitatively. Tumor visualization was assessed by identifying areas of significant accumulation compared to surrounding tissues. The maximum standardized uptake values (SUV_{max}) and the mean standardized uptake values (SUV_{mean}) for tumors, surrounding organs and left ventricular lumen were calculated using Advantage Workstation software version 3.2. The tumor-to-organ SUV ratios were calculated to standardize the assessment.

Surgical Validation and Follow-up

All patients underwent surgical resection based on the positive findings of localization procedures including ¹⁸F-exendin-4 imaging. Pathological confirmation of insulinoma and evaluation of the Ki-67 index were performed to determine the correlation between anatomical and imaging findings and differentiate between an insulinomas and other

172 lesions. Postoperative outcomes and symptom resolution were monitored through regular
173 follow-up visits.

174 175 *Statistical Analysis*

176 The primary outcome analysis focused on the sensitivity of ¹⁸F-exendin-4 PET/CT for
177 insulinoma detection. The Clopper–Pearson exact method was used to calculate the 95%
178 confidence intervals. A paired t-test was conducted to compare the SUVmax / SUVmean
179 between 60 and 120 min after ¹⁸F exendin-4 injection. Additionally, unpaired t-test of the
180 SUVmean for the head and tail/body of the pancreas 120 min after injection, SUVmean
181 between with or without diazoxide use 120 min after injection was performed. Patients
182 receiving oral prednisolone treatment were excluded from the diazoxide analysis.

183 Correlations between SUVmean measurements and clinical/pathological parameters were
184 assessed using Spearman's correlation coefficient. Each statistical analysis was
185 performed twice to verify the consistency of the results. All analyses were performed
186 using JMP Pro® version 17.0 (JMP Statistical Discovery LLC , Cary, NC, USA, 2022),
187 with statistical significance being set at $p < 0.05$.

Results

Patient Characteristics

This study enrolled a total of 12 patients (8 men and 4 women; age range, 25–80 years) with biochemically confirmed hyperinsulinemic hypoglycemia. The duration range of symptoms was 0.3–9.0 years. All patients exhibited low overnight fasting blood glucose levels with inappropriately elevated plasma C-peptide and insulin levels along with the positive results in the prolonged fasting test (Table 1). Upon enrollment, 6 patients were not receiving anti-hypoglycemia-related medications, whereas 5 were taking diazoxide (range, 50–275 mg/day) and 1 was on prednisolone (5 mg/day).

Conventional Imaging Findings

Prior to the ^{18}F Exendin-4 PET/CT imaging, the patients underwent standard imaging workup (Table 2). Detection rates varied across modalities, with CT identifying pancreatic tumors in 10/12 patients (83%), MRI in 5/8 patients (63%), and EUS in 9/10 patients (90%). SACST was positive in 8/9 patients (89%) (Figure 2). In one case with a negative SACST result, no tumor blush was observed on angiography. Calcium stimulation was performed on the superior mesenteric artery, gastroduodenal artery, right hepatic artery, and the distal, middle, and proximal segments of the splenic artery. However, insulin levels did not increase more than twice the baseline value. Additional nuclear medicine imaging studies, including ^{111}In pentetreotide single photon emission computed tomography/computed tomography (^{111}In -SPECT/CT) ($n = 5$), gallium-68 (DOTA⁰-Phe¹-Tyr³) octreotide PET/CT (^{68}Ga -DOTATOC PET/CT) ($n = 1$), and ^{18}F -fluorodeoxyglucose PET/CT (^{18}F FDG PET/CT) ($n = 1$), failed to identify tumors in any of the tested patients.

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215 *¹⁸F-exendin-4 Performance and Safety*

216 All 12 patients successfully completed ¹⁸F-exendin-4 PET/CT imaging. Only one patient
217 required a 50% glucose solution due to severe hypoglycemia, with blood glucose
218 dropping to 28 mg/dL at 43 minutes after ¹⁸F-exendin-4 administration; however, the
219 patient immediately recovered afterwards. No other adverse events, including the
220 previously reported nausea and vomiting (18), were observed, and no additional adverse
221 events were identified. ¹⁸F-exendin-4 PET/CT imaging demonstrated focal uptake in the
222 pancreas corresponding to insulinoma in all 12 patients (100% sensitivity, 95% CI:
223 73.5%–100%) (Figure 3). Among patients in whom conventional imagings had already
224 detected tumors suspected to be insulinomas, ¹⁸F-exendin-4 PET/CT findings
225 corresponded to the same locations. Notably, in one patient (Case 4) wherein initial CT,
226 MRI, and EUS results were negative in clinical practice, retrospective evaluation guided
227 by ¹⁸F-exendin-4 PET/CT findings revealed a corresponding lesion on repeat
228 conventional imagings (Table 3).

