JBUON 2020; 25(3): 1302-1314
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

REVIEW ARTICLE

Insulinomas: from diagnosis to treatment. A review of the literature

Dimitrios Giannis[1], Dimitrios Moris[2], Georgia-Sofia Karachaliou[3], Diamantis I. Tsilimigras[4], Georgios Karaolanis[1], Alexandros Papalampros[1], Evangelos Felekouras[1]

[1]1st Department of Surgery, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece. [2]Duke Surgery, Duke University Medical Center, Durham, NC, USA. [3]Department of Medicine, Division of Hematology/Oncology, The University of North Carolina, Chapel Hill, NC, USA. [4]Department of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center and James Cancer Hospital and Solove Research Institute, Columbus, OH, USA.

Summary

Insulinoma is the most common pancreatic neuroendocrine tumor (NET). Insulinomas are most commonly benign, well-differentiated NETs, whereas malignant neoplasms account for approximately 5-10% of all cases. Management includes conservative treatment with drugs targeting insulin-induced hypoglycemia, non-operative invasive procedures, as well as curative open or laparoscopic tumor resection. The current review aimed to summarize the current literature evidence on insulinoma and investigate the advantages and complications of available treatments.

Key words: *neuroendocrine tumors, pancreas, insulinoma, treatment, diagnosis*

Introduction

Neuroendocrine tumors (NETs) arise from the hormone-secreting cells and nerve cells mainly located in the gastrointestinal and respiratory tracts [1]. Gastroenteropancreatic NETs (GEP-NETs) are tumors that affect gastrointestinal tract and pancreas and are classified as functional (hormone producing, F-NETs) or nonfunctional (NF-NETs) [2]. Pancreatic NETs are further divided into 3 categories according to WHO 2017 classification: well-differentiated NET (G1, G2, G3), poorly differentiated neuroendocrine carcinoma (NEC G3) and mixed non-neuroendocrine-neuroendocrine neoplasm (MiNEN) [3].

Insulinoma is the most common pancreatic F-NET, deriving from β-pancreatic islet cells that secrete insulin, and is associated with hypoglycemic neuroglycopenic and sympathetic-overstimulation symptoms [4]. Insulinomas are most commonly benign, well-differentiated NETs, whereas malignant neoplasms account for approximately 5-10% of all cases [5]. Management includes conservative treatment with drugs targeting insulin-induced hypoglycemia, non-operative invasive procedures, as well as curative open or laparoscopic tumor resection [6]. The current review aims to summarize the current literature evidence on insulinoma and investigate the advantages and complications of available treatments.

Epidemiology

Insulinomas account for 1-2% of pancreatic tumors and affect approximately up to 3 patients per million per year [5,6]. In a case series study of 125 patients with pancreatic NETs, Phan et al reported that most F-NETs were insulinomas (55%),

Corresponding author: Dimitrios Moris, MD, MSc, PhD. Department of Surgery, Duke University Medical Center, 2301 Erwin Rd, 27710, Durham, NC, USA.
Tel: + 2165 716614, Fax: +1 9191063120, Email: dimmoris@yahoo.com
Received: 12/10/2019; Accepted: 15/11/2019

followed by gastrinomas (36%) [7]. Insulinomas may occur at any age, mainly during the 5th decade of life, and have a slight female predominance [8]. Placzkowski et al retrospectively investigated a total of 237 operatively confirmed cases and reported that 57% were females with a median age of 50 years (range 17-86) [9]. Multiple endocrine neoplasia type 1(MEN-1) is observed in about 4-7% of cases and is associated with younger tumor occurrence age (3rd decade of life) [10,11]. Among the 237 patients of the Mayo Clinic study, 14 patients (6%) had MEN-1 and 3 of them were diagnosed concurrently with the identification of insulinoma [9].

Insulinomas present with signs and symptoms early in their course and thus during diagnosis their size ranges between 0.5 cm and 2 cm [12,13]. Approximately 8-10% of these F-NETs are larger than 2 cm in diameter and have increased malignant potential [14-17]. A 60-year study between 1927 and 1986 by Service et al, involving 224 patients, reported an incidence of 4 cases per million per year and showed that 86.6% of them had single nonmalignant tumor in contrast to a minority of patients with multiple benign (7.1%) or malignant neoplasms (5.8%) [17]. Câmara-de-Souza et al, in a retrospective study of 103 patients, presented similar results regarding to patients having a benign tumor (87%) [18]. Hence, most insulinomas are single tumors, less than 2 cm in diameter, presenting with equal frequency among all anatomic sites of pancreas and only 8% of them exceed 5 cm in diameter [19].

Pathogenesis – Histopathology

Insulinomas most commonly are well-differentiated intrapancreatic G1-NETs, emerging as polyclonal or oligoclonal neoplasms that are subsequently outgrown by a malignant cell clone with metastatic potential [20,21]. Differentiation between benign and malignant tumors is sometimes difficult and is based on a combination of preoperative and intraoperative evidence (local invasion, lymph node and liver metastases) [22]. Histopathologic markers associated with the prognosis of insulinoma include Ki-67 proliferative index, tumor size, vascular invasion and local invasion [6,16,23].

The mTOR/PS0S6K molecular signaling pathway activation was significantly upregulated in tissue specimens derived from insulinomas compared to normal pancreatic islet tissue in an *in vitro* study by Zhan et al [24]. These findings suggest that mTOR could be a potential therapeutic molecular target of future insulinoma medical treatments through the use of mTOR inhibitors [24].

Histopathologic analysis demonstrates loss of pancreatic lobule architecture and a population of small-sized identical cells with loss of nuclear pleomorphism [25]. Immunohistochemical staining (IHC) reveals positive staining for chromogranin, synaptophysin and loss of p57 nuclear expression [25,26]. In addition, stromal amyloid aggregates, amylin and insulin positive IHC may be identified as insulinoma specific findings [20]. Nevertheless, in up to 20% of cases with compatible clinical diagnosis and symptoms resolution postoperatively tumors do not stain positive for insulin in IHC [27]. Therefore, Zhao et al propose that positive insulin IHC is not mandatory in order to confirm the diagnosis and the PanNET histopathologic result is sufficient in the context of hyperinsulinemia and postoperative subsidence of hypoglycemia [27]. Rare genetic syndromes associated with insulinoma include MEN-1 (menin tumor suppressor gene mutation) and tuberous sclerosis (TSC1/hamartin and TSC2/tuberin gene mutations) [9,28-30].

