Journal of Nuclear Medicine, published on July 16, 2021 as doi:10.2967/jnumed.121.262401

Values of ^{68}Ga-DOTATOC and Carbidopa-assisted ^{18}F-DOPA PET/CT for insulinoma localization

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Running Title: ^{68}Ga-DOTATOC vs. ^{18}F-DOPA for insulinoma

Keywords: neuroendocrine tumors; pancreas, insulinoma; ^{18}F-DOPA; ^{68}Ga-DOTATOC

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Disclosure summary: The authors declare that they have no conflict of interest

Abstract: 146; Document: 2733; Tables: 1; Figures: 2

ABSTRACT

To assess the value of ^{68}Ga-DOTATOC and carbidopa-assisted ^{18}F-DOPA in 21 hypoglycaemic patients.

Methods. All patients who underwent ^{68}Ga-DOTATOC and/or carbidopa-assisted ^{18}F-DOPA PET/CT for suspicion of insulinoma from January 2019 to January 2021 were retrospectively analysed. Insulinoma final diagnosis was defined according to pathological reports or consensus.

Results. During the study period, 21 patients underwent both ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT. A final diagnosis of insulin-secreting tumour was reached in 12 cases, including 11 insulinomas and 1 small mixed neuroendocrine/non-neuroendocrine neoplasm. ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT were positive in 5 (45%) and 7 (64%) of 11 cases, respectively, with 4 concordant positive findings. Moreover, 1 insulinoma was visualized exclusively by ^{18}F-DOPA PET/CT and 3 by ^{68}Ga-DOTATOC PET/CT only. ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT were falsely positive in 1 non-functioning pancreatic neuroendocrine tumour.

Conclusions. When ^{68}Ga-exendin-4 is not available, ^{68}Ga-SSTR PET/CT should be the first choice for insulinoma functional imaging.

INTRODUCTION

In adults, endogenous hyperinsulinaemic hypoglycaemia is commonly related to insulinoma. Insulinoma can induce severe debilitating and life-threatening hypoglycaemia. The average incidence of insulinoma is 1-4 cases per million persons per year, and more than 90% of insulinomas are solitary, sporadic and benign. In adults with hypoglycaemia and/or suggestive symptoms, the diagnosis of hyperinsulinaemic hypoglycaemia relies on a positive fasting test (*1*). In 5-10% of cases, insulinoma can occur in multiple endocrine neoplasia type-1. Parenchyma sparing (enucleation/pancreatic resection) surgery is the optimal strategy (cure rate: 98%), but it can be associated with complications. It is therefore of primary importance to accurately localize insulinoma.

Imaging work-up of patients with hyperinsulinaemic hypoglycaemia often requires a combination of anatomic and functional imaging modalities (*2*). ^{68}Ga-exendin-4, which targets the glucagon-like peptide 1 receptor, is expected to become the first-choice radiopharmaceutical for PET detection of benign insulinoma (*3*). However, it is available in only a few centres and is currently used as a part of clinical trials. A special advantage of ^{68}Ga-exendin-4 over other tracers is its unique value for distinguishing insulinoma from other neuroendocrine tumours – a condition of particular interest in the setting of multiple endocrine neoplasia type-1 patients, who often present with concomitant functioning and nonfunctioning pancreatic tumours. When ^{68}Ga-exendin-4 is not available for clinical use, either ^{68}Ga-radiolabelled somatostatin analogues (^{68}Ga-DOTA-SSA) or ^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA) can be used (*4*). ^{68}Ga-DOTA-SSA has shown encouraging preliminary results for insulinoma imaging in two recent retrospective studies (*5,6*). However, insulinoma detection remains challenging, mainly due to these tumours' limited SSTR2 expression profile and small size, and to the physiologically high ^{68}Ga-DOTA-SSA uptake

in the uncinate process (*7*). On the other hand, the value of ^{18}F-DOPA PET/CT is hampered by the relatively short duration of ^{18}F-DOPA tumour retention in insulinoma and the diffuse uptake in normal pancreatic parenchyma that may potentially mask insulinoma (*8*). To circumvent these major drawbacks, we previously proposed a revised imaging protocol based on dual-phase imaging acquisition and patient premedication with carbidopa (a peripheral aromatic amino acid decarboxylase inhibitor) to prevent ^{18}F-DOPA physiological pancreatic uptake (*9*).

