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Insulinoma: Not Anymore, A Hidden Challenge

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ABSTRACT

Insulinomas comprise 1-2% of all pancreatic tumours and their small size coupled with non-specific symptomatology and an uncanny ability to go undetected on conventional imaging techniques makes preoperative localisation a diagnostic challenge. The objective is to evaluate the utility of imaging modalities and to analyse the presentation and surgical outcomes. Twenty consecutive operated cases of Insulinomas were reviewed retrospectively & prospectively over a 10year period from March 2011 to February 2021. Elevan were female & 9 male, median age was 37± 16.2 (range 21 to 50) years. The most common presentation was pre-prandial hypoglycaemia with symptomatic improvement on sugar ingestion. Biochemical diagnostic criteria used were, fasting blood glucose levels <50 mg/dl with synchronous insulin levels of >3.0 µU/ml and C-peptide levels of >0.6 ng/ml. Tumour localisation was done using a combination of CT, MRI and/or EUS in most patients and a Ga^{68}-DOTATATE in some patients. The size ranged between 1-2 cm and their distribution was as follows: 10 in tail, 5 in body, 4 in the head of pancreas and 1 in the uncinate process. Enucleation was done in 12 patients and in 8 patients, distal pancreatectomy with/without splenectomy was done. All patients recovered uneventfully and were asymptomatic on an average follow-up of 2 years, except for one patient who developed a peripancreatic collection, detected 2 months after surgery and managed conservatively. Additionally, 2 patients had similar symptoms but were found to have nesidioblastosis and presacral soft tissue tumour.

Key words: Insulinoma, Whipple's triad, hypoglycaemia, neuroglycopenic symptoms, enucleation.

INTRODUCTION

Insulinomas are the most common functioning neuroendocrine tumour (NET) of pancreas (70-80%), but rare, with an incidence of 1 in 250000. It occurs in all age group with peak incidence from 3rd to 5th decade, and with a female preponderance of 60-70% [1] In 1902 Nicholls described the first islet cell adenoma and Whipple described the classic diagnostic triad in 1935 [2] William J Mayo attempted the first operation for Insulinoma in 1927 but, successful enucleation was done by Roscoe Graham in 1929 [3]

Insulinomas present as solitary, encapsulated lesions in the pancreatic parenchyma that are predominantly benign in nature and hence, surgical cure rates are highly favourable. Previously it was believed that they would be predominantly located in the tail [4] but these lesions are evenly distributed in head, body and tail of the pancreas. The diagnosis is presumed by the presence of Whipple's triad (Symptoms of hypoglycaemia provoked by fasting, Relief of symptoms with glucose administration, Circulating glucose level < 50 mg/dl).

Inappropriately elevated insulin level is the underlying pathology that causes symptoms of hypoglycaemia. Several pre-operative and intra-operative techniques have been

employed by different researchers over decades in order to localise the lesion. As these tumours are small in size and are non-specific in their presentation, they frequently go undetected on routine imaging and hence, are very difficult to diagnose unless there is a fair amount of suspicion. The localisation of Insulinoma by various techniques is extremely essential to improve operative success. As complete surgical excision is the only curative option, accurate preoperative and intraoperative localization of the Insulinoma is crucial.

The management of Insulinomas has seen little therapeutic advancement over the years, but pre-operative localization still remains a largely unsolved issue. There are three treatment options: medical treatment, minimally invasive ablative procedures and open and laparoscopic surgery. Medical treatment and ablative procedures are reserved for patients who are not surgical candidates, deny operative management or, in the very rare case, maybe suffering from a metastatic disease (7-10%). Optimal surgical procedure is the key to prevent post-operative complications.

This study was undertaken to evaluate the relative utility of various imaging modalities in diagnosing Insulinomas, analyse the variety in presentation and study the surgical outcomes.

MATERIALS & METHODS

A total of 20 cases of Insulinomas operated in a tertiary care hospital reviewed retrospectively & prospectively over a 10 year period from March 2011 to February 2021.

Cases of Insulinomas were identified and localization done accordingly [Figure 1]. After thorough screening on the basis of inclusion and exclusion criteria proper informed consent was obtained. The data of patients willing to be the part of study was collected in prescribed proforma. Identity of patients enrolled in the study was not revealed.

Patient, tumour and treatment variables were taken into consideration. Patient data included age, gender and presenting complaints. The biochemical as well as imaging findings were noted. The surgeries were all performed with the objective of complete removal of the tumour. Perioperative serum insulin levels, blood sugar levels and C-peptide levels were used to assess completeness of tumour excision.

