Original Article

Diagnostic Modalities, Management Considerations, and Outcomes of Insulinoma: A Case Series from a Tertiary Care Centre

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Abstract

Introduction: Insulinomas are rare, usually sporadic, and typically benign pancreatic neuroendocrine tumours. Pre-operative localization is challenging and evidence on comparative analysis of anatomic and scintigraphic modalities for pre-operative tumour localization is limited, even in contemporary series. **Methods:** The current study was designed to study the clinical features and management challenges of insulinomas managed at a tertiary care centre. Clinical features, diagnosis, imaging techniques, surgical procedures, and outcomes details were collated. Pre-operative imaging techniques (CT/MRI, nuclear scintigraphy) were compared with intraoperative and histopathological findings to assess their accuracy of localization. **Results:** Thirty-seven patients (15 females [42%]; median age 36 years [IQR 28–49]) were included in the study. In four patients (10.8%), the tumour occurred in the setting of multiple endocrine neoplasia type 1 (MEN 1) while the remaining were sporadic. The sensitivity of pre-operative localization was 61.5% (multiphasic CT), 66.6% (multiphasic MRI), 100% (68Ga Exendin-4 PET-CT), and 91.6% (EUS). Three patients with normal multiphasic CT had localization on 68Ga Exendin-4 PET-CT. The positive predictive value (PPV) of both Exendin-PET-CT and EUS was similar at 91.6% and 91.6%, respectively. All patients (except one with nesidioblastosis), who underwent enucleation or partial pancreatic resection, were cured. **Conclusion:** 68Ga Exendin-4 PET-CT based is a non-invasive imaging modality that has high sensitivity and PPV and can be used as a first-line imaging modality. The overall prognosis of these tumours is good with high cure rates attained following surgical resection.

Keywords: Endoscopic ultrasound, enucleation, F-DOPA PET, 68Ga-labeled exendin-4 PET, insulinoma, pancreatic neuroendocrine tumour

Introduction

Insulinomas are rare neuroendocrine tumours of the pancreas, with a reported annual incidence of 1 to 4 cases per million.[1] These are usually sporadic, typically less than 2 cm in size, solitary and benign (in at least 90% of cases), and are diagnosed at a mean age of 50 years.[2,3] However, multiple endocrine neoplasia type 1 (MEN-1) associated insulinomas, which account for nearly 10 to 30% of cases, occur at an earlier age (<40 years), are larger and are more frequently multicentric in origin.[4,5] In approximately 10% of cases, an insulinoma may be malignant with metastasis to the liver and peri-pancreatic lymph nodes.[6]

Insulinoma is a prototype disorder of endogenous hyperinsulinemic hypoglycaemia and is characterized by an inappropriate secretion of insulin, leading to hypoglycaemia. Patients may experience symptoms of hypoglycaemia due to a catecholamine surge (tachycardia, diaphoresis, tremors) and/or in the form of neuroglycopenia (confusion,

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seizures, behavioural changes, and coma. More often than not, the diagnosis is delayed as symptoms are misattributed to psychiatric, cardiac, and neurological disorders. Fasting hypoglycaemia is the usual manifestation seen in approximately 75% of cases, while up to 20% may have both fasting and postprandial hypoglycaemia.[2,6]

In the evaluation of insulinoma, there are two crucial steps: the first is to establish the diagnosis, and the second one is to localize the tumour. Establishing the diagnosis requires fulfilment of the classical Whipple's triad, which includes documented hypoglycaemia (plasma glucose <55 mg/dl), symptoms consistent with hypoglycaemia, and relief of hypoglycaemic symptoms on exogenous glucose administration.[7] Localization of the culprit lesion is the more challenging part, and multiple modalities have been employed for the same.[8] These include the routinely used computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), as well as the relatively newer methods such as somatostatin receptor scintigraphy-based imaging with 68Ga-DOTA PET-CT and the glucagon-like peptide 1 receptor-based 68Ga-Exendin-4 PET-CT scintigraphy, both of which are highly sensitive and specific for localizing insulinoma. The specialized method of selective intra-arterial calcium stimulation combined with hepatic venous insulin estimation may be required in some cases where other modalities fail to localize the insulinoma. Pre-operative localization of the tumour is helpful in decision-making for the appropriate surgical procedure that will most likely result in a cure, either that enucleation or pancreatic resection.

Surgical excision is the treatment of choice in all cases of insulinoma, irrespective of size. The risk of recurrence after surgery is 0–5% at 10 years and 0–7% at 20 years in sporadic insulinoma, while it is greater among patients with MEN-1 syndrome (up to 20% at 10 years).[9] Herein, we present our tertiary care centre experience of the clinical attributes, diagnostic methods, clinical outcomes, and long-term follow-up of insulinomas over a decade.

Materials and Methods

This was the data from a single tertiary care centre. A retrospective evaluation of medical records was performed for histopathologically confirmed cases of insulinoma from January 2011 to June 2021. Data regarding their demographic profile, clinical presentation, diagnostic workup, and medical and surgical treatment outcome were retrieved.

Biochemical diagnosis of insulinoma

The diagnosis of insulinoma was made based on the clinical signs and symptoms of hypoglycaemia. Subjects fulfilling the Whipple's triad were subjected to a prolonged supervised (48 to 72 hr) fast, after excluding factitious and systemic causes of hypoglycaemia. An inappropriately elevated level of insulin ≥3.0 µU/ml (18 pmol/l) and c-peptide ≥0.6 ng/ml (0.2 nmol/l) in the presence of documented hypoglycaemia <55 mg/dl (<3 mmol/l) with serum β-hydroxybutyrate level of ≤2.7 mmol/l, was considered diagnostic for endogenous hyperinsulinemic hypoglycaemia (EHH).[6] Insulin and c-peptide were estimated by electro-chemiluminescence-immuno-assay (ECLIA) [ELECSYS Roche Diagnostics COBAS 8000, Germany]. The intra- and inter-assay CV for C-peptide was 2.8% and 1.8%, respectively, by ECLIA and the same was 1.4% and 1.0%, respectively, for insulin. HbA1c was estimated by high-performance liquid chromatography (HPLC) using the Bio-Rad 10 system (Bio-Rad, Hercules, CA), with an intra-assay CV of 0.81% and an inter-assay CV of 2.35%. Biochemical parameters (glucose, liver, and renal function tests) were measured using the COBAS 8000 Analyser Roche Diagnostics, Germany).