229

230 *Surgical Outcomes*

231 All patients underwent surgical resection based on ¹⁸F-exendin-4 imaging findings.
232 Surgical procedures, including distal pancreatectomy, pancreaticoduodenectomy, and
233 tumor enucleation, were determined based on tumor location and diameter (30). Both the
234 macroscopic location observed during surgery and the pathological findings were
235 consistent with the site identified on ¹⁸F-exendin-4 PET/CT imaging. Pathological
236 examination confirmed the diagnosis of insulinoma in all cases, with most tumors having
237 been classified as NET G1 under the 2019 WHO classification (Ki-67 < 3%) (31).

Complete resolution of hypoglycemic symptoms was achieved in all patients after surgery, with no recurrence having been observed throughout the at least 9-month follow-up period (Table 4).

Quantitative Analysis of ^{18}F -exendin-4 PET/CT

SUVmax and SUVmean measurements 60 and 120 min after injection demonstrated consistent tumor visualization while accounting for interindividual variability (Table 5, 6). No significant differences were observed in SUVmax between 60 and 120 minutes, nor in SUVmean between 60 and 120 minutes. However, the tumor-to-surrounding organ SUVmean ratios tended to be higher at 120 min than at 60 min (Table 5, 6). Accumulation was particularly significant for the tumor-to-left ventricular lumen ratios.

In analyses of the influence of anatomical tumor localization, SUVmean of the tumors and the tumor-to-surrounding-organ ratios 120 min after administration found no significant differences between tumors in the pancreatic tail and body and those in the pancreatic head (Supplemental Table 1 [32]). Furthermore, diazoxide administration did not significantly affect SUVmean or SUVmax of the tumor or in the tumor-to-surrounding organ ratios, although ^{18}F -exendin-4 uptake tended to be reduced in cases where diazoxide was administered (Supplemental Table 2 [32]). In addition, we found no significant correlations between tumor SUVmean measurements at 120 min and clinical parameters (such as BMI, Fajans index, and ^{18}F -exendin-4 dose) or pathological features (such as tumor size and the Ki-67 index) (Supplemental Figure 1 [32]).

Discussion

This prospective single-center study demonstrated that ^{18}F -exendin-4 PET/CT could effectively and noninvasively detect benign insulinomas in clinically suspected cases. This approach allowed for a systematic comparison between ^{18}F -exendin-4 PET/CT and various conventional imaging modalities commonly used for the clinical diagnosis of insulinomas, and provided comprehensive clinical insights into the advantages of ^{18}F -exendin-4 PET/CT.

Conventional imaging methods, such as CT and MRI, often face challenges in identifying insulinomas given their typically small size, making detection difficult even for experienced radiologists (6). Our study found that the detection capabilities of CT and MRI aligned with findings from previous studies, reinforcing their limitations in this particular context. Although EUS-guided fine-needle aspiration cytology and SACST, which can provide functional evaluation, demonstrated a diagnostic accuracy superior to that of CT and MRI, these methods remain invasive and were unable to achieve complete diagnosis in all cases (10-13). Actually, in our study, one case (Case 1) rejected EUS due to its invasiveness, and SACST failed to provide the localization (Case 4). The negative results of SACST in Case 4 may be due to the tumor location, which appeared to be outside the pancreatic parenchyma and considerable atypical blood supply. Moreover, ^{68}Ga -DOTATOC PET/CT and ^{111}In -pentetreotide SPECT/CT produced negative results in our cases, whereas our probe demonstrated positive results in all cases. This is likely attributable to the low SSTR expression observed in our patients who had predominantly well-differentiated, low Ki-67 insulinomas (33). ^{18}F -exendin-4 PET/CT was capable of identifying tumors undetectable by CT, MRI, and SSTR-targeted imaging while maintaining diagnostic accuracy comparable to the more invasive EUS and SACST.

Notably, ^{18}F -exendin-4 PET/CT enabled the detection of insulinoma missed by conventional methods including CT, MRI, EUS and ^{111}In pentetreotide SPECT/CT in one case (Case 4).

In this study, EUS and SACST were finally performed in most cases and the surgical pathology was included in all cases, allowing for the practical comparisons with ^{18}F -exendin-4 PET/CT in real-world clinical settings. Previous studies on the other non- ^{18}F -labelled non-PEGylated Exendin-4 imaging did not include comparable data on the findings of EUS and SACST, or only involved a small number of cases with these modalities and pathological evaluations (18, 19). Therefore, this study suggests that ^{18}F -exendin-4 PET/CT, with its high diagnostic accuracy and noninvasiveness, could potentially serve the individually optimized diagnosis procedures for the patients with insulinomas and reduce the patient burden in clinical practice.

