

# **Updates in Management of Insulinoma**

*An essay*

Submitted for Partial Fulfillment of Master Degree in  
**General Surgery**

*Presented*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدقة الله العظيم

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## List of Abbreviations

Abbrev.	Meaning
<b>5-FU</b>	5-Flurouracil
<b>AJCC</b>	American joint comitee of cancer
<b>APUD</b>	Amino precursor uptake and decarboxylation
<b>ASVS</b>	Arterial stimulation venous sampling
<b>BMI</b>	Body mass index
<b>CgA</b>	chromogranin A
<b>CP</b>	Central pancreatectomy
<b>CT</b>	Computed tomography
<b>DM</b>	Diabetes mellitis
<b>DP</b>	Distal pancreatectomy
<b>DVT</b>	Deep venous thrombosis
<b>ENETS</b>	European neuroendocrine tumor society
<b>ESMO</b>	European Society for Medical Oncology
<b>EUS</b>	Endoscopic ultrasonography
<b>EUS-FNT</b>	Endoscopic ultrasonography-fine needle tattoing
<b>FNA</b>	Fine needle aspiration
<b>FDG</b>	F-labelled deoxy glucose
<b>GISTS</b>	Gastro-intestinal stromal tumors
<b>GLP-1</b>	Glucagon like peptide type 1
<b>GLP-2</b>	Glucagon like peptide type 2
<b>HPF</b>	High power field
<b>IGF-I</b>	Insulin like growth factor type 1

## *List of Abbreviations*

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<b>IGF-II</b>	Insulin like growth factor type 2
<b>IOUS</b>	Intraoperative ultrasonography
<b>IPMN</b>	Intrapapillary mucinous neoplasm
<b>ISGPF</b>	International Study Group of Pancreatic Fistula
<b>LAPD</b>	Laparoscopic assisted pancreatoduodenectomy
<b>LDP</b>	Laparoscopic distal pancreatectomy
<b>LPD</b>	Laparoscopic pancreatoduodenectomy
<b>MEN-1</b>	Multiple endocrine neoplasm type 1
<b>MIPD</b>	Minimally invasive pancreaticoduodenectomy
<b>MRI</b>	Magnetic resonance imaging
<b>mTOR</b>	Mammalian target of rapamycin
<b>NANETS</b>	North American neuroendocrine tumor society
<b>NCCN</b>	National Comprehensive Cancer Network
<b>NET</b>	Neuroendocrine tumor
<b>NF1</b>	Neurofibromatosis type 1
<b>NIPHH</b>	Non insulinoma persistent hyperinsulinemic hypoglycemia
<b>NIPHS</b>	Non insulinoma pancreatogenic hypoglycemia syndrome
<b>NSE</b>	Neuron-specific enolase
<b>OPD</b>	open pancreaticoduodenectomy
<b>OS</b>	overall survival

## *List of Abbreviations*

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<b>PDGF</b>	platelet derivated growth factor
<b>PDGFRs</b>	platelet derivated growth factor receptors
<b>PET</b>	Positron emission tomography
<b>PFS</b>	progression-free survival
<b>PG</b>	pancreaticogastrostomy
<b>PJ</b>	pancreaticojejunostomy
<b>PNETS</b>	pancreatic neuroendocrine tumors
<b>PPPD</b>	pylorus preserving pancreaticoduodenectomy
<b>PPV</b>	positive predictive value
<b>PRRT</b>	peptide receptor radiotherapy
<b>SACS</b>	selective arterial calcium stimulation
<b>SMA</b>	superior mesenteric artery
<b>SMV</b>	superior mesenteric vein
<b>sst2A</b>	somatostatin A
<b>TAE</b>	trans-catheter arterial embolization
<b>TACE</b>	trans-catheter arterial chemoembolization
<b>TLPD</b>	totally laparoscopic pancreaticoduodenectomy
<b>TNM</b>	tumor, node, metastasis staging system
<b>TS</b>	tuberous sclerosis
<b>US</b>	Ultrasonography
<b>VHL</b>	Von Hippel Lindau's disease
<b>VEGF</b>	Vascular endothelial growth factor

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## Abstract

**Background:** Among pancreatic endocrine tumors, insulinoma is the most common type. This tumor was reported in 1–4 people per one million person years. It can be seen at any age and occurs slightly more frequently in female than male . Usually insulinoma clinical presentation is benign, with a solitary and small size (<2 cm in diameter). Most are sporadic, however, 10 % of insulinomas are multiple and occur as part of multiple endocrine neoplasia syndrome type I (MEN–I). Because of nonspecific symptoms, insulinoma may be misdiagnosed with other disorders. Patients often present with hypoglycemia signs resulting from inappropriate insulin secretion. After biochemical confirmation of hyperinsulinism, preoperative localization of the tumor in the pancreas may be difficult. Surgical removal, often curative, continues to be the treatment of choice.