Clinical presentation

The diagnostic hallmark of insulinoma, the so-called "Whipple's triad" or "triad of insulinoma", was first described by Allen Whipple and Virginia Kneeland Frantz in the 1930s and consists of [31]:

- Symptoms caused by hypoglycemia;
- Low blood glucose level during the episodes;
- Symptoms relief upon blood glucose level normalization through glucose administration.

Hypoglycemic episodes caused by inappropriate insulin secretion are divided in two main categories, adrenergic and neuroglycopenic [22,32]. Adrenergic symptoms are caused by sympathetic nervous system (SNS) activation/catecholamines release and include diaphoresis, tremor, palpitations, anxiety, increased appetite and nervousness [22,32]. Neuroglycopenic symptoms, caused by decreased central nervous system (CNS) glucose supply, include impaired mental status and cognition, visual disturbances, disorientation, memory deficits, stupor, seizures and coma [22,32].

The majority of patients presents within 1.5 years of symptoms duration, but patients may be symptomatic for decades before being diagnosed [17]. Patients usually present with symptoms and signs precipitated during fasting periods, often upon awakening after the overnight fast or during exercise [33]. In order to avoid the occurrence of symptoms they frequently eat small meals and take snacks [33]. Infrequent presentation of insulinoma includes postprandial hypoglycemia, which may also be the only manifestation of hypoglycemia in some cases [9]. Common misdiagnoses include psy-

chiatric or neurologic disorders, such as seizures [17,34].

Diagnosis

Biochemical tests

Insulinoma diagnosis, in order to be absolutely established, requires compatible clinical presentation and the presence of the following 6 criteria [35]: blood glucose levels ≤ 40mg/dl, insulin ≥ 36 pmol/l, C-peptide ≥ 200 pmol/l, proinsulin ≥ 5 pmol/l, β-hydroxybutyrate ≤ 2.7 mmol/l and absence of plasma or urine sulfonylurea metabolites.

The 72-h fasting test, considered as the gold standard for confirmation of insulinoma diagnosis, consists of consecutive blood glucose and insulin levels measurement until the patient becomes symptomatic [2,27,36]. Most patients (80%) develop symptoms within 24h and are admitted in the hospital in order to undergo serial insulin, proinsulin, C-peptide and insulin/glucose ratio every 4-6h [33,37-40]. An insulin/glucose ratio > 0.3 has been found in all patients with confirmed insulinoma or other pancreatic islet disease associated with endogenous hyperinsulinemia [39]. Nevertheless, Hirshberg et al reported that almost all patients develop symptoms within 48h of fasting and thus the 48-h test should replace the 72-h test as the new diagnostic test of choice [41].

Interestingly, a controlled study by Vezzosi et al reported that the combination of proinsulin ≥ 5 pmol/l and blood glucose < 2.5 mmol/l (< 45 mg/dl) during 72h of fasting reached 100% sensitivity and specificity for the presence of endogenous hyperinsulinism [42]. The addition of C-peptide over 0.2 nmol/l to the aforementioned criteria was diagnostic for insulinoma in patients with endogenous hyperinsulinism [42].

Secretin stimulation test-induced insulin response (IV 2U/kg) is a useful method to differentiate between multiple adenomas and nesidioblastosis or single adenomas [32,43]. Specifically, underlying nesidioblastosis or single tumors do not respond to secretin in contrast to multiple adenomas demonstrating a significantly increased insulin secretion upon secretin administration [32].

Differential diagnosis of hypoglycemia

Insulinoma biochemical disturbances may be observed in other conditions associated with fasting hypoglycemia or postprandial hypoglycemia. Oral hypoglycemic agents (meglitinides or sulfonylureas) and insulin are the most common pharmaceutical causes of factitious self-induced hypoglycemia [44-46]. Renal failure, liver failure, sepsis, non-pancreatic tumors and adrenal insufficiency (hypocortisolemia) should also be included in the differential diagnoses [44,47-49]. Autoimmune diseases, such as systemic lupus erythematosus, or multiple myeloma may result in the production of anti-insulin or anti-insulin receptor antibodies [50,51] that act through binding of an unregulated release of insulin or via direct insulin receptor stimulation respectively [50,51].

Post-gastric bypass hyperinsulinemic postprandial hypoglycemia has been described due to postoperative nesidioblastosis in obese patients undergoing bariatric surgery and should be considered as an alternative cause in this population [52,53]. Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), a rare form of adult nesidioblastosis, manifesting with postprandial hyperinsulinemic hypoglycemia within 2-4 h after a meal should be considered in diagnostic dilemma cases [54].

Most common causes that should be included in the differential diagnosis are summarized in Table 1.

Tumor localization

As soon as insulinoma clinical diagnosis is established, anatomic detection of the tumor should be the next step combined with investigation of the presence or absence of metastatic disease. Localization of insulinomas prior to surgery is of great importance because up to 30% are <1 cm and in 10% of cases the disease is multilocular [32]. Initial diagnostic imaging tests include ultrasound (U/S), computed tomography (CT) and magnetic resonance imaging (MRI), which detect up to 80% of the cases [55-57]. Furthermore, Wei et al investigated 33 consecutive patients retrospectively and reported preoperative detection sensitivity of 72 % for CT and 75% for MRI [57].