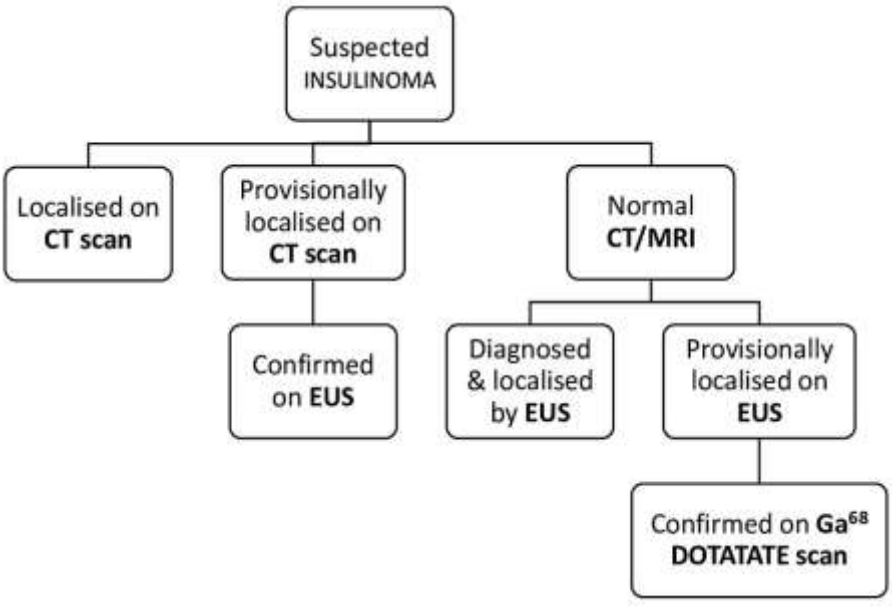

Figure 1: Localisation Algorithm

CT scan- Computed tomography scan, MRI- Magnetic resonance imaging, EUS- Endoscopic ultrasound

RESULT

With our diagnostic algorithm we were able to diagnose and localize all the tumours preoperatively. Median age was 37 ± 16.2 (range 21 to 50) years. There was a slightly higher incidence in females than males (F: M :: 11:9). The most common presentation was pre-prandial hypoglycaemia with symptomatic improvement with sugar ingestion but patients also presented with other symptoms including seizure, weakness, giddiness, light-headedness and confusion (Table 1).

Symptom	Frequency
Unconsciousness	10
Weakness	8
Giddiness	7
Seizures	3
Behavioral changes	3
Light headedness	2
Palpitation	1
Obesity	1
Recurrence of symptoms after being operated for Insulinoma	1

Table 1: Symptomatology

Biochemical diagnostic criteria used were fasting blood glucose levels <50 mg/dl with corresponding insulin levels of >3.0 µU/ml and C-peptide levels of >0.6 ng/ml. Blood Insulin levels were monitored intra-operatively as well as post-operatively at 5, 10 and 15 minutes.

The average size of the lesions was between 1-2 cm. CT scan was sufficient for the diagnosis and localisation of the lesion in 6 patients. In 3 cases where CT was unable to sufficiently pin-point the location of the tumour an EUS helped to localise the lesion. 6 patients were diagnosed and localize by an EUS who came with outside MRI report with provisional diagnosis of Insulinoma and in 5 patients in whom the tumour was provisionally localized on EUS a functional (68Ga-DOTATATE) scan helped in accurate localisation. 10 of the lesions were found in the pancreatic tail, 5 in the body, and 4 in the head and 1 in the uncinate process. Although on table USG is also a good investigation, we did not feel the need to use it as all tumours were localised pre operatively and an on-table palpation confirmed the location.

Additionally, two patients presented with clinical diagnosis of Insulinoma and were treated accordingly but later diagnosed with a nesidioblastosis and pre sacral soft tissue tumour on histopathology.

Enucleation was done in 12 patients. In 8 patients distal pancreatectomy was done, of which 3 required a splenectomy as well. 19 patients recovered uneventfully while one patient developed a peripancreatic collection that was detected 2 months after surgery and was managed conservatively. All patients were asymptomatic on an average follow-up of 2 years.