Pre-operative localization of insulinoma

After confirming EHH, appropriate imaging modalities, including CT abdomen (dual-phase or triple-phase), MRI abdomen, and endoscopic ultrasound, were performed to localize the lesions. The usual institutional protocol included an initial anatomic localization (CT), followed by MRI, if not localized by CT. Subsequently, a scintigraphy-based anatomic and functional localization (either the SRS-based 68Ga-DOTATATE/DOTANOC PET-CT or the F-DOPA PET CT) or the later introduced 68Ga-Exendin-4 PET-CT was performed. Endoscopic ultrasound (EUS) was performed in cases where the culprit lesion was not localized, or in cases of discordance between anatomic and scintigraphy-based imaging. In a subset of subjects in whom the lesions were either not identified by the abovementioned modalities or were multiple, the selective intra-arterial calcium stimulation (SACS) test was performed.

Following pre-operative localization, patients underwent surgery (either enucleation or pancreatic resection). During the procedure, the concordance of pre-operative imaging with intraoperative findings was further compared to evaluate the accuracy of localization. After resection of the lesion, the sample was submitted for frozen section analysis and histopathology examination to confirm the presence of a neuroendocrine tumour (NET) and establish its WHO grade. Immunohistochemical analysis was also performed for insulin and chromogranin.

Patients were considered to be in remission if there were no recurrent episodes of hypoglycaemia following the surgical intervention, irrespective of documented post-operative rebound hyperglycaemia.

Statistical analysis

Statistical analyses were performed using the statistical package Graph pad software (Prism version 9.0, California, San Diego). Continuous variables were expressed as mean ± SD or median with the interquartile range as per normality using the Kolmogorov–Smirnov test and classified as parametric or nonparametric. All comparisons were done at a level of significance of 0.05 (*P* value). Sensitivity and positive predictive values of the various imaging modalities

were evaluated considering the intraoperative localization and/or histopathological demonstration of the lesion as the gold standard. The accuracy of the different imaging modalities used for tumour localization was compared with the gold standard.

Ethical aspects

The study was approved by Institutional Ethics Committee, PGIMER, Chandigarh, India (IEC 07/2020 1715). Written informed consent was taken from all the patients during admission and/or follow up of this study. It was as per the declaration of Helsinki.

Results

There were a total of 37 patients with histopathologically proven disease, including 36 cases of insulinoma and 1 case of adult nesidioblastosis, over the past decade. The protocol for their diagnosis and evaluation is depicted in Figure 1. Their clinico-demographic characteristics, biochemical and hormonal evaluation, pre-operative localization, management, and outcomes are summarized below.

Clinical and demographic characteristics

There were a total of 15 females (42%), with a median age of 36 years (IQR 28–49) and a body mass index of 27.5 kg/m^2 (IQR 23.5–30.4). The most common pattern was sporadic (89.1%), and in four patients (10.8%), the tumour occurred in the setting of possible or proven MEN 1. There were four patients (10.8%, one female) with multiple insulinomas, two of them associated with MEN 1. Two patients with insulinoma associated with MEN 1 had prolactinoma before the diagnosis of insulinoma and the other was diagnosed with acromegaly during the follow-up. Two of them had primary hyperparathyroidism. In the third patient, there was no PHPT even after 4 years of follow-up; her mutation analysis for the *Menin* gene was negative; hence, she was diagnosed as a MEN 1 phenocopy [Figure 2]. In four patients, insulinoma was multifocal, while in the rest, it was a single lesion. Metastatic malignant insulinoma was present in three patients, most commonly with metastases to the liver, lymph nodes, and bone.

The median time from symptom onset to diagnosis was 1.2 years (0.5–3.5). Weight gain was present in 63.6% (26/35) of the patients, and a history of weight loss was not present in any of the patients. All patients reported a history of fasting hypoglycaemia, and episodic post-prandial hypoglycaemia was found in 56.7% (17/30) patients. Neuroglycopenic symptoms were present in (86.4% of patients and adrenergic in 81% of patients. Confusion (n = 24, 64.8%) was the most common neuroglycopenic symptom. Medical management was used prior to diagnosis in 59.4% patients, and approximately 80% of these were inadvertently prescribed anti-epileptic agents. These parameters are summarized in Table 1.

Biochemical parameters

Prolonged supervised fast was done in 70.2% of patients (26 of 37), and the median duration of the fast required to attain symptomatic hypoglycaemia was 4.5 hours (IQR 3.75–16.5). The median nadir plasma glucose was 30 mg/dl (IQR 26–36 mg/dl). Concomitant