Computerized tomography is currently considered the first-line imaging diagnostic test in the insulinoma visualization procedure [6]. Insulino-

Table 1. Hypoglycemia associated conditions in the differential diagnosis of insulinoma

Oral hypoglycemics (sulfonylureas, meglitinides)
Exogenous insulin administration
Systemic conditions (renal failure, liver failure, sepsis, non-pancreatic malignancies, adrenal insufficiency)
Autoimmune disease (SLE)
Multiple myeloma
Post-gastric bypass hypoglycemia
NIPHS

mas and their liver metastases (in the case of malignant tumors) are typically highly vascularized lesions showing enhancement compared to normal pancreatic tissue with IV contrast administration on CT [6,58,59]. Therefore, contrast enhanced CT in the context of thin-slices techniques should be used in order to efficiently detect these neoplasms [58]. Calcifications, if present, are more commonly associated with the presence of malignant tumors [58]. Atypical presentations on contrast enhanced CT include hypodense tumors with decreased vascularity or lesions with increased density prior to contrast administration [6,59].

Magnetic resonance imaging (MRI) is emerging as an appropriate, safe, non-invasive alternative with high sensitivity in the localization of insulinomas and metastatic disease [6,59,60]. In comparison to normal pancreatic parenchyma β-pancreatic islet cell tumors manifest low signal intensity on T1-weighted and increased signal intensity on T2-weighted images [59,60]. The pattern of enhancement is attributed to the classic hypervascularity of these tumors and is usually homogeneous or ring enhancing in tumors >2 cm [57,59]. Metastases follow a similar enhancement pattern as well [59]. Nevertheless, MRI role in the detection of insulinomas is limited by the typical contraindications to MRI use [6].

Prior to CT introduction in the diagnosis of insulinomas, digital substraction angiography (DSA) was the gold standard to detect tumor location [50]. Nowadays, angiography is applied in the context of selective arterial secretagogue injection (SASI) test, which utilizes the pancreatic F-NET hormone secretion to localize the tumor [50,61]. SASI test is done through the selective intra-arterial administration of calcium gluconate (secretagogue of insulin) into the supplying arteries of pancreas and the hepatic arteries [61]. Hepatic venous blood sampling is achieved through a catheter placed in the hepatic vein and the post-injection increase in the serum immunoreactive insulin is evaluated to determine the tumor location [22,35,61]. SASI test sensitivity has been reported to range between 84-100% and is the most sensitive method, independent of tumor size, to localize insulinomas preoperatively [61-63]. Figure 1 demonstrates a summary of U/S, CT and MRI appearance of insulinomas.

Endoscopic ultrasound (EUS) sensitivity ranges between 70-95% and is the test of choice in the case of inconclusive results in the aforementioned first-line imaging tests [35]. EUS in combination

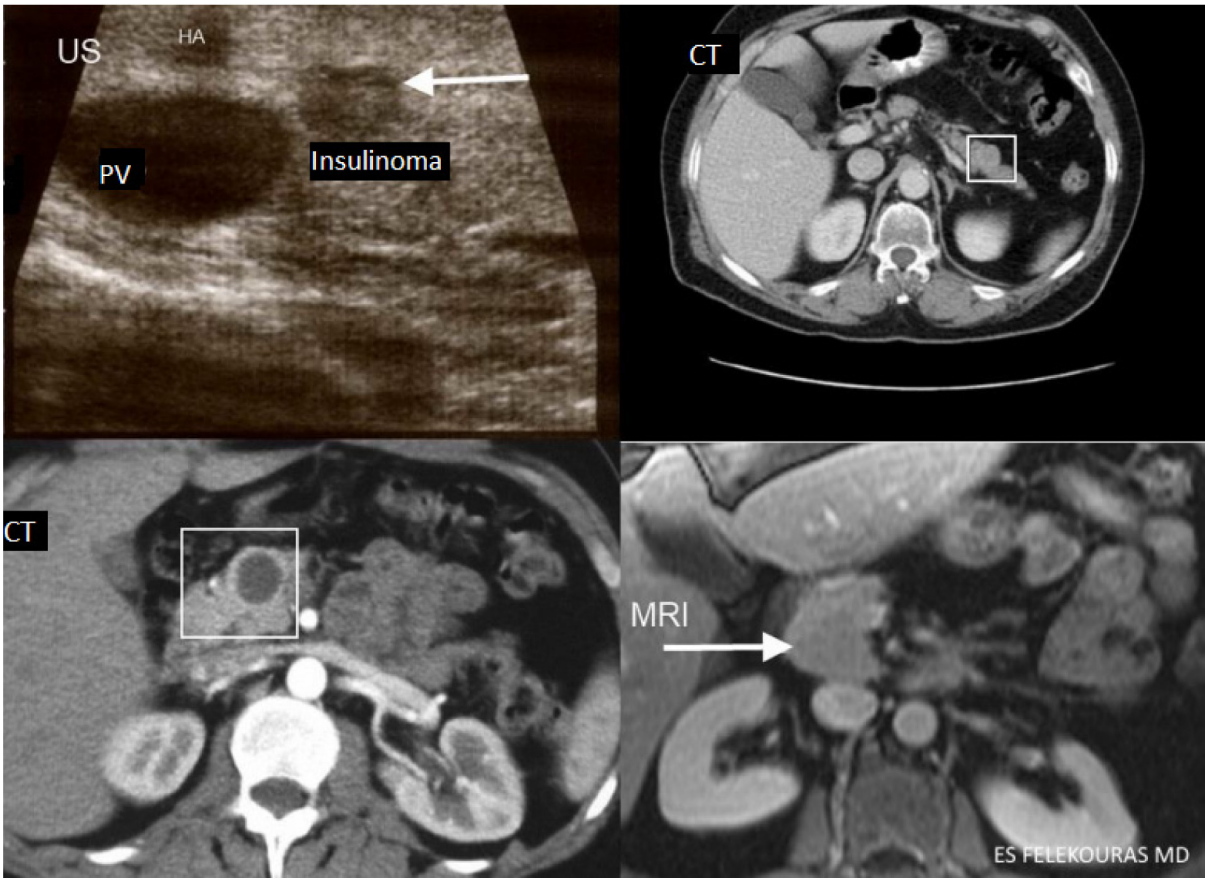

Figure 1. U/S, CT and MRI appearance of insulinoma. Preoperative imaging confirmation and localization are of great importance in the context of surgical planning.

with fine needle aspiration biopsy (FNA) achieves sensitivity up to 94% and specificity up to 95% [64-67].