DISCUSSION

Most individuals present with symptoms of hypoglycaemia responding to sugar or food intake. Other symptoms can be attributed to Neuroglycopenic symptoms (altered mental status, amnesia, abnormal behaviour, seizures, and visual disturbances) and to Adrenergic (catecholamine) overdrive (sweating, palpitations, weakness, tremors and obesity). In our study, a similar symptomatology was observed (Table 1).

Often these patients are referred to psychiatrists or labelled as malingers due to behavioural changes before the correct diagnosis of Insulinoma is made.

Insulinoma represents 70-80% of clinically symptomatic pancreatic neuroendocrine tumours and can occur in all age groups with a peak incidence from the 3rd to 5th decade. Our study also shows a comparable age and gender incidence, median age of 37 ± 16.2 (range 21 to 50) years with maximum number of patients between the age group of 41-50 years of which 55% were females, which is consistent with the available literature [5].

Previously it was believed that they would be predominantly located in the tail but these lesions are evenly distributed in head, body and tail of the pancreas. Insulinomas rarely may be found at ectopic sites, namely stomach, duodenum, Meckel's diverticulum, bile duct, ovary, omentum or maybe mimicked by nesidioblastosis or soft tissue tumour. In our study, 50% (10) of the

lesions were in the pancreatic tail and 25% (5) in body, 20% (4) in the head of pancreas and 5% (1) in the uncinate process. 12 lesions were less than 2 cm in size & 8 were 2 or more than 2 cm in size but less than 3 cm in size.

Insulinomas are usually benign (90%) and exhibit an overall survival rate as high as 97%. Malignant Insulinomas are usually over 3 cm in size and metastasis is evident in 1/3rd of the patients at the time of diagnosis [6]. Radical resections benefit patients with malignant Insulinomas [7]. 10% of Insulinomas are multifocal.

Biochemical tests to diagnose Insulinomas include hypoglycaemia (fasting blood glucose levels <50 mg/dl) with elevated insulin (>3.0 µU/ml), proinsulin and c-peptide levels (>0.6 ng/ml). We followed the same criteria for arriving at a diagnosis in our cases and used increased blood sugar level of the patients to determine the completeness of tumour excision including a perioperative insulin assay. Tumour localisation was done using a combination of CT, MRI and/or EUS in 15 patients and in 5 patients in whom it was not localised by these modalities a nuclear scan (68Ga-DOTATATE) was done. CT scan is the first investigation, however if a patient is referred with an MRI done elsewhere, then CT is not done.

Non-invasive imaging studies include trans-abdominal ultrasonography, CT, MRI and Nuclear scans. These modalities have the advantage of being readily available and non-invasive but, accuracy in spotting the tumour is very low, especially for lesions which are less than 2 cm in size [8]. Invasive modalities include EUS, Intra-operative USG and Portal venous sampling. The various diagnostic tests available are enumerated in (Table 2).

Biochemical diagnosis	Blood glucose level < 50 mg%, Insulin level > 3 µU/ml, C- peptide level > 0.6 ng/ml
Imaging (Confirmation & localization)	USG, CT scan, MRI, EUS, Ga68- DOTATATE scan, Intraoperative USG
Some other modalities	Transhepatic portal venous sampling, Intra-arterial calcium stimulation

Table 2: Diagnostic Modalities

USG- Ultrasound sonography, CT scan- Computed Tomography scan, MRI- Magnetic Resonance Imaging, EUS- Endoscopic ultrasound, Ga68- DOTATATE scan- 68-Gallium DOTATATE scan

The sensitivities of transabdominal ultrasonography, CT and MRI are 9-67%, 16-73% and 7-45% respectively [8]. On the other hand, EUS has a sensitivity of 88% with the highest accuracy for tumours in the pancreatic head [9]. Among all investigations, the highest sensitivity is that of IO-US (95%). The detection rate of Insulinomas with laparoscopic ultrasonography can be as high as 96.9% [10] and its sensitivity is comparable to that of manual palpation along with intraoperative ultrasonography during open surgery; thus, it ensures the feasibility of laparoscopic management of Insulinoma and reinforces its advantage as a minimally invasive procedure [11,12]. Trans-hepatic selective portal venous sampling after calcium stimulation can localize Insulinomas with a sensitivity of 77-100%. In our study, 9 patients underwent a CT-based diagnosis [Figure *2*]