Currently, there remains a certain degree of uncertainty regarding the optimal first-choice tracer for patients with insulinoma suspicion in the absence of ^{68}Ga-exendin-4. The aim of the present study was to describe the value of ^{68}Ga-DOTA-SSA and carbidopa-assisted ^{18}F-DOPA in a retrospective series of hypoglycaemic patients evaluated by both tracers.

MATERIALS AND METHODS

Patients

This retrospective study was conducted in the departments of nuclear medicine of 3 university hospitals in France (Strasbourg, Marseille, and Nancy). We performed a comprehensive search of our databases to identify all patients evaluated by ^{68}Ga-DOTA-SSA and/or carbidopa-assisted ^{18}F-DOPA PET/CT for clinical, biological, and/or radiological suspicion of insulinoma-related HH from January 2019 to January 2021 (Figure 1). Concerning patients underwent ^{18}F-DOPA and ^{68}Ga-DOTA-SSA PET/CT, only those studied within a 3-months period without therapeutic intervention or change between the two PET studies were included. All data (clinical, biological and imaging) were extracted from institutional medical datafiles (Table 1). The

Institutional review board approved this retrospective study and the requirement to obtain informed consent was waived.

Imaging Protocols

All examinations were performed by combined PET/CT devices equipped with 3D-time of flight technology. Patients were injected with 2-3 MBq/kg ^{68}Ga-DOTATOC and 3-4 MBq/kg ^{18}F-DOPA (2h after carbidopa premedication, 200-mg orally) without fasting before radiotracer administration. ^{68}Ga-DOTATOC included a whole-body acquisition from the upper thigh to the top of the skull (3-5 min/step), starting at 60 min after radiotracer injection. Dual-time-point ^{18}F-DOPA PET/CT included an early scan of the upper abdomen (at 5 min, 10-min step) and a delayed whole-body acquisition (at 30 min, 3-5 min/step). In all cases, a low dose non-enhanced CT was performed and used for attenuation correction.

A pancreatic abnormality was defined as a focal area of increased radiotracer uptake compared to surrounding tissue, considering potential pitfalls for both tracers. For ^{18}F-DOPA PET/CT, a positive early phase, followed by a negative delayed scan, was considered a pathological study. Semi-quantitative analysis was performed by placing a spherical VOI centred on the uptake foci.

Gold Standard

The final diagnosis of insulinoma was defined according to pathological results when available. In the remaining patients, the diagnosis was reached by a consensus considering clinical,

biological (positive fast test), and radiological (CT/MRI typical enhancement) parameters and follow-up.

Statistical Analysis

The results for continuous data are expressed as the mean ± standard deviation or median and range as appropriate, whereas categorical variables are presented as numbers and percentages. Detection rate, sensitivity, and specificity are provided for both modalities.

RESULTS

Patient Population

A total of 32 patients were evaluated during the study period: 9 with ^{18}F-DOPA PET/CT alone, 2 with only ^{68}Ga-DOTATOC PET/CT, and 21 with both tracers (Figure 1). The latter 21 cases constituted the study population. The patients' characteristics are summarized in Table 1.

Fourteen of 21 patients had a positive 72-h fasting test, whereas 7 had doubtful results. In patients with borderline biochemical and imaging findings, the indication for further evaluation was decided in the setting of institutional multidisciplinary meetings.

A final diagnosis of an insulin-secreting tumour was reached in 12 patients, including 11 insulinomas (one occult) and 1 small mixed neuroendocrine/non-neuroendocrine neoplasm with 15% insulin cell positivity. Among them, the fasting test was positive in 10 patients, and inconclusive in the remaining 2 cases. Among the 11 insulinomas, 8 were pathologically proven, and in the latter 3 cases, the diagnosis was reached by consensus. In 7 patients without detectable

pancreatic target lesion on both anatomic and functional imaging, the diagnosis of insulinoma was excluded by follow-up. In the other 2 cases, the diagnosis turned out to be nonfunctioning pancreatic neuroendocrine tumours confirmed by surgery or endoscopic ultrasound-guided fine-needle aspiration biopsy and follow-up.