Somatostatin receptor scintigraphy (SRS) test is positive in only up to 50% of cases due to low density or absence of somatostatin receptor subtypes 2 and 5 (sst2,sst5) [35,68,69]. In a small proportion of patients with negative imaging PET/CT with 68Ga-DOTATOC or 68Ga-NOTA-exendin-4 is necessary in order to localize the tumor preoperatively [35,64].

Newer data suggest that insulinomas highly express glucagon-like peptide-1 receptors (GLP-1R) and thus are labeled with a GLP-1R agonist (111 In-DOTA-exendin-4), which has been used successfully in the detection of small tumors both pre- and intraoperatively [71-74]. In many cases insulinomas can not be identified preoperatively and there is a need of a more sensitive non-invasive diagnostic test. Specifically, a recent systematic review by Mehrabi et al, evaluating 2.379 cases investigated after 2000, reported mean sensitivity of 85.3, 75.5, 57.7, 53.7 for SASI test, EUS, MRI and CT respectively [44].

Occult or non-detectable insulinomas are a diagnostic challenge for both radiologists and surgeons. The combination of CT, MRI and EUS achieves almost 100% sensitivity and occult tumors are not frequent [32,65]. Recent data suggest that occult neoplasms are more frequently in the pancreatic head [65]. Norton et al in their case series study reported that only 33% of pancreatic head insulinomas were palpable intraoperatively in contrast to intraoperative ultrasound (IOUS), which precisely detected all of the neoplasms [75]. Intraoperative palpation combined with IOUS is very effective (up to 93% detection rate) in the hands of surgeons trained on IOUS and familiarity with insulinomas [22,32,44,76]. Figure 2 summarizes out proposed diagnostic and localization algorithm.

Treatment

Nonoperative

Treatment of insulinomas is mainly surgical and the patient should be operated only if the diagnosis is confirmed, considering that currently blind pancreatectomy is not an appropriate therapeutic choice [32,77]. As soon as the diagnosis is confirmed, one of the most important aspects is the prevention of severe hypoglycemia through frequent meals and drugs, such as diazoxide administered in dosages 50-300 mg/d [39,78]. Diazoxide is the typical antihypoglycemic drug acting as a potassium channel opener on β-pancreatic islet cells resulting in decreased insulin secretion [78-81]. It is useful in approximately 2/3 of the patients, but should be stopped at least 1 week prior to surgical intervention due to risk of intraoperative hypotension [39,78]. Side effects of diazoxide include peripheral edema, congestive heart failure, hypotension, renal dysfunction, weight gain and hypertrichosis [15]. Other drugs, that inhibit the biosynthesis or release of insulin and have been mentioned as a potential therapy in the literature, include streptozocin, verapamil and phenytoin [44]. Somatostatin analogs (SSAs), such as octreotide, are effective in the prevention of hypoglycemia

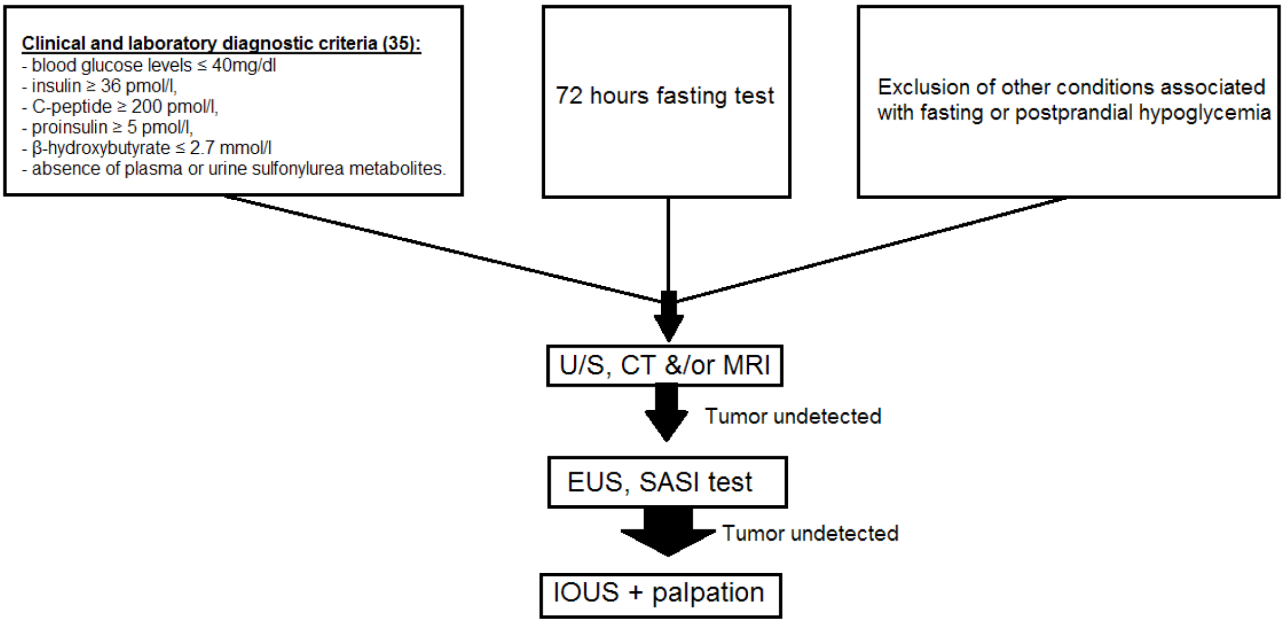

Figure 2. Proposed algorithm for the diagnosis and localization of insulinomas.

in 40-60% of the cases and this variable response is most probably attributed to the variable distribution of somatostatin receptors on insulinomas [39,82-85]. Ocreotide is used in long-acting release form at a monthly dose of 30 mg intramuscularly and the most common side effects include abdominal pain and flatulence as well as long-term complications (malabsorption, cholelithiasis) [82,86,87]. Despite of decreasing plasma insulin levels in 65% of patients, SSAs also inhibit counteractive hormones secretion (glucagon and growth hormone) and their administration may result in exacerbation of hypoglycemia [80,88-91].