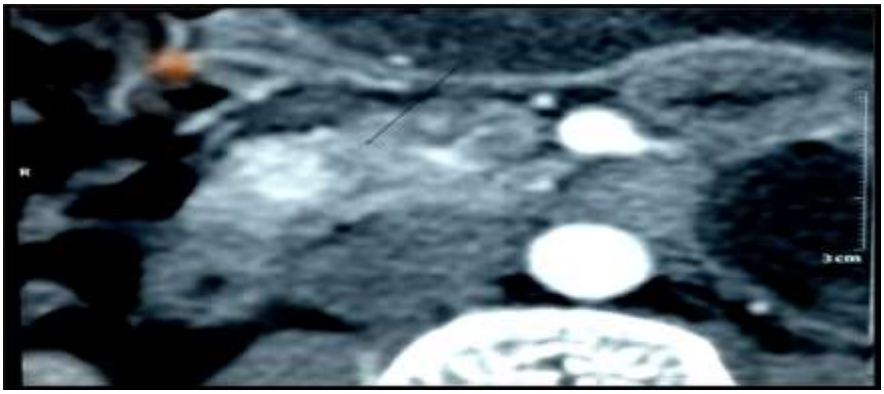

Figure 2: Computed tomography appearance

Insulinomas(arrow) are hypervascular and as a result demonstrate a greater degree of enhancement than normal pancreatic parenchyma during the arterial phase of contrast bolus.

out of which, localisation was confirmed with EUS for 3 patients. MRI and EUS were also required for 6 patients who could not be diagnosed on routine CT scans [Figure 3].

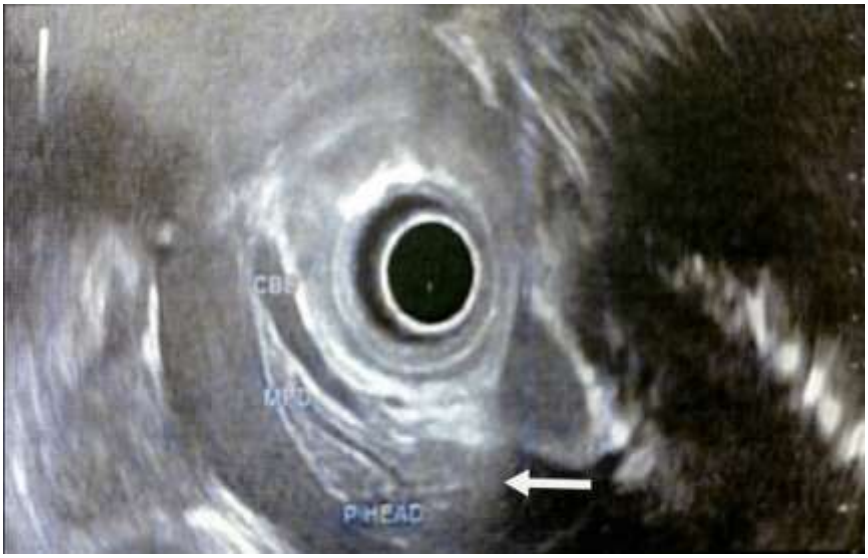

Figure 3: Endoscopic ultrasound (EUS) appearance

Small uniformly hypoechoic lesion in the head of pancreas. CBD- Common Bile Duct, MPD- Main Pancreatic Duct, P head- Pancreatic head

There were 5 cases that could not be localised on CT, MRI or EUS and underwent nuclear scans with 68Ga-DOTATATE and were found to have a somatostatin receptor positive tumour in the pancreas [Figure 4].

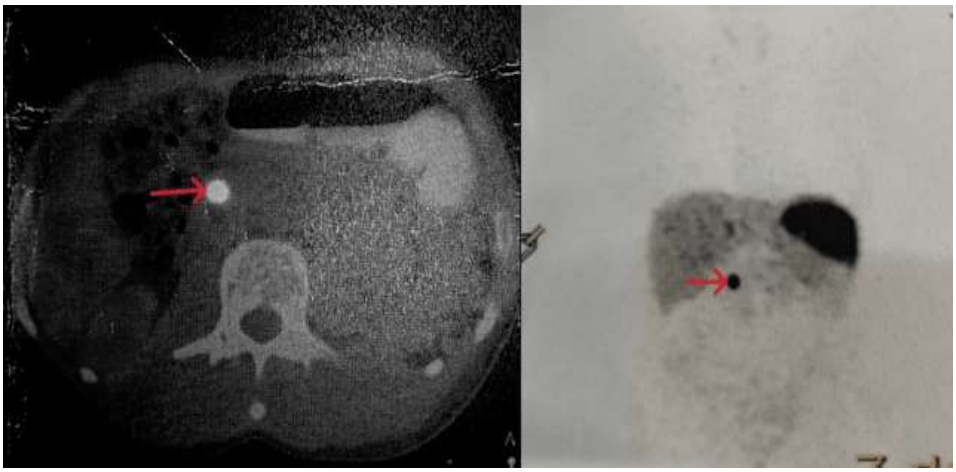

Figure 4: 68Ga-DOTATATE appearance

Insulinoma (arrow) with normal physiological uptake in spleen.