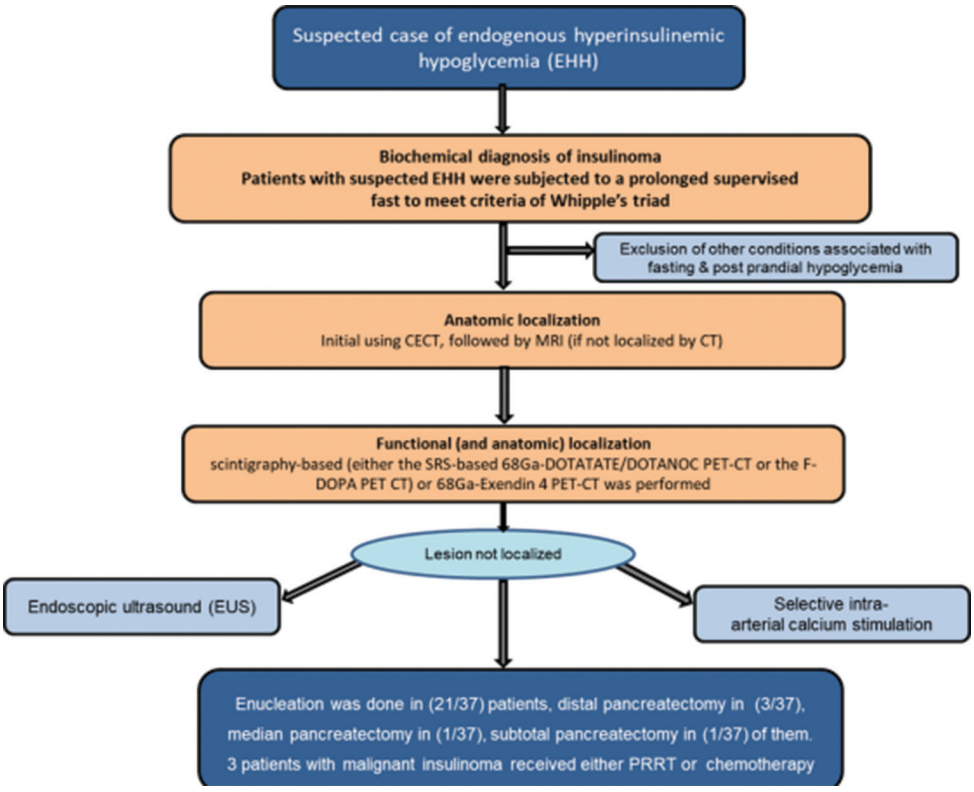

Figure 1: Flowchart depicting the protocol for diagnosis and evaluation of patients with suspected endogenous hyperinsulinemic hypoglycaemia at our institution

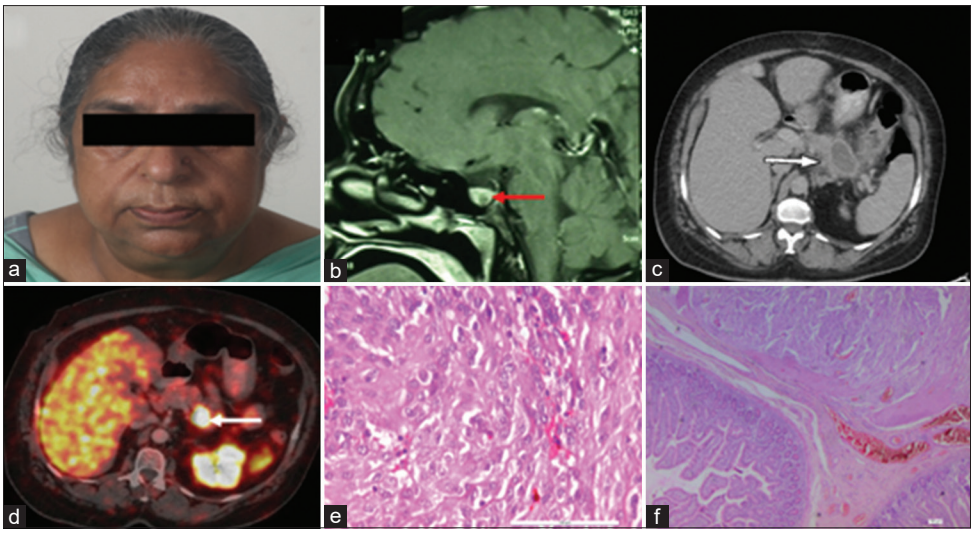

Figure 2: Panel of photographs of a 53-year-old female patient with endogenous hyperinsulinemic hypoglycaemia who had (a) coarse facial features due to underlying acromegaly which was due to a pituitary microadenoma on contrast-enhanced sagittal section MRI of the pituitary (red arrow) and/or insulinoma as depicted by the 2.5 × 2.4 cm lesion in the tail of pancreas depicted by the white arrow on contrast-enhanced CT (c). The pancreatic lesion was concordant on (d) 68Ga DOTATATE PET-CT with intense avidity (SUV Max 56.4) represented by the white arrow. The patient underwent distal pancreatectomy, and histopathology revealed a WHO grade 2 insulinoma with (e) showing a nesting pattern with nuclear atypia and prominent nucleoli (H and E 4×) and (f) shows tumour in the submucosa of the small intestine with normal mucosa (H and E 40×)

median plasma insulin during episodes of hypoglycaemia was 21.9 mIU/ml (IQR 12–36 mIU/ml) and c-peptide was 4.5 ng/ml (IQR 3.0 to 7.5 ng/ml). Median glycated haemoglobin was 4.8% (IQR 4.3–5.0%). The median cortisol was inappropriately low (median 344 nmol/l, IQR 200 to 456).

Localization studies

After confirmation of EHH, different imaging modalities were used to localize the culprit lesion. Computed tomography (CT) and MRI localized the lesion in 64.7% (22/34) and 64.3% (9/14) cases, each [Table 2]. In two of the patients who had more than one lesion at surgery, CT picked up only one and missed the additional lesion. MRI picked up the lesion in two patients which was missed by CT but was falsely normal in one patient.

68Ga DOTANOC/DOTATATE or 18F-DOPA PET/CT correctly localized the tumour in 11 of 17 patients. It was falsely normal in 3 and localized to the wrong site in another patient. Metastases to the liver and lymph nodes were seen in one patient and multiple diffuse lymph nodal uptake was seen in another [Figure 3]. 68Ga Exendin-4 PET-CT was done in 15 patients and rightly localized the tumour in 13 of them, including one with nesidioblastosis. Of the 12 patients who had undergone Exendin PET for whom histopathology (HPE) was available, the lesion was localized correctly in 91.2% (11/12) of them [Table 2]. The sensitivity of CT and MRI, in localizing the tumour, was 61.5% and 66.6%, respectively. The sensitivity and PPV of Exendin PET were 100% and 91.6%, respectively [Table 3].