In terms of probe accumulation in the tumor as well, our study highlights the clinical utility of ^{18}F -exendin-4 PET/CT in detecting small insulinoma by leveraging the superior spatial resolution. Our results demonstrate that ^{18}F -exendin-4 PET/CT consistently visualized tumors both 60 and 120 min after ^{18}F -exendin-4 injection, with stable SUVmean and SUVmax values having been observed over time. Higher tumor-to-organ SUVmean ratios tended to be observed at 120 min, particularly for tumor-to-left ventricular lumen ratios, likely due to improved delivery of tumor-targeting probes facilitated by PEGylation, which enhances signal-to-background contrast as non-specific activity diminishes (25). Furthermore, the lack of significant differences in the SUVmean and tumor-to-organ ratios based on tumor localization within the pancreas indicates that the developed imaging technique was effective across various anatomical pancreatic sites. Although previous studies using ^{68}Ga -exendin-4 have highlighted the risk of false

negatives for tumors near the kidneys (34), no such cases were observed in the current study, suggesting that ^{18}F -exendin-4 PET/CT in clinical settings was a reliable, dependable, and clinically useful imaging modality for insulinomas. Although ^{18}F -exendin-4 uptake tended to be lower in cases using diazoxide, no significant differences were observed and the diagnostic accuracy was not affected. This observation suggests that the developed diagnostic modality performs reliably even in cases under the treatment with diazoxide use.

Regarding safety, patients undergoing ^{18}F -exendin-4 PET/CT in this study experienced no gastrointestinal symptoms, such as nausea or vomiting, which have been reported in previous studies using other GLP-1 receptor-targeted probes. For example, Antwi et al. documented nausea in 40% of patients using ^{111}In -DOTA-exendin-4 and 20% of those using ^{68}Ga -DOTA-exendin-4, with 40% of patients receiving ^{111}In -DOTA-exendin-4 experiencing vomiting (18). Additionally, hypoglycemia has been a potential risk in patients with insulinomas due to fasting time during the scans. During ^{18}F -exendin-4 PET/CT imaging in this study, effective glucose management through intravenous administration ensured safety in all but one patient, with no additional adverse events having been identified. Pancreatic islet absorption doses from ^{18}F -exendin-4 remained consistently low, minimizing the potential risk of diabetes even with repeated imaging (35). Considering the high diagnostic accuracy and absence of significant adverse events, our findings strongly support the clinical utilization of ^{18}F -exendin-4 PET/CT as a safe and effective diagnostic tool, demonstrating comparable or superior safety profiles to other GLP-1 receptor-targeted probes.

Extensive studies have been available on tracer selection, with previous studies reporting the clinical applications of exendin-4 imaging using ^{68}Ga , $^{99\text{m}}\text{Tc}$, and ^{111}In (18-22). From

the perspective of diagnostic accuracy, a previous study reported a sensitivity of 93.9% (95% CI; 87.8-97.5%) using ^{68}Ga -DOTA-exendin-4 PET/CT, suggesting our study using ^{18}F -exendin-4 PET/CT demonstrated comparable sensitivity (22). Although the positron emitter ^{68}Ga only can be prepared using generators, its limited spatial resolution restricts its clinical applications (36). Moreover, ^{68}Ga exendin-4 has strong renal uptake signals making it pitfall in detecting insulinoma in the tail of the pancreas (27, 34). On the other hand, the low positron emission energy with high resolution of fluorine-18 enables optimal imaging acquisition 2 h after ^{18}F -exendin-4 administration, with a confirmed safety profile. The successful clinical application of ^{18}F -labeled probes, such as ^{18}F FDG, underscores the practical utility of our probes. Furthermore, this study demonstrated ^{18}F -exendin-4 PET/CT could successfully visualized insulinomas in pancreatic tail without interference of renal uptake signals.

Our study using ^{18}F -exendin-4 PET/CT has certain limitations; since our cases predominantly featured tumors with relatively low Ki-67 indices, the utility data of ^{18}F -exendin-4 for malignant insulinomas, where might exhibit decreased GLP-1 receptor expression (37), is still lacking. Tumor dedifferentiation may trigger the loss of GLP-1 receptor expression, with reports indicating significantly reduced PET/CT positivity rates in previous studies using ^{68}Ga , $^{99\text{m}}\text{Tc}$, and ^{111}In -labeled probes (19, 20). Therefore, further investigation utilizing ^{18}F -exendin-4 PET/CT is warranted for the evaluation of malignant insulinomas. Additionally, in this study, all cases initially enrolled with biochemical hyperinsulinemic hypoglycemia were confirmed as insulinomas with postoperative pathological diagnosis as a result. This may be due to the relative rarity of non-insulinoma pancreatic endocrine hypoglycemia syndrome and post-gastric bypass hypoglycemia. Therefore, the concise evaluation of specificity should be provided in further