Recently, an inhibitor of the mTOR kinase (everolimus) has been reported to be an effective agent in the prevention of hypoglycemic episodes in patients with inoperable or malignant insulinomas (median duration of therapeutic effect: 6.5 months) [35,92-99]. Tyrosine kinase inhibitor agents, including sutinib malate, have also been tested, presenting a relative success and may have a future role in the treatment of insulinomas [100].

CT guided radiofrequency ablation (RFA) has been successfully used in the treatment of insulinoma of an elder patient with hypoglycemia resistant to diazoxide, who was surgery ineligible due to other health issues [101]. Newer treatment options include US-guided ablation with ethanol, peptide receptor radionuclide therapy (PRRT), image-guided robotic radiosurgery and irreversible electroporation (IRE) [98,102-104].

Surgical

Open surgery

Despite development and advances in laparoscopic surgery, insulinoma open surgery is the most widely accepted method [44]. Intraoperative palpation of pancreas combined with IOUS identification of homogeneous, hyperechoic masses permits the detection of over than 80% of tumors [105,106]. Nevertheless, approximately 10% of insulinomas are not palpable and remain undetected without IOUS [15,107,108].

The preferred surgical procedure, first performed in 1931, is enucleation, especially in the management of small (<2.5 cm), benign, unilocular, superficial insulinomas located more than 2-3 mm distal to the main pancreatic duct and major vessels [109-117]. Lymph node dissection is not in-

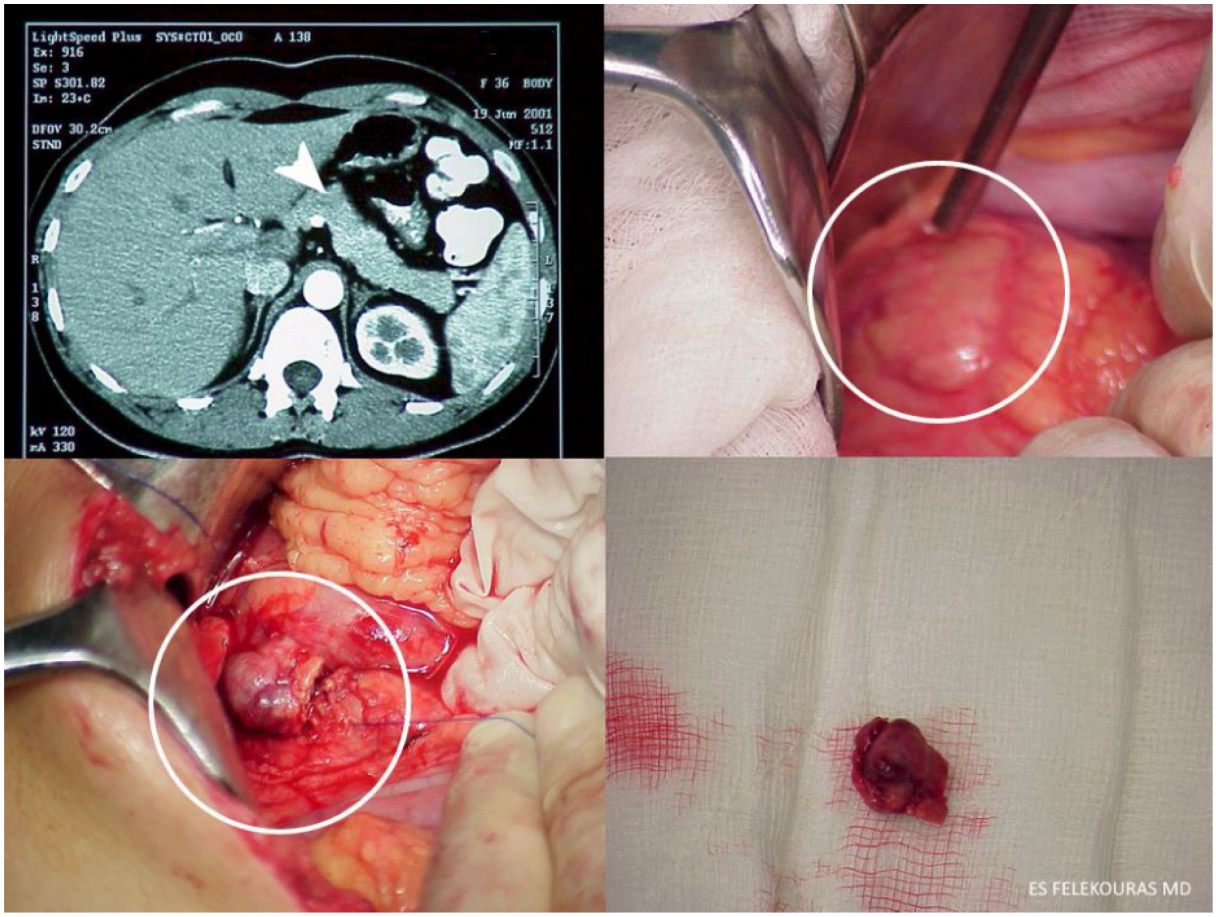

Figure 3. Open enucleation of insulinoma located in the body of pancreas that was preoperatively detected in CT. A small gray-red tumor was identified after resection and incision.

cluded as routine treatment in patients with benign neoplasms, but is considered mandatory in cases of malignant tumors in the context of more extensive pancreatectomies [110-114]. Careful hemostasis and avoidance of main pancreatic duct injury are of extreme importance in order to decrease the risk of pancreatic fistula formation [116-118].

Large tumors, high suspicion of malignancy or metastases indicate the need of pancreatectomy as the procedure of choice instead of enucleation [33,115]. Spleen preserving distal pancreatectomy or pylorus preserving pancreatoduodenectomy are safe and appropriate depending on the tumor location [44,119-122]. Distal pancreatectomy, applied on lesions located in the body or tail of pancreas, is less invasive and associated with lower morbidity and mortality compared to Whipple procedure [115]. Central pancreatectomy is an appropriate option for pancreatic isthmus or body tumors in order to preserve adequate functional pancreatic parenchyma [123].