EUS revealed a lesion in 14 of the 17 patients in whom it was performed. Out of 25 patients with HPE available, 14 had undergone EUS of which 12 were positive (85.7%, 12/14) [Table 2]. The sensitivity and PPV of EUS were both

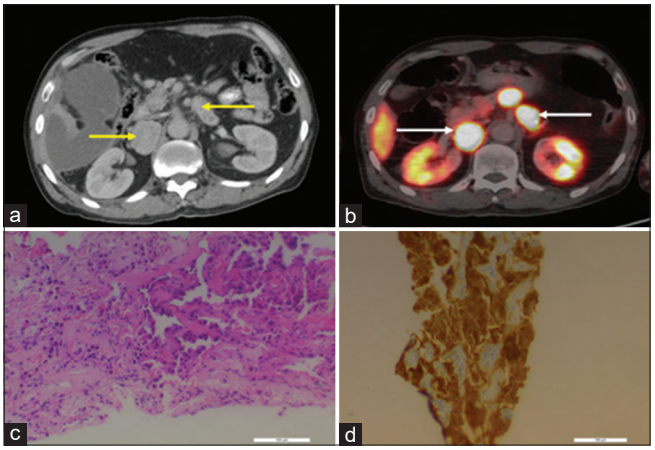

Figure 3: Image panel of a 62-year-old male with endogenous hyperinsulinemic hypoglycaemia with (a) showing mesenteric and retroperitoneal lymphadenopathy on contrast-enhanced CT of the pancreas represented by white arrows and (b) depicting the showing intensely tracer avid enlarged enhancing celiac axis, paraaortic, perigastric, peripancreatic, retrocaval, aortocaval, and mesenteric (largest 3.4 × 2.6 cm, SUV max 57.6) lymph nodes represented by yellow arrows on 68GaDOTATATE PET-CT. The patient underwent a core biopsy which revealed a tumour showing papillary architecture (H and E 20×). The IHC for insulin shows strong cytoplasmic positivity (IHC × 20×). He was managed with adjuvant everolimus therapy

similar at 91.6% [Table 3]. Multiple lesions were there in three patients. EUS picked up a lesion that CECT, MRI, and F-DOPA missed [Figure 4]. The site of occurrence of the culprit lesion for insulinoma was slightly different between the two modalities, namely the CT and EUS. While CT localized the tumour to pancreatic head (2), tail (5), between the junction of body and tail (1), body (1), neck (3), junction between body and

Table 1: Clinical, demographic, and biochemical parameters of the cohort

Parameter	Value
Age (years)	36.0 (28.0 to 49.0)
Gender (% females)	42%
Median duration of symptoms prior to diagnosis (months)	15 (6 to 42)
Fasting hypoglycaemia symptoms (%)	97.2%
Postprandial symptoms (%)	56.7% (17/30)
Both fasting and postprandial symptoms (%)	60% (15/25)
Weight gain (%)	74.2% (26/35)
BMI (kg/m^2)	27.5 (23.5 to 30.4)
Medical treatment before diagnosis (%)[#]	81.4% (22/27)
Syndromic association[^]	10.8% (4/37)
ALT (IU/l)	32 (22 to 47)
AST (IU/l)	31 (23 to 41)
Alb (g/dl)	4.1 (3.6 to 4.2)
Creatinine (mg/dl)	0.80 (0.60 to 0.95)
Total cholesterol (mg/dl)	152 (125 to 165)
LDL (mg/dl)	96 (73 to 111)
HDL (mg/dl)	36 (26 to 41)
Triglycerides (mg/dl)	120 (91 to 214)
Parameters during the prolonged supervised fast	
Time to hypoglycaemia during supervised fast (hrs)	4.5 (3.75 to 16.5)
Fasting plasma glucose (mg/dl)	30 (26 to 36)
Glucose during prolonged supervised fast (mg/dl)	31 (26 to 37)
Ketones-β-hydroxybutyrate (mIu/ml)	0.17 (0.10 to 0.20)
Insulin level (μU/ml)	21.9 (12.0 to 63.1)
C-peptide (ng/ml)	4.5 (3.0 to 7.5)
HbA1c (%)	4.8 (4.3 to 5.0)
Cortisol (nmol/l)	344 (200 to 456)

Values are expressed in frequency (*n*%) or median (IQR), as appropriate. [#]—Mostly anti-epileptics due to inadvertent diagnosis of seizure disorder or in patients who presented with neuroglycopenic symptoms, [^]—Mostly patients with MEN-1 syndrome. BMI—Body mass index, MEN 1—Multiple Endocrine Neoplasia, ALT—Alanine transaminase, AST—Aspartate transaminase, Alb—Albumin

neck (1) and uncinate process (3), the tumour location based on EUS was in the pancreatic head (2), tail (2), between the junction of body and tail (3), body (5), neck (1), and uncinate process (5). Overall, the tumour localization was as follows: CT-Head (5), Body (6), Tail (5) and EUS-Head (3), Body (13), Tail (2).

Selective arterial calcium stimulation (SACS) was done in three patients in whom localization of the tumour was not possible by other methods. Localization was successful in two of the three patients. The one in whom localization was not possible had nesidioblastosis.

Treatment

Eighteen patients (48.6%) required pharmacotherapy for the management of hypoglycaemia in the pre-operative period during the hospital admission, which included diazoxide (n = 14), octreotide (n = 8), nifedipine (n = 2) and verapamil (n = 1) in addition to frequent complex carbohydrate meals. The medical management was decided as per availability and/or patient preference. Two patients having metastatic malignant insulinoma were treated with everolimus, and one of them was also given capecitabine. One patient with malignant insulinoma received peptide receptor radionuclide therapy (PRRT) in the form of ^{177}Lutetium-based therapy (three cycles), with each cycle followed by oral capecitabine. Of these, the two patients who did not receive PRRT succumbed to the disease, whereas the one who was managed with PRRT and capecitabine, survived.

Among the total of 37, 26 underwent surgery. Of the 11 patients, three patients who had metastatic insulinoma were not subjected to surgery in view of metastatic disease and received either chemotherapy or PRRT. Two patients with a clinical diagnosis of MEN1, one diagnosed during the third trimester of pregnancy who received medical management and another young male, went into remission following their parathyroidectomy. Data about surgery and follow-up were not available in the remining six patients owing to the retrospective nature of the analysis. Enucleation was done in 80% (21/26) patients, distal pancreatectomy in 12% (3/26), and median pancreatectomy in 4% (1/26) of them. The patient with nesidioblastosis underwent a subtotal pancreatectomy. The maximum tumour dimension was ≤1 cm in three patients, 1–2 cm in five patients, 2 to 3 cm in one patient, and ≥3 cm in three patients. Intraoperative ultrasound was used to confirm insulinomas before proceeding to enucleation or pancreatic resection, in 13 patients, and all these patients were cured. All patients underwent surgery by the open route and none was operated laparoscopically.