**Aim of the Work:** The aim of this work is to give an updated and detailed view of the management of patients with insulinoma.

**Conclusion:** Benign insulinomas are cured by surgical removal and its recurrency is extremely rare. Recurrence is a frequent finding and therefore reoperation for metastatic disease is frequently needed and can result in excellent long term survival of up to 70% after 10 years. The median overall survival (OS) of patients with Stages I, II, III and IV was 112, 63, 36 and 14 months, respectively .

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**Keywords:** Insulinoma, Pancreas, Diagnosis, Management, Surgery

# Introduction

Insulinomas are the most common functional neuroendocrine tumor of pancreas and can occur sporadically (90%) or as part of multiple endocrine neoplasia type 1 (MEN-1) syndrome (10%). Accounting for 70-80% of all pancreatic neuroendocrine neoplasm (**Saclarides et al., 2015**).

Insulinomas are rare endocrine tumors developed from pancreatic beta cells. Their incidence is about 1 in 250,000 patient-years (**Cryer, 2008**). The median age at surgical diagnosis was found to be 47 years (8 to 82), 59% being females (**Vezzosi et al., 2007**).

90% of insulinomas are single, benign and sporadic tumours that are located in the pancreas. The diagnostic and therapeutic strategy of benign sporadic insulinomas has been now established by a recent expert consensus (**Cryer et al., 2009**).

There are 4 genetic disorders that are known to be responsible for pancreatic endocrine tumours in adult patients: multiple endocrine neoplasia 1, Von Hippel Lindau's disease, tuberous sclerosis (TS) (a disease that is known to involve a dysregulation of the mTOR pathway) and neurofibromatosis type 1 (**Jensen et al., 2008**).

Insulinomas are the most common cause of

hypoglycemia related to endogenous hyperinsulinism. The episodic nature of the hypoglycemic attack is due to the intermittent secretion of insulin by the tumor (**Oberg et al., 2012**). Common autonomic symptoms of an insulinoma diaphoresis, tremors and palpitations, where as neuroglycopenic symptoms include confusion, behavioral changes, visual disturbances, seizures and coma (**Suzuki et al., 2007**).

The classical diagnosis of insulinoma depends on satisfying the criteria of Whipple's triad, which remains the cornerstone of the screening process: (1) hypoglycemia (plasma glucose < 50 mg/dL); (2) neuroglycopenic symptoms; and (3) prompt relief of symptoms following the administration of glucose (**Rostambeigi and Thompson, 2009**)

Insulinomas are evenly distributed over the entire pancreas. Most insulinomas are located in the pancreas or are attached directly to the pancreas. Extra pancreatic insulinomas causing hypoglycemia are extremely rare (incidence < 2%); extrapancreatic insulinomas are most commonly found in the duodenal wall (**Oberg et al., 2012**).

Following biological and biochemical confirmation of an insulinoma, preoperative localization is sought using computed tomography (CT) magnetic resonance imaging

(MRI) (**Anaye et al., 2009**), endoscopic ultrasonography (EUS), intra-arterial calcium stimulation test with hepatic venous sampling(**Tseng et al., 2007**),and/or angiography and arterial stimulation venous sampling (ASVS) (**Guettier et al., 2009**).

Surgical resection is the primary treatment modality for insulinomas, and so accurate localization of the tumor before or during surgery is important. Intraoperative manual palpation of the pancreas by an experienced surgeon and intraoperative ultrasonography are both sensitive methods with which to localize insulinomas, supporting the argument by some surgeons that preoperative localization of the tumors is not necessary (**Shin et al., 2009**).

Surgery remains the only curative treatment of insulinomas. Long-term remission can be achieved by surgery in 95% of patients according to a recent study (**Zhao et al., 2011**). Two different types of surgery can be performed: minimal resection i.e. either tumour enucleation whenever it is possible or central pancreatectomy, or a more extended resection, i.e. left-sided pancreatectomy or pancreaticoduodenectomy. The type of surgery depends on the size and the location of the tumour and of its proximity with specific anatomical structures (pancreatic duct, vessels, and adjacent organs) (**Fendrich et al., 2009**).