In the presence of multiple adenomas, enucleation of head tumors with distal pancreatectomy is an alternative to total or subtotal pancreatectomy [44,124]. Only 0.6% of insulinomas are treated with total pancreatectomy and it is well established that this extensive procedure should be avoided in most cases due to increased morbidity and mortality [44].

Currently, enucleation is performed in 56% of patients, distal pancreatectomy in 32%, Whipple in 3%, subtotal pancreatectomy in less than 3%, whereas 0.5% of cases undergo exploratory laparotomy and biopsy [44].

Figure 3 demonstrates a case of insulinoma open enucleation in the context of preoperative CT mediated tumor localization.

Laparoscopic surgery

Laparoscopic excision of insulinoma in the form of enucleation or pancreatectomy is performed in 5.5% of cases [44]. Gagner et al were the first to report laparoscopic enucleation of insulinoma in 1996 [125]. In a study by Sa Cunha et al, comparing laparoscopic and classic open enucleation, pancreatic fistula rate was significantly lower in the laparoscopic approach (14 vs 100%, p=0.015) [126]. Mean duration of hospitalization was 13±5.9 days for the laparoscopic vs 17.6±7.5 days for the open procedure (nonsignificant difference) [126]. Newer evidence indicates the plausibility and safety of laparoscopic enucleation of insulinomas, especially in the treatment of distally located lesions [126-129].

Laparoscopic enucleation is not free of obstacles both pre- and intraoperatively. Preoperative localization of the neoplasm is significant considering that in laparoscopic surgery palpation of the pancreas is impossible [45,130]. Laparoscopic IOUS (LIOUS) is an invaluable tool and the sensitivity is comparable to IOUS during open surgery [131, 132].

Approximately 17-25% of laparoscopic procedures are converted to open surgery due to difficulties in surgical maneuvers, hemostasis or detection as a result of tumor location [27,127]. Other conversion reasons include intrabdominal adhesions, malignancy, multiple adenomas and proximity to splenic vein [44].

Minimal invasive distal pancreatectomy establishment in the treatment of insulinoma is relatively recent [133]. Sussman et al reported a series of sporadic tumors excised with laparoscopic stapler mediated distal pancreatectomy assisted with LIOUS [134]. There is congruence upon use of the aforementioned procedure, but the popularity and clinical experience remains limited [135-137]. In selected cases and in the hands of experienced surgeons laparoscopic approach is associated with faster recovery and acceptable perioperative morbidity [138]. Park et al, in a case series study of 23 successfully completed laparoscopic distal pancreatectomies, reported 0% perioperative mortality and complications incidence of 16% [139].

Hand-assisted laparoscopic surgery facilitates intraoperative pancreas palpation and probably the new generation robotic systems will definitely resolve this problem [140,141].

Treatment complications

Mehrabi et al reported almost equal morbidity for open (35.4%) and laparoscopic (32.8%) insulinoma excision operations and the most common complication in both approaches was pancreatic fistula (Open: 14.6% vs Laparoscopic: 7.2%) [44]. In a multicenter study by Kooby et al, there was no significant difference in the frequency of fistulas between open left-sided and laparoscopic left-sided pancreatectomy [142].

Fistulas are more common in patients treated with tumor enucleation compared to other aforementioned types of neoplasm excision [22,143]. Nevertheless, enucleation associated fistulas are less anatomically complicated due to low output and absence of pancreatico-jejunal or pancreatico-gastric anastomosis and are usually conservatively treated, self-limited within 6 weeks [22,129,144]. Alternative approaches in the management of fistulas include percutaneous drainage, parenteral nutrition with SSAs and in most severe cases ERCP with sphincterotomy or reoperation [44,145].

According to Mehrabi et al, other common complications include those associated with either open or laparoscopic pancreatectomy, such as abscess (Open: 4.8% vs Laparoscopic: 2%), pseudocyst (Open: 3% vs Laparoscopic: 3.2%) and other observed only in open approach, such as diabetes mellitus (7.5%), pancreatitis (3.1%) and pulmonary embolism (1.8%) [44].

Survival, Prognosis and Follow-up

Approximately 90-95% of insulinomas are benign with an expected 5-year survival rate following resection as high as 95-100% [22]. Relapse has been reported to be at the level of 3-5.4% in previous large series [146]. Patients may develop metastatic disease several years after excision of insulinomas initially considered to be benign and this relapse risk is more probable in grade G2 tumors [17,146,147].

Benign and malignant tumors are difficult to differentiate on histopathologic examination and frequently the diagnosis of a malignant insulinoma is confirmed by the presence of metastatic disease [148]. Most patients with malignant disease have lymph node or liver metastases and only rarely bony or other tissue metastases [149-151].

Service et al observed 196 patients, initially symptomless for 6 months postoperatively and thus considered to be in remission, and reported recurrences between 4 and 18.5 years after initial tumor excision with a cumulative relapse frequency of 6% at 10 years and 8% at 20 years [17].

Despite the availability of multimodal treatment options, including surgery, chemotherapy, embolization, RFA and SSAs, malignant insulinoma prognosis is poor and the median survival duration is approximately 2 years [79,150,152]. Currently, chemotherapy in the treatment of malignant insulinomas is based on a combination of capecitabine and temozolomide, but the older combination of streptozocin and doxorubicin (or 5-fluorouracil) is still in use [153]. Prognosis in metastatic disease is poor even after R0 resection, but the treatment of metastatic disease should not be considered futile considering the improved quality of life [44]. In addition, liver or lymph node metastases are not always associated with poor prognosis [41,44, 79,150].