Except for one patient who had histology consistent with nesidioblastosis, the rest had demonstrable pancreatic neuroendocrine tumours, with immunohistochemistry positive for chromogranin A, synaptophysin, and insulin. Histopathological evaluation was available in 26 patients, of whom most insulinomas (77%, n = 10/13) were well-differentiated tumours either of low-grade or moderate-grade malignancy (WHO grades G1 or G2). Neuroendocrine carcinoma (G3 WHO grade) was present in (23%, n = 3/13) patients. There was one patient with nesidioblastosis. The rest 12 patients had unclassified WHO grading. Ki67 was less than 3% in most of the patients (9 out of 12).

Post-operative rebound hyperglycaemia occurred in 29.1% (7/24) of patients who were operated on. Subcutaneous insulin was transiently used in these patients in the post-operative period for glycaemic control and was gradually tapered and discontinued in all but one patient who needed it briefly (2 weeks) following discharge. The period of follow-up ranged from 3 months to 10 years, with a mean duration of 5.4 ± 2.9 years. Two patients were lost to follow-up after the immediate post-operative period. All, except three patients who were operated on, were cured with a single surgical intervention. The patients who had persistent disease following surgery included a case of nesidioblastosis (managed post-operatively with long-acting octreotide, diazoxide, and

Table 2: Imaging modalities in the diagnosis and management of hyperinsulinemic hypoglycaemia

Imaging modality	Localization accuracy of the imaging modality in the cohort	Concordance with intraoperative findings or histopathological evaluation based on positive imaging findings	Detection rate of culprit lesion by a particular imaging modality (using HPE as the gold standard)
CT (*n*=34)	Localized lesion in 64.7% (22/34) Normal pancreas in 12; Atrophic pancreas with paracaval, paraaortic, paracoeliac location lymph nodes in 1 patient, liver mets in another patient	63.6% (14/22)	Out of 25 with HPE available, 24 had undergone CT of which 13 were positive 54.2% (13/24)
MRI (*n*=14)	Localized lesion in 64.3% (9/14) Normal pancreas in 5	55.6% (5/9)	Out of 25 with HPE available, 9 had undergone MRI of which 5 were positive 55.6% (5/9)
EUS (*n*=17)	Localized lesion in 82.3% (14/17) Normal pancreas in 3; Multiple lesions in 3	75% (12/16)	Out of 25 with HPE available, 14 had undergone EUS of which 12 were positive 85.7% (12/14)
Ga68 DOTANOC/ DOTATATE or F-DOPA PET-CT (*n*=17)	Localized lesion in 73.3% (11/15) Normal pancreas in 4; Metastases (liver and lymph node in 1, multiple diffuse lymph node uptake in 1)		
Ga68 Exendin PET CT (*n*=15)	Localized lesion in 80% (12/15) Diffuse uptake alone in 3; 1 with diffuse pancreatic uptake and peripancreatic LN, 1 with diffuse pancreatic uptake with two additional focal lesions in the neck of the pancreas	91.2% (11/12)	Out of 25 with HPE available, 12 had undergone Exendin PET of which 11 were positive 91.2% (11/12)
Selective arterial calcium stimulation (SACS) (*n*=3)	Done in three patients; Localization successful in 2 (Splenic in 1, Splenic and SMA in another)		-

MRI, magnetic resonance imaging; CT, computed tomography; EUS, Endoscopic ultrasonography; CECT, contrast-enhanced computed tomography; EUS, endoscopic ultrasound; PET/CT, positron emission tomography/computed tomography. Values are expressed in frequency (%) with actual numbers of each parameter in brackets. Histopathological evaluation was available in 26 patients, of whom 77% (10/13) had Grade I NET or Grade II NET, and 23% (3/13) had neuroendocrine carcinoma. There was one patient with nesidioblastosis. The rest 12 had unclassified WHO grading

Table 3: Details of various imaging modalities in patients with hyperinsulinemic hypoglycaemia

Imaging	True Positive	False negative	False positive	True negative
CECT[¶] (*n*=34)	15	10	0	1
MRI[ᵝ] (*n*=14)	6	3	0	1
Exendin*(*n*=15)	11	0	1	0
Endoscopic ultrasound[#] (*n*=17)	11	1	1	1

Values are as number of patients. [¶]In the CECT group, seven patients did not undergo surgery or HPE results was not available. [ᵝ]In the MRI group four patients did not undergo surgery or HPE results were not available. *In the Exendin group three patients did not undergo surgery. [#]In the Endoscopic Ultrasound group two patients were lost to follow up and one patient did not undergo surgery. In 1 patient EUS picked up a lesion in the tail while the intraoperatively lesion was at the junction of body and neck it was taken as false positive

everolimus) and three with malignant insulinomas (one of whom required adjuvant everolimus, another one received capecitabine, everolimus, and PPRT and the last one received octreotide, diazoxide, and everolimus).

Discussion

Endogenous hyperinsulinemic hypoglycaemia is an uncommon clinical entity encountered by a clinician. Insulinoma is common in this subgroup of patients. This retrospective study established that insulinomas are usually benign (~95%), small (1–2 cm), and solitary tumours. Our study did not show a predilection of insulinoma for females (42%), which is unlike what has been reported in other series.[2] Fasting hypoglycaemia occurred in all the patients, and nearly half of them additionally had postprandial hypoglycaemia. This higher rate of postprandial hypoglycaemia and the younger at diagnosis of our cohort are also different from previous reports.[6,10] The median duration of symptoms prior to diagnosis (15 months) was comparable to prior large series.[11] There was a high rate of misdiagnosis as epilepsy and intervention with anti-epileptic agents. The inappropriately low cortisol suggests either a lag in cortisol rise or blunting of response due to repeated episodes of hypoglycaemia.[12]

It is imperative to localize by imaging modalities before planning for surgical resection as it results in a better cure rate and decreases operating time.[13,14] The current study also looked at the concordance of positive imaging findings with intraoperative findings or histopathological evaluation for accuracy. Among non-invasive modalities, the rates of detection of the culprit lesion were similar between multiphasic CT and MRI. However, MRI accurately localized the lesion in two patients, which was missed by the CT scan. On the other hand, MRI failed to localize the tumour in one patient, which