Surgery is the only curative option for any functional neuroendocrine tumour, and allows for complete tumour removal, histology and immunochemical analyses.

Much attention and investigation have been dedicated to the localization of Insulinomas. Exact localisation reduces surgical time and hence decreases morbidity. Type of surgery depends on the size & location of the tumour. Enucleation is the most commonly

performed surgery is done for lesions < 2 cm and/or away from PD (pancreatic duct). For lesions 2 or more than 2 cm and/or in close proximity to PD, distal pancreatectomy with or without splenectomy done. Other procedures include central pancreatectomy or rarely pancreatico-duodenectomy especially in malignant tumours. Laparoscopic surgery is an excellent option if localisation is accurate pre-operatively.

Pancreatic leakage has been seen to be the most frequent complication after Insulinoma resection followed by delayed gastric emptying and wound infections. Therefore, adequate precautions must be taken while resecting lesions that are near the pancreatic duct. We have been prudent in our dissections around the pancreatic duct without compromising the principles of optimal resection. 2 patients developed a pancreatic leak in our series (10%), both having undergone enucleation for a pancreatic head lesion. Fortunately, they were low volume pancreatic fistulae and could be safely managed non-operatively with supportive care, including parenteral nutrition. One patient (5%) developed an intra-abdominal collection 3 months post-operatively and was managed conservatively.

We sent an intra-operative frozen section in all our patients, which was suggestive of Insulinoma in 10 cases and the remaining were provisionally diagnosed as neuro-endocrine tumours of the pancreas. All 20 cases were confirmed as an Insulinoma on final histopathology. Cells showed a nested appearance on microscopy and typical small cells with salt pepper appearance of nucleus. Microscopy also revealed typical hyalinised fibrovascular stroma with amyloid deposit in some cases. [Figure 5,6]