Jonkers et al investigated 62 sporadic insulinoma cases (44 benign and 18 metastatic tumors) in order to identify reliable markers of metastatic disease by the use of comparative genomic hybridization (CGH) [148]. Analysis revealed that the total number of genomic defects per tumor differed significantly between malignant and benign neoplasms (14.1 vs 4.2, respectively, $p<0.0001$) [148]. Chromosome 6q losses and 12q, 14q, 17q gains were found to be strong predictors for the metastatic potential of the tumor and perfomed better than histopathologic parameters, such as tumor size or proliferation index [148].

Insulinoma survivors should be followed-up at 3,6,12 months interval postoperatively and subsequently annually, especially patients with malignant disease or MEN1 associated tumors due to higher risk of relapse [17,35,44,154]. Disease remission is defined by a symptomless 6-months interval postoperatively and recurrence is extremely unlikely at ≥ 20 years after initial tumor excision [17,35,147]. Concise history should be obtained during follow-up reexamination including symptomatology associated with hypoglycemia and workup should include fasting glucose, insulin, C-peptide, proinsulin measurements as well imaging tests, such as CT or MRI [155].

Conclusion

Insulinoma is the most common pancreatic F-NET, occurs mostly during the 5th decade of life and is, in most cases, associated with excellent prognosis. Treatment is mainly surgical, but preoperative tumor localization is of extreme importance and is mediated through imaging tests, such as CT, MRI, EUS. If preoperative identification is not successful, palpation and IOUS are useful and reliable alternatives. Surgical options include open or laparoscopic resection, tumor enucleation or distal pancreatectomy. Nevertheless, open approach in the excision of insulinomas is the most popular method. Operative plan may be modified in the presence of malignancy, multiple or large size neoplasms or lesions in proximity to the main pancreatic duct or major blood vessels. Complications may occur and the most frequent is pancreatic fistula in both open and laparoscopic procedures. Malignant metastatic disease mainly affects liver and lymph nodes. Most patients have benign disease and excellent prognosis after tumor resection, but malignant insulinomas have a poor prognosis, higher recurrence rates and decreased survival.

Conflict of interests

The authors declare no conflict of interests.

References

1. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing But NET: A Review of Neuroendocrine Tumors and Carcinomas. Neoplasia 2017;19:991-1002. doi:10.1016/j.neo.2017.09.002
2. Ehehalt F, Saeger HD, Schmidt CM, Grützmann R. Neuroendocrine tumors of the pancreas. Oncologist 2009;14:456-67. doi: 10.1634/theoncologist.2008-0259. Epub 2009 May 1
3. Inzani F, Petrone G, Rindi G. The New World Health Organization Classification for Pancreatic Neuroendocrine Neoplasia. Endocrinol Metab Clin North Am 2018;47:463-70. doi: 10.1016/j.ecl.2018.04.008. Epub 2018 Jul 11.
4. Metz, David C, Robert T Jensen. "Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors." Gastroenterology 2008;135:1469-92. doi:10.1053/j.gastro.2008.05.047
5. de Herder WW, Niederle B, Scoazec JY et al. Frascati Consensus Conference; European Neuroendocrine Tumor Society.: Well-differentiated pancreatic tumor/carcinoma: insulinoma. Neuroendocrinology 2006;84:183-8. Epub 2007 Feb 20.
6. Okabayashi T, Shima Y, Sumiyoshi T et al. Diagnosis and management of insulinoma. World J Gastroenterol 2013;19:829-37. doi: 10.3748/wjg.v19.i6.829.
7. Phan GQ, Yeo CJ, Hruban RH et al. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. J Gastrointest Surg 1998;2:472-82.
8. Bouslama K, Maghrebi H, Bedioui H, Bouslama K. Pancreatic insulinoma: diagnostic approach and therapeutic modalities. J Afr Hépatol Gastroentérol 2014;8:11-15. doi: 10.1007/s12157-014-0505-9
9. Placzkowski KA, Vella A, Thompson GB 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. doi: 10.1210/jc.2008-2031. Epub 2009 Jan 13.
10. Sakurai A, Yamazaki M, Suzuki S et al. Clinical features of insulinoma in patients with multiple endocrine neoplasia type 1: analysis of the database of the MEN Consortium of Japan. Endocr J 2012;59:859-66. Epub 2012 Jun 16.
11. Bresler L, Boissel P, Conroy T et al. Pancreatic islet cell carcinoma with hypercalcemia: complete remission 5 years after surgical excision and chemotherapy. Am J Gastroenterol 1991; 86:635-8.
12. Lew SK, Giannis D, Babaie NS et al. Competing mortality in patients with neuroendocrine tumors. Am J Clin Oncol 2019;42:668-74.
13. Soga J. Statistical evaluation of 2001 carcinoid cases with metastases, collected from literature: a comparative study between ordinary carcinoids and atypical varieties. J Experim Clin Cancer Res 1998; 17:3-12.
14. Soga J, Yakuwa Y, Osaka M: Insulinoma/hypoglycemic syndrome: a statistical evaluation of 1085 reported cases of a Japanese series. J Exp Clin Cancer Res 1998;17:379-88.
15. Stefanini P, Carboni M, Patrassi N et al. Beta-islet cell tumors of the pancreas: results of a study on 1,067 cases. Surgery 1974; 75:597-609.
16. Kloppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer 2011; 18 (Suppl 1):S1-16.
17. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning Insulinoma - Incidence, Recurrence, and Long-Term Survival of Patients - a 60-Year Study. Mayo Clinic Proceedings 1991; 66:711-9.
18. Câmara-de-Souza AB, Toyoshima MTK, Giannella ML3 et al. Insulinoma: A retrospective study analyzing the differences between benign and malignant tumors. Pancreatology 2018;18:298-303. doi: 10.1016/j.pan.2018.01.009. Epub 2018
19. Bret PM, Reinhold C. Magnetic resonance cholangiopancreatography. Endoscopy 1997; 29:472-86.
20. Guilmette JM, Nosé V. Neoplasms of the Neuroendocrine Pancreas: An Update in the Classification, Definition, and Molecular Genetic Advances. Adv Anat Pathol 2019;26:13-30. doi: 10.1097/
21. Perren A, Roth J, Muletta-Feurer S et al. Clonal analysis of sporadic pancreatic endocrine tumours. J Pathol 1998 Dec;186:363-71.
22. Nikfarjam M, Warshaw AL, Axelrod L et al. Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital. Ann Surg 2008;247:165-72.
23. Wolf P, Winhofer Y, Smajis S et al. Clinical presentation in insulinoma predicts histopathological tumour characteristics. Clin Endocrinol (Oxf) 2015;83:67-71.
24. Zhan HX, Cong L, Zhao YP et al. Activated mTOR/P70S6K signaling pathway is involved in insulinoma tumorigenesis. J Surg Oncol 2012; 106:972-80.
25. Bhatti TR, Ganapathy K, Huppmann AR et al. Histologic and molecular profile of pediatric insulinomas: evidence of a paternal parent-of-origin effect. J Clin Endocrinol Metab 2016;101:914–22.
26. Callacondo D, Arenas JL, Ganoza AJ, Rojas-Camayo J, Quesada-Olarte J, Robledo H.: Giant insulinoma: a report of 3 cases and review of the literature Pancreas 2013 Nov;42:1323-32. doi: 10.1097/MPA.0b013e318292006a.
27. Zhao YP, Zhan HX, Zhang TP et al. Surgical management of patients with insulinomas: Result of 292 cases in a single institution. J Surg Oncol 2011;103:169-74.
28. Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjöld M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature 1988;332:85-7.
29. Eledrisi MS, Stuart CA, Alshanti M. Insulinoma in a patient with tuberous sclerosis: is there an association? Endocr Pract 2002;8:109-12.
30. Merritt JL , Davis DM, Pittelkow MR, Babovic-Vuksanovic D: Extensive acrochordons and pancreatic islet-cell tumors in tuberous sclerosis associated with TSC2 mutations. Am J Med Genet A 2006;140:1669-72.
31. Whipple AO, Frantz VK. Adenoma of Islet Cells with Hyperinsulinism: A Review. Ann Surg 1935;101:1299-335.