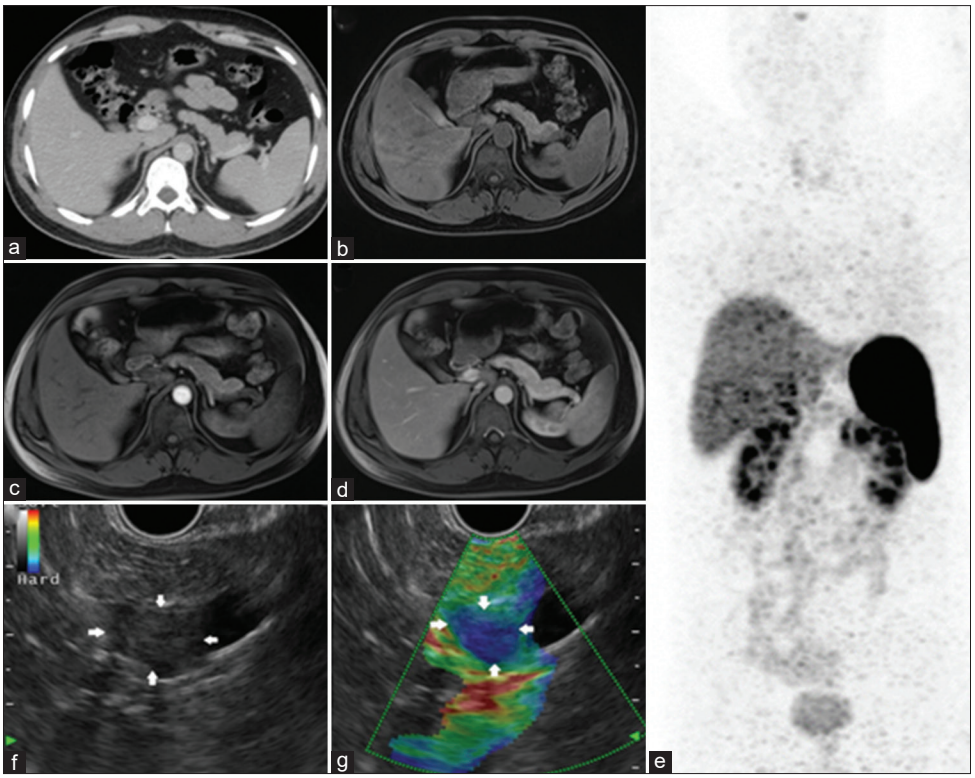

Figure 4: Panel of photographs of a 28-year-old male who presented with multiple episodes of symptomatic hypoglycaemia which were confirmed to be due to endogeneous hyperinsulinemic hypoglycaemia. CECT (a), Multiphasic MRI (b) and F-DOPA PET scan failed to localize the culprit lesion but (c) EUS showed a well-defined hypoechoic lesion in the tail of pancreas adjacent to the splenic vein (white arrows). EUS elastography (d) shows the lesion to be stiff (purple colour; white arrows). The patient underwent distal pancreatectomy successfully, which revealed a NET grade 1 tumour (insulin immunostaining positive) and was cured

was correctly identified by CT. We did not find a significant difference in the sensitivity of MRI and CECT for pre-operative localization, with no specific advantage of one over the other. Out of the five patients who underwent MRI and EUS, four patients had concordant lesions, whereas, in one patient, EUS picked up a lesion that MRI did not.

Besides anatomical imaging, rapid advances have been made in the last couple of decades for the localization of insulinoma in the form of functional imaging using radioactively labelled peptide analogues which generally target the SSTR subunits (mainly SSTR2) or large amino acid transport 1 and the more recent glucagon-like receptor 1 (GLP1). Detection of a lesion by nuclear scintigraphy depends on many factors including the size of the tumour, location, receptor density, and the target-to-background ratio.[15] Various studies have shown a sensitivity of 66% to 85% with the use of 68Gallium SSTR PET-CT (either 68Ga-DOTATOC or DOTATATE or DOTANOC PET-CT).[14,16] In the current study, the 68Ga DOTANOC/DOTATATE or 18F-DOPA PET-CT accurately localized the tumour in 73.3% of patients (11/15), which was higher than both CT and MRI. In one of the patients with multiple lesions, CECT failed to localize the additional lesion, while 68Ga DOTA PET-CT was accurately able to locate the other lesion. This emphasizes the utility of nuclear scintigraphy which incorporates both anatomical and functional aspects, in the pre-operative localization of insulinomas.

However, it is well known that nearly 30% of insulinomas do not express SSTR2 and SSTR5 adequately, which can lead to high false negative results in this subgroup of patients.[17] In fact, the greater density of GLP-1R in benign insulinomas and SSTR preponderance in malignant insulinomas, is reported.[18] GLP-1R is expressed with a high frequency as well as density in almost 92% of benign insulinomas and clinical studies with the 68Ga-labelled Exendin-4 scan have shown high sensitivity and positive predictive value (nearly 95 to 100%).[19] The sensitivity (100%) and PPV (91.6%) of 68Ga-labelled Exendin-4 PET-CT in our cohort was similar to that shown in prior studies.[20] It was higher than other available investigation modalities, as has been reported in other studies.[15,21] Hence, it might be a more accurate screening test for insulinoma localization in patients with EHH. Further, three patients who had normal pancreatic imaging on CECT were accurately localized on 68Ga-labelled Exendin-4 PET-CT. The high sensitivity and PPV may be attributed to the excellent spatial resolution of the modality which helps in exact localization and tumour quantification pre-operatively. Hence, they can be used to guide surgical management, thereby improving the success rate of surgical excision.

The first-choice tracer is usually 68Ga-SSTR PET, based on more evidence available with the same, wider availability and

both higher sensitivity as well as detection rates with similar specificity as compared to FluoroDopa PET CT.[22] But, when available, 68Ga Exendin-4 PET-CT is a non-invasive imaging modality that has high sensitivity and PPV and can be used as a first-line imaging modality, based on the results of the current study.