investigations including the cases of non-insulinoma pancreatic endocrine hypoglycemia syndrome and post-gastric bypass hypoglycemia. As an additional limitation, this study design is not a prospective randomized controlled trial since insulinoma is a rare disease, and therefore, the use of ^{18}F -exendin-4 PET/CT was not employed in head-to-head comparisons with other conventional modalities. Importantly, direct comparison between ^{18}F -exendin-4 PET/CT and the other GLP-1 receptor-targeted techniques should be warranted in the further clinical trials, especially in the setting of occult insulinoma or tumors located near the kidneys (27, 34, 36). Nevertheless, this study incorporated ^{18}F -exendin-4 PET/CT as one of the diagnostic imaging modalities in real-world clinical practice and provided the comparable findings among multiple diagnostic modalities including EUS and SACST. Additionally, the analyses of inter-imaging accuracies were conducted both before and after performing ^{18}F -exendin-4 PET/CT to avoid or evaluate the sequential influence of the tests. Moreover, the healthcare insurance system in Japan only covers ^{111}In pentetreotide (Octreoscan[®]) SPECT and not somatostatin receptor-targeted PET such as ^{68}Ga DOTATOC, limiting the opportunities for comparison with SSTR-targeted PET in this study.

In summary, ^{18}F -exendin-4 PET/CT demonstrated sufficient sensitivity compared to conventional localization methods with established clinical advantages. This method, which combines safety and practicality, represents a promising option for the diagnosis of insulinomas. Further multicenter studies are required to validate these findings in larger and more diverse populations.

Conclusion

^{18}F -exendin-4 PET/CT represents a promising advancement in

insulinoma imaging, offering superior detection capability through a noninvasive approach. The high sensitivity and specificity of this imaging modality, combined with its high safety profile, suggest that it could become a valuable first-line diagnostic tool for the localization of insulinomas.

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure Legends

Figure 1. Imaging protocol of [¹⁸F]FB(ePEG12)12-exendin-4 (¹⁸F-exendin-4) positron emission tomography/computed tomography (PET/CT).

The imaging protocol scheme of [¹⁸F]FB(ePEG12)12-exendin-4 (¹⁸F-exendin-4) positron emission tomography/computed tomography (PET/CT). ¹⁸F-exendin-4; [¹⁸F]FB(ePEG12)12-exendin-4, PET/CT; positron emission tomography/computed tomography.

Figure 2. Representative conventional images in cases with tumors of the pancreatic head and tail.

(A; Case 3, D; Case 5) Unenhanced computed tomography (CT) scan. (B; Case 3, E; Case 5) Contrast-enhanced CT scan (early phase). (C; Case 3, F; Case 5) Non-contrast-enhanced magnetic resonance imaging (MRI) (T2-weighted image). Tumor localization is marked with yellow arrows when visible on CT or MRI.

Figure 3. Representative images of [¹⁸F]FB(ePEG12)12-exendin-4 (¹⁸F-exendin-4) positron emission tomography/computed tomography (PET/CT).

(A; Case 3, E; Case 5) Maximum intensity projection (MIP) image performed after 60 min. (B; Case 3, F; Case 5) Fusion image with simple computed tomography (CT) and ¹⁸F-exendin-4 PET performed after 60 min. (C; Case 3, G; Case 5) MIP image performed after 120 min. (D; Case 3, H; Case 5) Fusion image with simple CT and ¹⁸F-exendin-4 PET performed after 120 min. Tumors are highlighted using yellow arrows.

Table 1. Characteristics of enrolled patients.

Fajans index was defined as the ratio of immunoreactive insulin to plasma glucose confirmed during the prolonged fasting test. IQR: interquartile range.

Table 2. Imaging outcomes before conducting [¹⁸F]FB(ePEG12)12-exendin-4 (¹⁸F-exendin-4) positron emission tomography/computed tomography (PET/CT).

Comparison of imaging modalities conducted prior to ¹⁸F-exendin-4 PET/CT. In cases wherein a tumor was confirmed via endoscopic ultrasonography (EUS), the maximum diameter of the tumor was measured. MRI; magnetic resonance imaging, SACST; selective arterial calcium stimulation, ⁶⁸Ga-DOTATOC PET/CT; gallium-68 (DOTA⁰-Phe¹-Tyr³) octreotide PET/CT, ¹¹¹In-SPECT/CT; ¹¹¹In pentetreotide single photon emission computed tomography/computed tomography, ¹⁸F FDG PET/CT; ¹⁸F-fluorodeoxyglucose PET/CT. M, male; F, female; NA, not available.

Table 3. Retrospective evaluation of conventional imaging outcomes incorporating findings from [¹⁸F]FB(ePEG12)12-exendin-4 (¹⁸F-exendin-4) PET/CT.