PET/CT Findings

The PET/CT findings are summarized in Figure 1. For insulinoma, ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT were positive in 5/11 and 7/11 cases, respectively, with concordant positive findings in 4 patients. Moreover, 1 insulinoma was visualized exclusively by ^{18}F-DOPA PET/CT, and 3 were visualized only by ^{68}Ga-DOTATOC PET/CT (Figure 2). On ^{18}F-DOPA PET/CT, delayed phase imaging failed to detect one insulinoma that was correctly identified by early ^{18}F-DOPA phase and ^{68}Ga-DOTATOC PET/CT (Figure 2). In this case, the insulinoma was related to multiple endocrine neoplasia type-1 syndrome, and the patient had a previous history of 3 benign insulinomas that were positive on somatostatin receptor scintigraphy and successfully treated by surgery. In the other cases, insulinomas were sporadic. One 10-mm G1 mixed neuroendocrine-non neuroendocrine neoplasm remained occult for both ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT, likely due to the small percentage of the neuroendocrine component.

Among 2 cases with non-functioning pancreatic NETs, ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT were falsely positive in one case and negative in the latter case. The diagnosis of insulinoma was excluded in 7 additional cases without identifiable pancreatic target images on both PET imaging studies. Overall, detection rate, sensitivity, and specificity were respectively 45%, 42%, 89% for ^{18}F-DOPA, and 64%, 58%, 89% for ^{68}Ga-DOTATOC PET/CT.

The tumour-to-background uptake ratios were more favourable with ^{68}Ga-DOTATOC than with ^{18}F-DOPA PET. The mean values of tumour SUVmax and tumour SUVmax/normal pancreas SUVmean were 6.7 and 1.5 for early phase ^{18}F-DOPA, 6.3 and 2.7 for delayed phase ^{18}F-DOPA, and 45.2 and 10.8 for ^{68}Ga-DOTATOC PET/CT, respectively.

DISCUSSION

The present study aimed to describe the values of ^{68}Ga-SSTR PET/CT and carbidopa-assisted ^{18}F-DOPA in a series of hypoglycaemic patients. The principal conclusions that can be drawn from this study include: firstly, a high detection rate of ^{68}Ga-DOTATOC PET/CT in insulinoma, although its value is less than that for nonfunctioning pancreatic NETs due to a lack of SSTR2 expression in a subgroup of insulinomas (*10*); and secondarily, ^{68}Ga-DOTATOC PET/CT can be positive when ^{18}F-DOPA fails (3 cases) and vice versa (1 case). The latter point is easily comprehensible due to the various molecular determinants of tracer uptake and retention in both conditions.

Although our study was not designed to perform a reliable comparison between ^{68}Ga-SSTR PET/CT and ^{18}F-DOPA (mainly due to its retrospective nature and the limited number of included cases), we suggest using ^{68}Ga-SSTR PET as the first-choice tracer when ^{68}Ga-exendin-4 is not available. This position could be supported by several arguments. Two recent retrospective studies showed very promising results concerning the use of ^{68}Ga-SSTR PET/CT in patients with insulinoma-related HH, allowing for the identification of pancreatic secreting tumours in 9 of 10 (90%) and 11 of 13 cases (85%), respectively (*5*,*6*). The greater sensitivities described in these studies compared to our study could be related to the inclusion of solely pathologically proven insulinomas (*5*,*6*), excluding cases with non-operated ^{68}Ga-SSTR-negative insulinoma.

Furthermore, based on the widely admitted expression of SSTR2 in two-thirds of insulinomas (*10*), it is expected that ^{68}Ga-SSTR PET/CT sensitivity in real-life situations should be less than previously reported with an *on-off* uptake pattern, depending on SSTR2 expression. The use of ^{68}Ga-SSTR PET/CT also has practical advantages over ^{18}F-DOPA in terms of availability and cost for teams skilled and suitably equipped for ^{68}Ga-radiolabelling.