Multiple studies have shown EUS to be positive in 70–95% of cases in experienced centres.[23,24] In the current study, EUS had a sensitivity of 91.6% in localizing insulinoma, and this is comparable to a prior study.[25] We also demonstrated the comparable sensitivity, as well as PPV of EUS and 68Ga-labelled Exendin-4 PET-CT in the accurate localization of insulinomas. There were three patients with multiple lesions, all were missed by CT but picked up by EUS. However, in one of the patients, EUS identified the lesion in the tail of the pancreas while intraoperatively, the lesion was at the junction of the body and neck. Recent advances in EUS include elastography that can be used in combination with conventional EUS. This non-invasive method measures tissue stiffness and helps in locating and further characterization of small insulinomas. This technique was successfully used in one patient in the current study where other imaging modalities (CT, MRI, F-DOPA PET-CT) were negative. The further utility of EUS lies in guiding biopsy of selected cases of insulinomas (limited to specific indications such as inconclusive biochemical tests, suspected malignancy, or extra-pancreatic lesions) or rarely, for radiofrequency ablation.[26,27]

Localization with SACS was successful in two of the three patients in whom it was performed and the third one had nesidioblastosis. Hence, the sensitivity of SACS was 100%. According to the literature, SACS is reported to have a sensitivity of 77–100%.[11] In a prior series from Maryland where 45 sporadic insulinomas were not localized by any imaging modalities, SACS correctly localized the lesion in 84% of the cases.[28] However, SACS in that study was compared only to anatomical imaging (USG, CT, or MRI) and no nuclear scintigraphy was performed. Considering the lower sensitivity and the invasive and expensive nature of this test, it can be best reserved for cases with solitary tumours where all imaging modalities have failed or in cases of multiple tumours to identify the predominant site of secretion.

The treatment of choice for insulinomas is surgical excision, and it predominantly entails enucleation, as the majority of the lesions are solitary and benign.[9] In the current study, enucleation was done in 21 patients with a cure being achieved in the vast majority (~95%) of patients. Pancreatectomy (partial or subtotal) was required in five patients. All except one (with nesidioblastosis) of these five patients underwent a cure for the EHH. One of them who underwent subtotal pancreatectomy had nesidioblastosis and was not cured despite the procedure.

A review of the relevant studies published from India was also compared and contrasted with the current study and the findings are summarized in Table 4.[25,29-32] We found a male preponderance in our series which was like a prior report from India, contrasting with many Western series with female preponderance. Further, while the calculated sensitivity of CT scan was similar to our study, MRI in this series demonstrated better sensitivity than our study (85.7% vs 64.3%). In another

Table 4: Comparative analysis of the current study with other series from India

	Paul TV *et al*.	Gopal RA *et al*.	Anakal MG *et al*.	Jyotsna VP, *et al*.	Sharma A, *et al*.	Present Study
Year	2008	2010	2014	2016	2022	2024
Number (*n*)	18	26	19	35	9	37
Gender (M/F)	1.2:1	0.3:1	1.1:1	1.2:1	0.3:1	1.5:1
72 hr fast test	18/18	17/26	4/19	4/35	9/9	26/37
Malignant Cases (*n*)	1	0	0	0	0	3
Anatomic localization						
CECT						
Cases (*n*)	10	26	9	29	9	34
Sensitivity (%)	62.5	68.4	26.31	79	89	61.5
MRI						
Cases (*n*)	10	3	11	20	Not done	14
Sensitivity (%)	85.7	33.3	26.31	85		66.6
Functional localization						
68GaDOTATATE/F-DOPA PET CT						
Cases (*n*)	Not done	Not Done	1	20	4	17
Sensitivity (%)			100	25	50	
68Ga-Exendin-4 PET-CT						
Cases (*n*)	Not done	Not done	Not done	Not done	1	15
Sensitivity (%)				Not done	100	100
Endoscopic ultrasound						
Cases (*n*)	3	3	Not done	22		17
Sensitivity (%)	100	75		95		91.6

study from India, CT showed a high sensitivity of 89%; however, it included only nine patients. Localization with SACS was successful in two of the three patients in whom it was performed and the third one had nesidioblastosis. Hence, the sensitivity of SACS was 100%. This is similar to one of the Indian series where SACS was used in five patients.

This study had some limitations, including the retrospective nature of the study, lack of all information on all patients, and changes in the diagnostic protocol with the introduction of newer modalities, especially nuclear scintigraphy. Though there is some data on the utility of continuous glucose monitoring for the screening of patients presenting with hypoglycaemia, we did not use it in the current study.[33] However, the strengths of the study are single-centre data thereby ensuring uniformity in diagnosis and management, and the use of both anatomic and some form of scintigraphic modalities in the majority of patients, which enabled us to compare the utility of both in pre-operative localization.

Conclusion

Insulinomas are usually benign, solitary, and small tumours that have an excellent prognosis after enucleation once they are localized either by imaging or endoscopic ultrasound. 68Ga-labelled Exendin-4 PET-CT has high sensitivity and positive predictive value and can be used as in the initial strategy for pre-operative localization of the culprit lesion.

Authors' contribution

AJS was involved in data curation, methodology, and writing the first draft of the manuscript. LD was involved in data curation, formal analysis, methodology, writing, and editing of the manuscript. RK provided the nuclear medicine expertise and edited the manuscript. HS was involved in investigation, methodology, and editing of the manuscript. SSJ was involved in data curation and resources. SKB was involved in investigation, project administration, and editing of the manuscript. AG provided the radiological expertise and edited the manuscript. SSR was involved in resources and editing the manuscript. UNS provided the histopathological expertise and edited the manuscript. AB provided the surgical expertise and edited the manuscript. BRM was involved in investigation, supervision, and editing of the manuscript. RW was involved in data curation, investigation, methodology, resources, and editing of the manuscript. PD was involved in conceptualization, investigation, methodology, project administration, supervision, and editing of the manuscript. All authors have read and approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

Data Availability statement

All the raw data will be provided to competent authorities on reasonable request to corresponding author i.e Dr Pinaki.