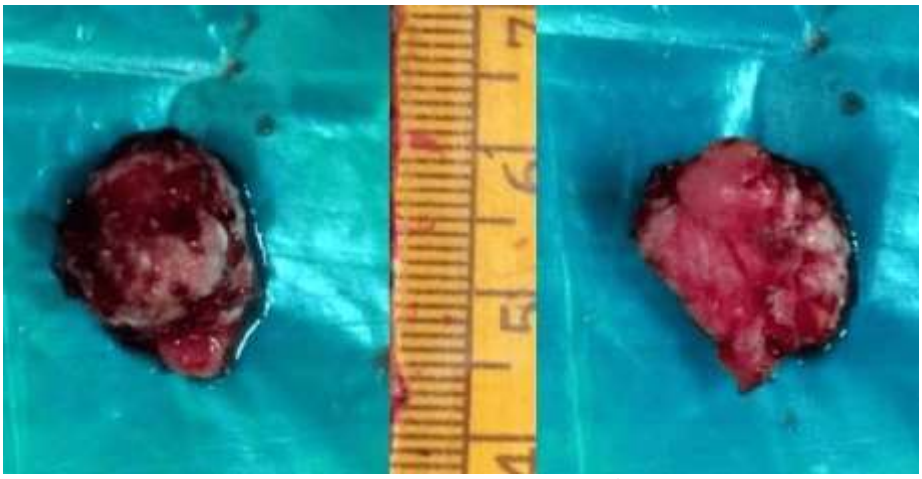

Figure 5: Gross appearance and Cut section of the tumour

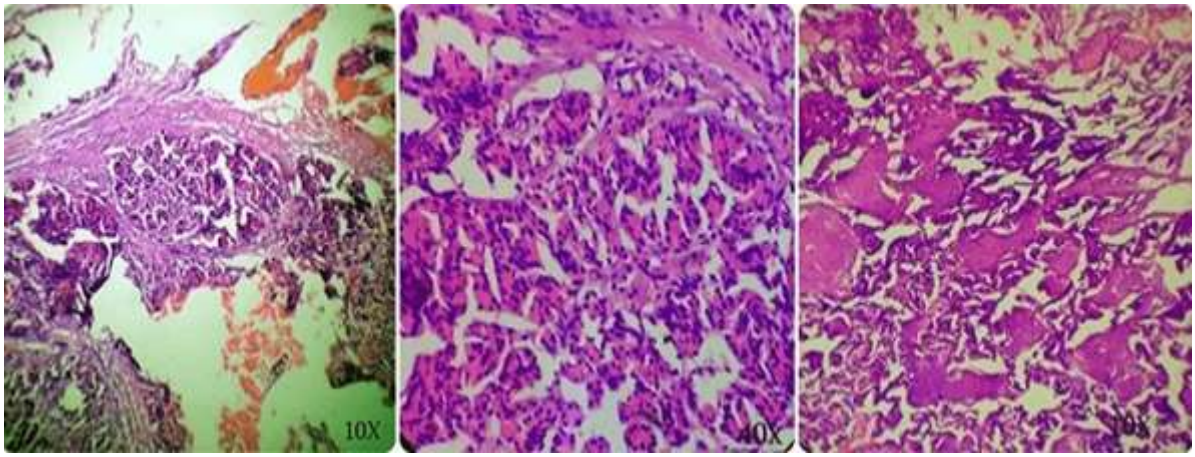

Figure 6: Microscopic appearance

Immunohistochemistry studies shows: nested appearance of tumour cells, salt pepper chromatin in the nucleus, hyaline fibrovascular stroma with amyloid deposit

If surgery is not feasible or in patients who refuse surgery, minimally invasive ablative procedures can be performed by interventional radiology which can lead to partial or complete remission of hormone hypersecretion and tumour control in Insulinoma patients [13]. Non-surgical treatment options include dietary modifications, pharmacologic agents and minimally invasive ablative procedures (Table 3).

Dietary modification	Small, frequent complex carbohydrate meals throughout the day and night
Pharmacologic agents	Diazoxide, Octreotide acetate, Verapamil
Minimally invasive ablative procedures	Tumor embolization, Ethanol ablations, RFA, HIFU ablation, Irreversible electroporation, Percutaneous microwave ablation

Table 3: Management Options

RFA-Radiofrequency ablation, HIFU ablation- High Intensity Focused Ultrasound ablation

Limitation for non-operative treatment is partial remission of hormone hyper secretion & inadequate tumour control.

In our series, additionally, two patients presented with clinical diagnosis of Insulinoma and were treated accordingly but later diagnosed with a nesidioblastosis and pre sacral soft tissue tumour on histopathology. Nesidioblastosis is an ill-understood pathological entity that occurs mainly in childhood and may represent the effect of a yet unidentified beta cell-tropic agent or a genetic variant of MEN-I. In a minority of patients, the tumours (hepatomas, fibromas, and fibrosarcomas are the most common among many) release enough IGF-2-related peptides into the circulation to mimic the fasting hypoglycaemia characteristics of patients with insulin-producing islet-cell tumours [14,15]. Some of the difficult scenarios faced could be of a 'missing' Insulinoma, in which case possibility of Nesidioblastosis or soft tissue lesion or ectopic location should be considered. Recurrence of symptoms after surgery may be due to multiplicity or inadequate excision.

With this study it maybe apt to conclude that Insulinomas have a varied presentation and remain a diagnostic and therapeutic challenge and a Team approach including an Endocrinologist, Radiologist, Pathologist, and Surgeon is mandatory. Contrast-enhanced multiphasic CT/MRI along with EUS have a complementary role in the diagnosis and localisation of these lesions. EUS, 68 Ga DOTATATE scan and intraoperative USG are the specialised imaging modalities along with on table palpation to diagnose and localize Insulinomas which cannot be detected on CT/MRI. Accurate pre-operative localization helps in performing a safe and effective surgery, open or laparoscopic, which is the cornerstone of treatment.

CONCLUSION

Insulinomas have a varied presentation and remain a diagnostic challenge for surgeons and endocrinologists alike. Contrast-enhanced multiphasic CT/MRI along with EUS have a complementary role in the diagnosis and localisation of these lesions. Accurate pre-operative localization helps in performing a safe and effective surgery, which is the cornerstone of treatment for this small subset of patients.

Declaration by Authors

Ethical Approval: Approved, approval for the study was obtained from institutional research ethics board letter no. ECARP/2017/24.

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Conflict of Interest: The authors declare no conflict of interest. The authors have no relevant affiliations or financial involvement

with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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