While the use of carbidopa-assisted ^{18}F-DOPA PET/CT remains controversial (*11*), the present study showed that it can be useful for SSTR-negative insulinoma and therefore can be considered a second-choice tracer when ^{68}Ga-SSTR PET/CT fails to detect the tumour. The lower rate of positivity of ^{18}F-DOPA PET/CT compared to previous reports could also be related to selection bias. As highlighted in the flow chart, 5 insulinomas, including 4 with ^{18}F-DOPA positive findings, did not undergo ^{68}Ga-SSTR PET/CT. With these patients, the rate of positivity would therefore be 56% (9/16). Physicians should be aware that imaging protocol should be adapted including carbidopa premedication We previously showed in a preclinical model that the use of carbidopa did not inhibit insulinoma ^{18}F-DOPA uptake (*12*), a phenomenon that was described for beta-cell hyperplasia (*13*). In the present study, delayed acquisition missed one insulinoma, and early acquisition was never inferior to delayed acquisition. In a previous study that included 24 patients, 4 cases were only detected by early phase acquisition (*14*).

CONCLUSION

Despite the limitations that have been pointed out, this study provided new data on both tracers in this rare but curable disease. When ^{68}Ga-exendin-4 is not available, we suggest using SSTR analogues as first-choice PET tracer and considering carbidopa-assisted ^{18}F-DOPA as a valid alternative in cases of inconclusive results.

ACKNOWLEDGEMENTS

None

KEY POINTS

Question

What is the best radiopharmaceutical for insulinoma localization in absence of ^{68}Ga-exendin-4?

Pertinent findings

When ^{68}Ga-exendin-4 is not available, ^{68}Ga-SSTR should be considered as the first-choice PET tracer. Carbidopa-assisted ^{18}F-DOPA PET remains a valid option in cases of inconclusive results.

Implications for patient care

^{68}Ga-SSTR PET/CT enables detection of insulinoma, allowing curative sparing surgery (enucleation/pancreatic resection) and resolution of preoperative symptoms.

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Table 1. Patient population with suspected insulinoma who underwent both carbidopa-assisted ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT imaging.

Pt	Age (y)	Sex	24h-Fast test	Medical treatment	CT/MRI	EUS	Early/delayed ^{18}F-DOPA/SSTR-PET/CT	Final diagnosis	Gold standard
1	62	W	positive	diazoxide	+/+, head	+, head	+/+/+, head	Insulinoma, 10-mm, grade-1, Ki67:2%	Pathology (surgery)
2	31	W	doubtful	diazoxide	-/-	?, body	-/-/-	Insulinoma excluded	Consensus
3	16	W	positive	diazoxide	-/-	-	-/-/-	Insulinoma excluded	Consensus
4	70	M	positive	diazoxide	+/+, tail		+/+/+, tail	Non-functioning pNET, 66-mm, grade-3, Ki67:25%	Pathology (surgery)
5	19	W	positive		-/-		-/-/-	Insulinoma excluded	Consensus
6	62	W	positive		+/na, body	+, body	-/-/+, body	Insulinoma, 17-mm	Pathology (FNAB)
7	71	W	doubtful		-/na	-	+/+/+, head	Insulinoma, 18-mm, grade-1, Ki67:1%	Pathology (surgery)
8	77	W	doubtful		-/-	?, tail	-/-/-	Insulinoma excluded	Consensus
9	65	M	positive		-/-	+, body	-/-/-	MiNEN, 10-mm, grade-1 (IHC:15% insulin+, 90% SST+),	Pathology (surgery)
10	48	W	positive		+/+, tail		+/+/+, tail	Insulinoma, 17-mm, grade-1, Ki67:1%	Pathology (surgery)
11	78	W	positive	diazoxide	+/na, tail		-/-/-	Insulinoma, 12-mm, grade-1, Ki67:2%	Pathology (surgery)
12	64	W	positive		-/-		-/-/-	Insulinoma excluded	Consensus
13	27	W	doubtful		+/+, head		+/-/+, head	Insulinoma, 10-mm (MRI)	Consensus
14	64	M	doubtful		-/-		-/-/-	Insulinoma excluded	Consensus
15	78	W	doubtful		-/na		-/-/-	Insulinoma excluded	Consensus
16	29	W	positive		-/+, tail		+/+/-, tail	Insulinoma, 12-mm, grade-1, Ki67:1%	Pathology (surgery)
17	67	W	positive	diazoxide	-/-	-	-/-/-	Insulinoma (occult)	Consensus
18	64	W	doubtful		-/+, body	+, body	-/-/-	No-functioning pNET, 5-mm, grade-1, Ki67:1%	Pathology (FNAB)
19	72	M	positive	diazoxide	+/na, head	+	-/-/+, head	Insulinoma, 10-mm	Pathology (FNAB)
20	93	M	positive	diazoxide	+/na, tail	-	-/-/+, tail	Insulinoma, 13-mm	Consensus
21	52	M	positive		na/+, head	+, head	-/-/-	Insulinoma, 22-mm	Pathology (FNAB)