References

1. Salazar R, Wiedenmann B, Rindi G, Ruszniewski P. ENETS 2011 consensus guidelines for the management of patients with digestive neuroendocrine tumors: An update. Neuroendocrinology 2012;95:71-3.
2. Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, *et al*. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. J Clin Endocrinol Metab 2009;94:1069-73.
3. Kurakawa KI, Okada A, Manaka K, Konishi T, Jo T, Ono S, *et al*. Clinical characteristics and incidences of benign and malignant insulinoma using a national inpatient database in Japan. J Clin Endocrinol Metab 2021;106:3477-86.
4. Demeure MJ, Klonoff DC, Karam JH, Duh QY, Clark OH. Insulinomas associated with multiple endocrine neoplasia type I: The need for a different surgical approach. Surgery 1991;110:998-1005.
5. Sada A, Habermann EB, Yamashita TS, Thompson GB, Lyden ML, Foster TR, *et al*. Comparison between sporadic and multiple endocrine neoplasia type 1–associated insulinoma. J Am Coll Surg 2022;235:756-63.
6. Jensen RT, Cadiot G, Brandi ML, De Herder WW, Kaltsas G, Komminoth P, *et al*. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: Functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012;95:98-119.
7. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, *et al*. Evaluation and management of adult hypoglycemic disorders: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2009;94:709-28.
8. Refardt J, Hofland J, Wild D, Christ E. Molecular imaging of neuroendocrine neoplasms. J Clin Endocrinol Metab 2022;107:e2662-70.
9. Mehrabi A, Fischer L, Hafezi M, Dirlewanger A, Grenacher L, Diener MK, *et al*. A systematic review of localization, surgical treatment options, and outcome of insulinoma. Pancreas 2014;43:675-86.
10. Toaiari M, Davì MV, Dalle Carbonare L, Boninsegna L, Castellani C, Falconi M, *et al*. Presentation, diagnostic features and glucose handling in a monocentric series of insulinomas. J Endocrinol Invest 2013;36:753-8.
11. Nikfarjam M, Warshaw AL, Axelrod L, Deshpande V, Thayer SP, Ferrone CR, *et al*. Improved contemporary surgical management of insulinomas: A 25-year experience at the Massachusetts General Hospital. Ann Surg 2008;247:165-72.
12. Rhyu YA, Jang JY, Park S, An JH, Kim DL, Kim SK, *et al*. Impaired cortisol and growth hormone counterregulatory responses among severe hypoglycemic patients with type 2 diabetes mellitus. Endocrinol Metab 2019;34:187-94.
13. Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa Y, *et al*. Diagnosis and management of insulinoma. World J Gastoentrol 2013;19:829.
14. Pattison DA, Hicks RJ. Molecular imaging in the investigation of hypoglycaemic syndromes and their management. Endocr Relat Cancer 2017;24:R203-21.
15. Yang Y, Shi J, Zhu J. Diagnostic performance of noninvasive imaging modalities for localization of insulinoma: A meta-analysis. Eur J Radiol 2021;145:110016.
16. Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr Rev 2003;24:389-427.
17. Virgolini I, Traub-Weidinger T, Decristoforo C. Nuclear medicine in the detection and management of pancreatic islet-cell tumours. Best Pract Res Clin Endocrinol Metab 2005;19:213-27.
18. Christ E, Antwi K, Fani M, Wild D. Innovative imaging of insulinoma: The end of sampling? A review. Endocr Relat Cancer 2020;27:R79.
19. Luo Y, Pan Q, Yao S, Yu M, Wu W, Xue H, *et al*. Glucagon-like peptide-1 receptor PET/CT with 68Ga-NOTA Exendin-4 for detecting localized insulinoma: A prospective cohort study. J Nucl Med 2016;57:715-20.
20. Burghardt L, Meier JJ, Uhl W, Kahle-Stefan M, Schmidt WE, Nauck MA. Importance of localization of insulinomas: A systematic analysis. J Hepatobiliary Pancreat Sci 2019;26:383-92.
21. Antwi K, Fani M, Heye T, Nicolas G, Rottenburger C, Kaul F, *et al*. Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas:

Evaluation of diagnostic accuracy in a prospective crossover imaging study. Eur J Nucl Med Mol Imaging 2018;45:2318-27.
22. Imperiale A, Boursier C, Sahakian N, Ouvrard E, Chevalier E, Sebag F, *et al*. Value of 68Ga-DOTATOC and carbidopa-assisted 18F-DOPA PET/CT for insulinoma localization. J Nucl Med 2022;63:384-8.
23. Patel KK, Kim MK. Neuroendocrine tumors of the pancreas: Endoscopic diagnosis. Curr Opin Gastroenterol 2008;24:638-42.
24. Wang H, Ba Y, Xing Q, Du JL. Diagnostic value of endoscopic ultrasound for insulinoma localization: A systematic review and meta-analysis. PLoS One 2018;13:e0206099.
25. Jyotsna VP, Pal S, Kandasamy D, Gamanagatti S, Garg PK, Raizada N, *et al*. Evolving management of insulinoma: Experience at a tertiary care centre. Indian J Med Res 2016;144:771.
26. Kann PH, Moll R, Bartsch D, Pfützner A, Forst T, Tamagno G, *et al*. Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) in insulinomas: Indications and clinical relevance in a single investigator cohort of 47 patients. Endocrine 2017;56:158-63.
27. Marx M, Trosic-Ivanisevic T, Caillol F, Demartines N, Schoepfer A, Pesenti C, *et al*. EUS-guided radiofrequency ablation for pancreatic insulinoma: Experience in 2 tertiary centers. Gastrointest Endosc 2022;95:1256-63.
28. Guettier JM, Kam A, Chang R, Skarulis MC, Cochran C, Alexander HR, *et al*. Localization of insulinomas to regions of the pancreas by intraarterial calcium stimulation: The NIH experience. J Clin Endocrinol Metab 2009;94:1074-80.
29. Paul TV, Jacob JJ, Vasan SK, Thomas N, Rajarathnam S, Selvan B, *et al*. Management of insulinomas: Analysis from a tertiary care referral center in India. World J Surg 2008;32:576-82.
30. Gopal RA, Acharya SV, Menon SK, Bandgar TR, Menon PS, Shah NS. Clinical profile of insulinoma: Analysis from a tertiary care referral center in India. Indian J Gastroenterol 2010;29:205-8.
31. Anakal MG, Kalra P, Dharmalingam M, Indushekhar S, Rao V, Kumar KP. Insulinoma case series: Experience of a tertiary care center. Indian J Endocrinol Metab 2014;18:858.
32. Sharma A, Varshney P, Kasliwal R, Nagar A, Venkatatelikicherla K, Sarin S, *et al*. Insulinoma—accurate preoperative localization is the key to management: An initial experience. Indian J Surg Oncol 2022;13:403-11.
33. Ma J, Huang X, Zhao J, Lu J, Lu W, Bao Y, *et al*. CGM for insulinoma screening: A prospective and observational case-control study. Endocr Relat Cancer 2021;28:291-300.