Findings validated after ¹⁸F-exendin-4 PET/CT are marked in bold text and a shaded background. MRI; magnetic resonance imaging, EUS; endoscopic ultrasonography, SACST; selective arterial calcium stimulation, ⁶⁸Ga-DOTATOC PET/CT; gallium-68 (DOTA⁰-Phe¹-Tyr³) octreotide PET/CT, ¹¹¹In-SPECT/CT; ¹¹¹In pentetreotide single photon emission computed tomography/computed tomography, ¹⁸F FDG PET/CT; ¹⁸F-fluorodeoxyglucose PET/CT. M, male; F, female; NA, not available.

Table 4. Surgery outcomes of respective insulinomas.

Summary of the surgical outcomes, including tumor localization and histopathological findings.

Table 5. Summary of the maximum standardized uptake values (SUVmax) according to timing of imaging after administration.

Analysis of SUVmax (mean $\pm$ SD) 60 and 120 min after [^{18}F]FB(ePEG12)12-exendin-4 injection.

Table 6. Summary of the mean standardized uptake values (SUVmean) according to timing of imaging after administration.

Analysis of SUVmean (mean $\pm$ SD) 60 and 120 min after [^{18}F]FB(ePEG12)12-exendin-4 injection.

Table 1.

Age (years)	mean $\pm$ SD Median (IQR)	60.6 $\pm$ 18.7 66.5 (50.8; 75.3)
Sex		
Male	number (%)	8 (66.7%)
Female	number (%)	4 (33.3%)
Body mass index (kg/m²)	mean $\pm$ SD Median (IQR)	24.9 $\pm$ 3.44 25.5 (23.3; 27.6)
Duration of the disease (years)	mean $\pm$ SD Median (IQR)	2.04 $\pm$ 2.70 1.10 (0.575; 1.45)
Overnight fasting plasma glucose (mg/dL)	mean $\pm$ SD Median (IQR)	46.6 $\pm$ 13.7 43.0 (37.7; 55.1)
Overnight fasting c-peptide (ng/mL)	mean $\pm$ SD Median (IQR)	3.20 $\pm$ 1.93 2.45 (1.97; 4.42)
Overnight fasting insulin (mU/L)	mean $\pm$ SD Median (IQR)	16.0 $\pm$ 12.4 11.9 (8.11; 23.9)
Prolonged fasting test duration (hours)	mean $\pm$ SD Median (IQR)	14.7 $\pm$ 11.4 13.0 (6.53; 22.8)
Prolonged fasting plasma glucose (mg/dL)	mean $\pm$ SD Median (IQR)	39.3 $\pm$ 5.31 41.0 (36.0; 42.7)
Prolonged fasting c-peptide (ng/mL)	mean $\pm$ SD Median (IQR)	2.76 $\pm$ 1.84 1.92 (36.0; 42.7)
Prolonged fasting insulin (mU/L)	mean $\pm$ SD Median (IQR)	13.0 $\pm$ 12.2 8.30 (5.23; 20.7)
Fajans Index	mean $\pm$ SD Median (IQR)	0.407 $\pm$ 0.405 0.380 (0.150; 0.664)

618
619 Table2.
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Case No.	Age	Sex	CT	MRI	EUS	SACST	Other Imaging
1	58	M	+	+	NA	+	⁶⁸ Ga-DOTATOC PET/CT (-), ¹⁸ F FDG PET/CT (-)
2	63	F	+	-	+	NA	
3	70	F	+	-	+	+	¹¹¹ In-SPECT/CT (-)
4	73	F	-	-	-	-	¹¹¹ In-SPECT/CT (-)
5	25	M	-	NA	+	+	
6	53	M	+	+	+	NA	¹¹¹ In-SPECT/CT (-)
7	80	F	+	NA	+	+	
8	50	M	+	+	+	NA	
9	76	F	+	NA	+	+	
10	79	F	+	+	NA	+	
11	28	F	+	NA	+	+	¹¹¹ In-SPECT/CT (-)
12	72	F	+	+	+	+	¹¹¹ In-SPECT/CT (-)

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623 Table 3.
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Case No.	Age	Sex	¹⁸ F-exendin-4 PET/CT	CT	MRI	EUS	SACST	Tumor Size (EUS, cm)
1	58	M	+	+	+	NA	+	NA
2	63	F	+	+	-	+	+	1.0
3	70	F	+	+	-	+	+	1.1
4	73	F	+	+	+	+	-	1.8
5	25	M	+	-	NA	+	+	0.9
6	53	M	+	+	+	+	+	1.2
7	80	F	+	+	NA	+	+	1.6
8	50	M	+	+	+	+	+	2.3
9	76	F	+	+	NA	+	+	2.0
10	79	F	+	+	+	+	+	1.4
11	28	F	+	+	NA	+	+	1.1
12	72	F	+	+	+	+	+	1.1