W: woman, M: man, FNAB: fine-needle aspiration biopsy, na: not available, +: positive result, -: negative result, ?: doubtful result, MiNEN: mixed neuroendocrine-non neuroendocrine neoplasm

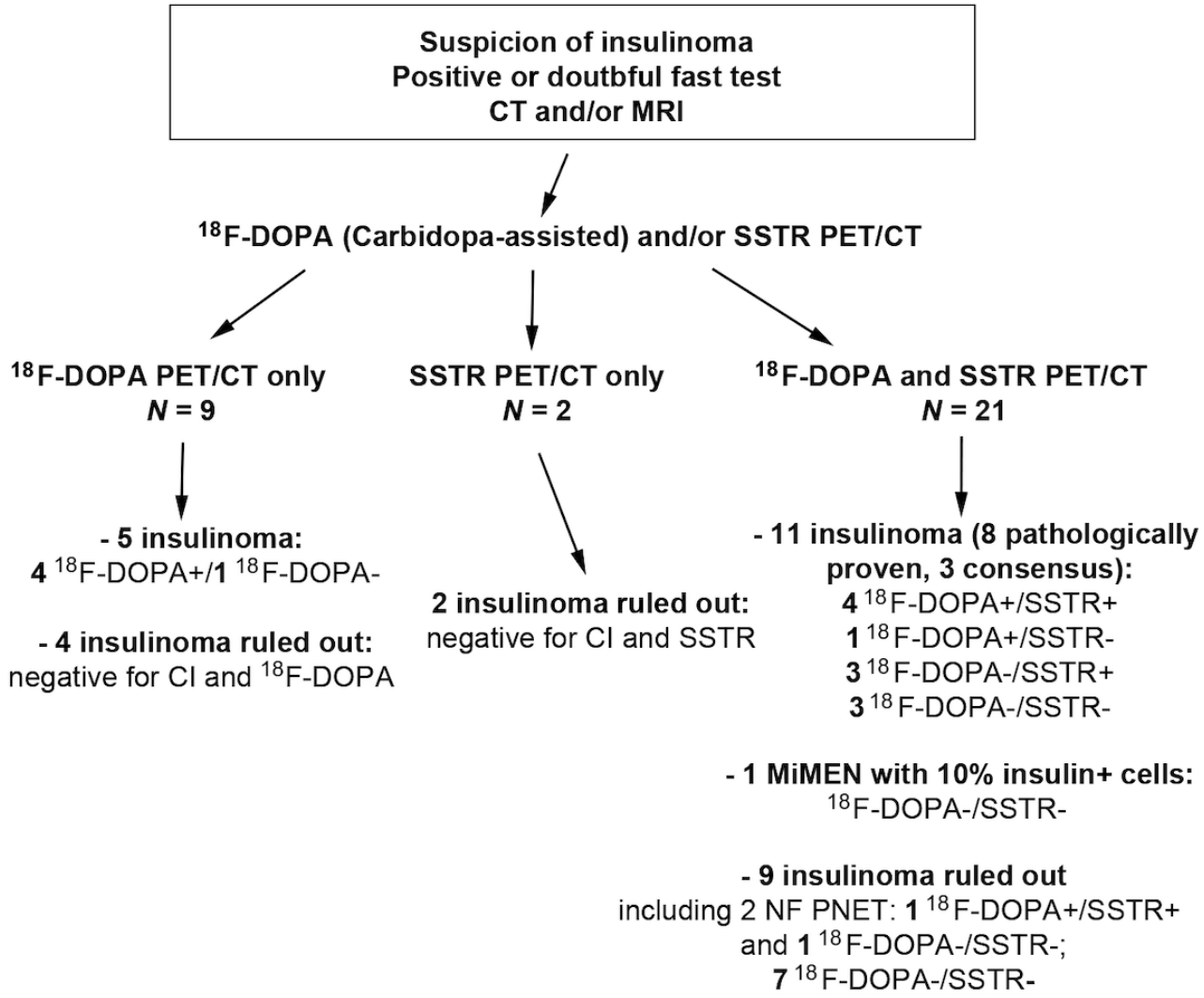

Figure 1. Flowchart summarizing the study design and key PET/CT imaging findings.

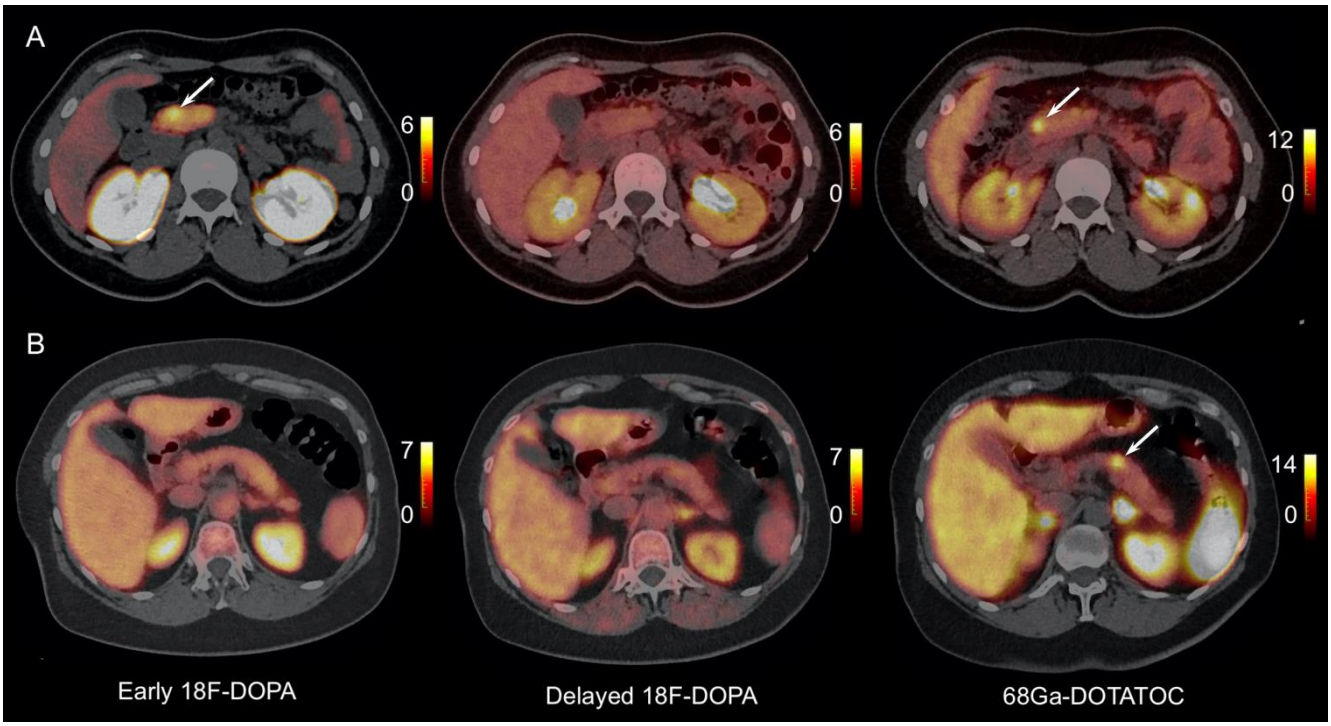

Figure 2. Discordant results of carbidopa-assisted ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT in two patients with pathologically proved insulinoma (arrows). (**A**) Early ^{18}F-DOPA+/Delayed ^{18}F-DOPA -/^{68}Ga-DOTATOC+. (**B**) Early ^{18}F-DOPA-/Delayed ^{18}F-DOPA-/^{68}Ga-DOTATOC+.

Graphical Abstract