Updates in Management of Insulinoma

An essay

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List of Abbreviations

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

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

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

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 neuroglycopenenic 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 pancreatico-duodenectomy. 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).**