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629 Table 4.
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Case No.	Surgery Details	Tumor site in pancreas	Tumor Size (cm)	Ki-67 (%)	WHO NET Grade (25)	Disappearance of hypoglycemia
1	Enucleation	Tail	2.5	2.0	NET G1	Yes
2	Enucleation	Head	2.6	2.0	NET G1	Yes
3	Distal pancreatectomy	Tail	1.0	0.6	NET G1	Yes
4	Enucleation	Body	2.3	0.8	NET G1	Yes
5	Pancreaticoduodenectomy	Head	1.2	<5	NET G1 or G2	Yes
6	Pancreaticoduodenectomy	Head	1.1	<1	NET G1	Yes
7	Pancreaticoduodenectomy	Head	1.9	<1	NET G1	Yes
8	Enucleation	Tail	1.6	<5	NET G1 or G2	Yes
9	Enucleation	Tail	1.9	0.6	NET G1	Yes
10	Enucleation	Head	1.7	2.2	NET G1	Yes
11	Distal pancreatectomy	Tail	1.4	3.3	NET G2	Yes
12	Enucleation	Tail	1.2	1.0	NET G1	Yes

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634 Table 5.
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	tumor	tumor / pancreas	tumor / liver	tumor / spleen	tumor / kidney	tumor / left ventricular lumen
60 min	17.99 ± 17.55	6.91 ± 6.03	14.36 ± 16.87	15.24 ± 12.40	0.20 ± 0.19	5.78 ± 5.87
120 min	21.67 ± 18.56	8.57 ± 5.53	21.17 ± 23.12	22.05 ± 15.55	0.29 ± 0.26	9.81 ± 7.92
p-value	0.62	0.49	0.41	0.27	0.32	0.17

636
637
638
639 Table 6.
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	tumor	tumor / pancreas	tumor / liver	tumor / spleen	tumor / left ventricular lumen
60 min	9.59 ± 5.75	6.05 ± 2.97	11.92 ± 7.23	12.72 ± 5.50	5.37 ± 2.71
120 min	12.91 ± 9.79	8.90 ± 4.48	23.20 ± 17.95	21.95 ± 12.52	12.48 ± 7.51
p-value	0.32	0.08	0.56	0.29	0.006**

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Figure 1.

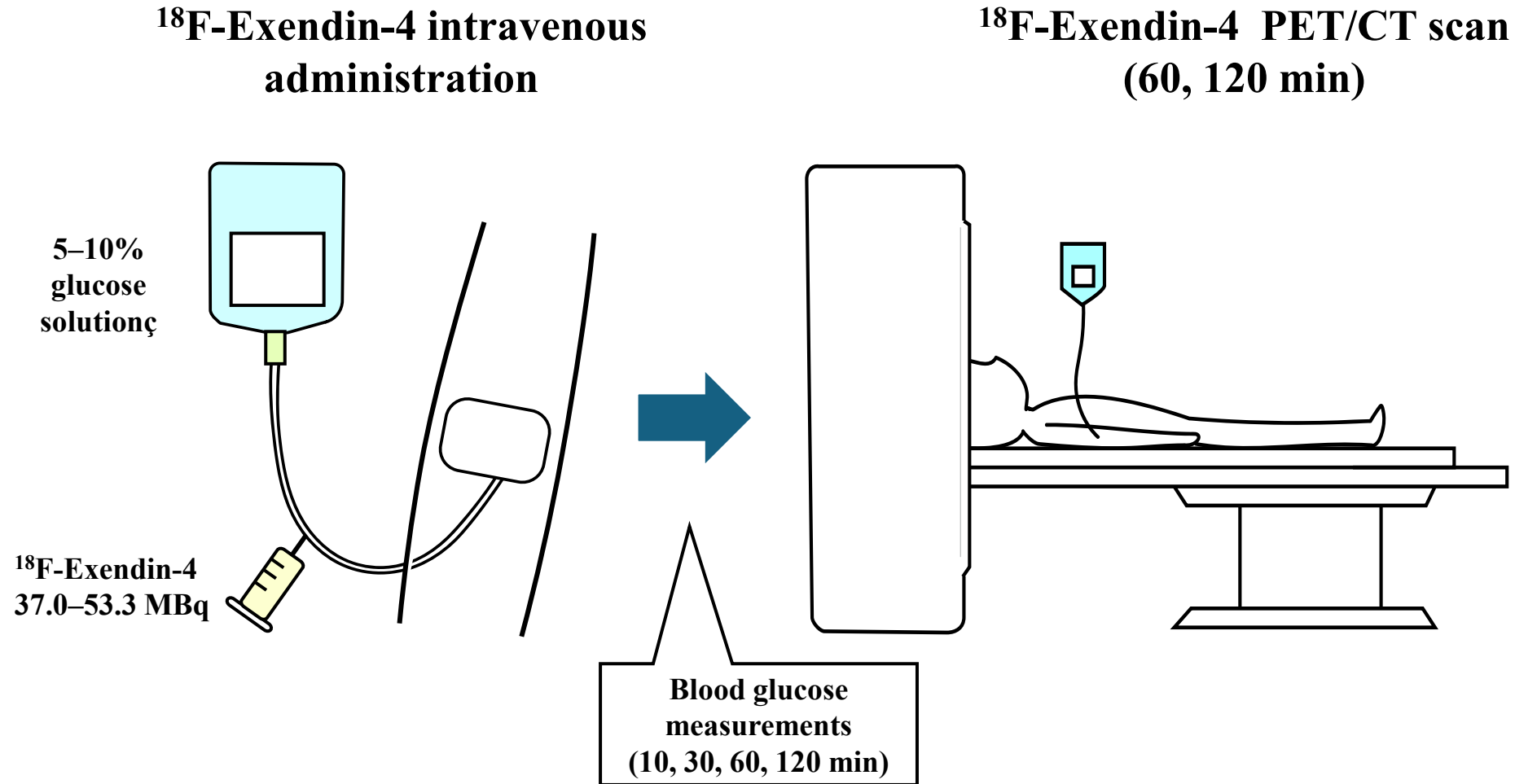
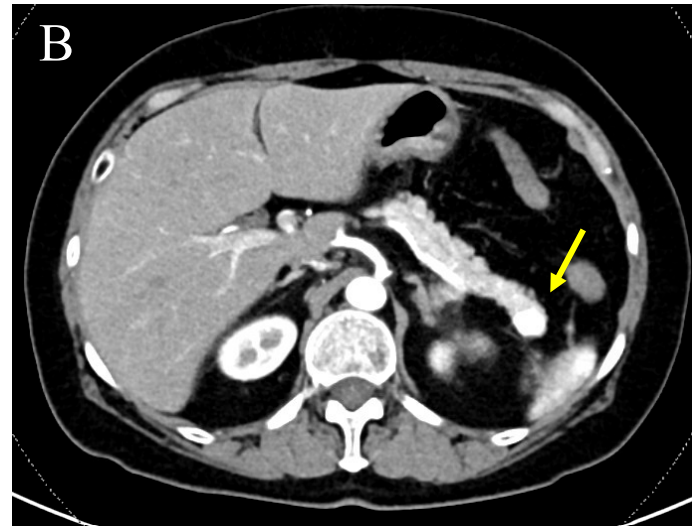
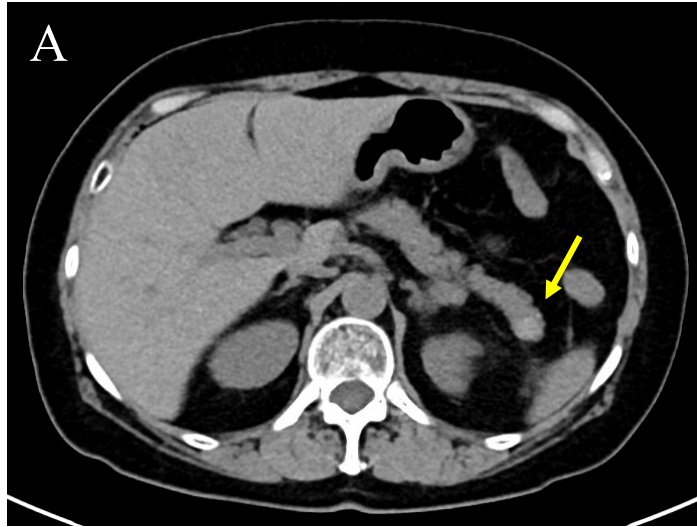




Figure 2.

Case 3: 70 y.o. Female.



Case 5: 25 y.o. Male.

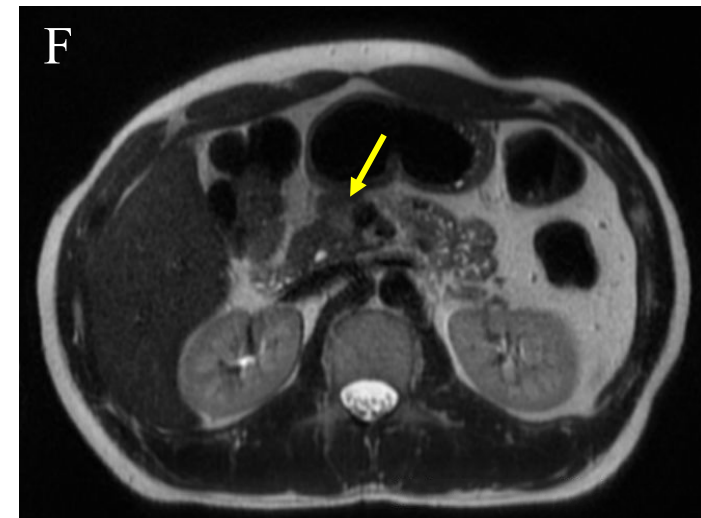
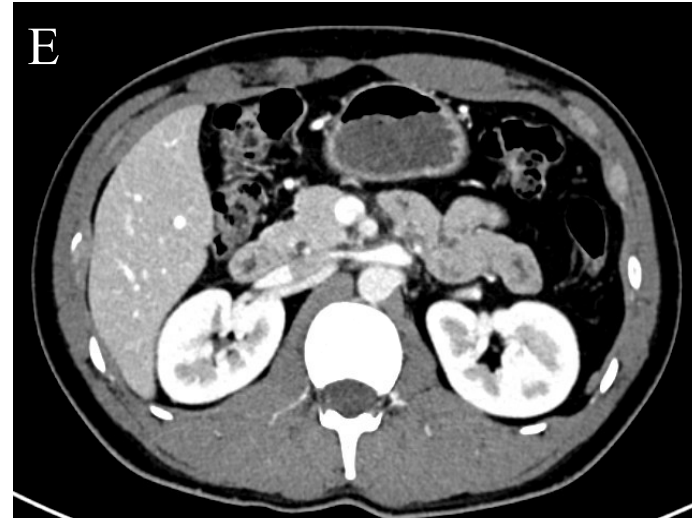
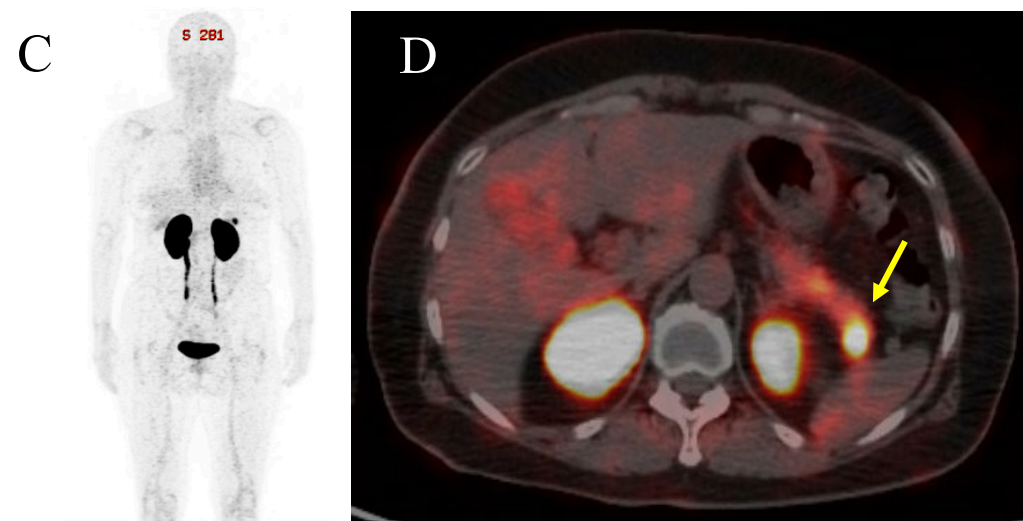
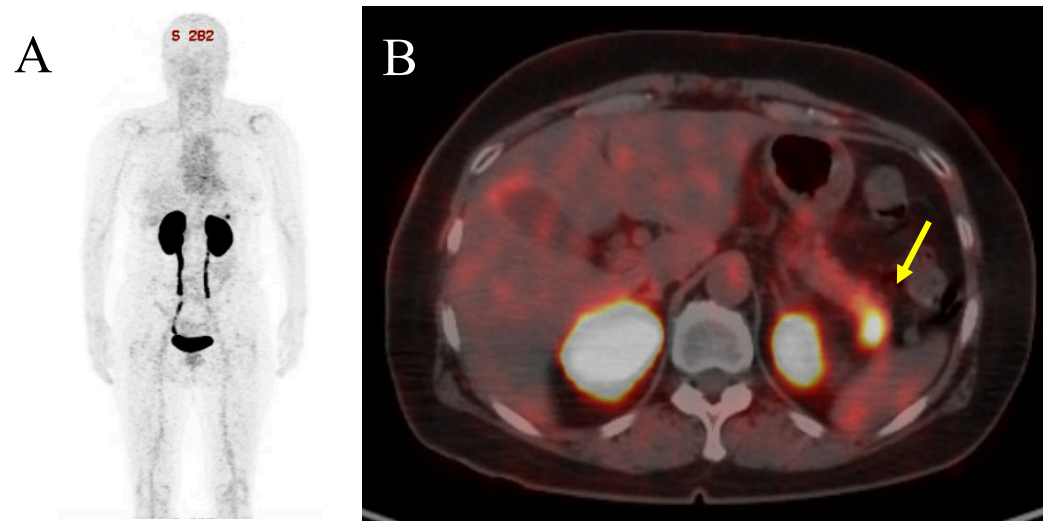


Figure 3.

Case 3: 70 y.o. Female.



Case 5: 25 y.o. Male.