32. Vinik A, Feliberti E, Perry RR. Insulinomas. In: De Groot LJ, Chrousos G, Dungan K et al. (Eds): Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000.
33. Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol 2005; 19:783-98.
34. Service FJ, Dale AJ, Elveback LR, Jiang NS: Insulinoma: clinical and diagnostic features of 60 consecutive cases. Mayo Clin Proc 1976 Jul;51:417-29.
35. Jensen RT, Cadiot G, Brandi ML et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012; 95:98-119.
36. Service FJ. Hypoglycemic disorders. New Engl J Med 1995; 332: 1144-52.
37. Grama D, Eriksson B, Martensson H et al. Clinical characteristics, treatment and survival in patients with pancreatic tumors causing hormonal syndromes. World J Surg 1992; 16: 632-9.
38. Fajans SS, Vinik AI. Insulin-producing islet cell tumors. Endocrinol Metab Clin North Am 1989; 18:45-74.
39. Maggio I, Mollica V, Brighi N et al. The functioning side of the pancreas: a review on insulinomas. J Endocrinol Invest 2020;43:139-48.
40. Virally ML, Guillausseau PJ. Hypoglycemia in adults. Diabetes Metab 1999; 25:477-90.
41. Hirshberg B, Livi A, Bartlett DL et al. Forty-eight-hour fast: the diagnostic test for insulinoma. J Clin Endocrinol Metab 2000; 85:3222-6.
42. Vezzosi D, Bennet A, Fauvel J et al. Insulin, C-peptide and proinsulin for the biochemical diagnosis of hypoglycaemia related to endogenous hyperinsulinism. Eur J Endocrinol 2007; 157:75-83.
43. Glaser B, Shapiro B, Glowniak J et al. Effects of secretin on the normal and pathological beta-cell. J Clin Endocrinol Metab 1988; 66:1138-43.
44. Mehrabi A, Fischer L, Hafezi M et al. A systematic review of localization, surgical treatment options, and outcome of insulinoma. Pancreas 2014; 43:675-86.
45. Guettier JM, Gorden P. Insulin secretion and insulin-producing tumors. Expert Rev Endocrinol Metab 2010; 5:217-27.
46. Seltzer HS. Drug-induced hypoglycemia. A review of 1418 cases. Endocrinol Metab Clin North Am 1989; 18:163-83.
47. Fischer KF, Lees JA, Newman JH. Hypoglycemia in hospitalized patients. Causes and outcomes. N Engl J Med 1986; 315:1245-50.
48. Kwong PY, Teale JD. Screening for sulphonylureas in the investigation of hypoglycaemia. J R Soc Med 2002; 95:381-5.
49. Service FJ. Recurrent hyperinsulinemic hypoglycemia caused by an insulin-secreting insulinoma. Nat Clin Pract Endocrinol Metab 2006; 2:467-70; quiz following 470.
50. Schizas D, Mastoraki A, Bagias G et al. Clinicopathological data and treatment modalities for pancreatic vipomas: a systematic review. JBUON 2019;24:915-23.
51. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycemia. Medicine (Baltimore). 2009;88:141-53. doi: 10.1097/MD.0b013e3181a5b42e
52. Patti ME, McMahon G, Mun EC et al. Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. Diabetologia 2005;48:2236-40. Epub 2005 Sep 30.
53. Clancy TE, Moore FD Jr, Zinner MJ. Post-gastric bypass hyperinsulinism with nesidioblastosis: subtotal or total pancreatectomy may be needed to prevent recurrent hypoglycemia. J Gastrointest Surg 2006;10:1116-9.
54. Service FJ, Natt N, Thompson GB et al. Noninsulinoma pancreatogenous hypoglycemia: a novel syndrome of hyperinsulinemic hypoglycemia in adults independent of mutations in Kir6.2 and SUR1 genes. J Clin Endocrinol Metab 1999;84:1582.
55. Zhu L, Xue H, Sun Z et al. Prospective comparison of biphasic contrast-enhanced CT, volume perfusion CT, and 3 Tesla MRI with diffusion-weighted imaging for insulinoma detection. J Magn Reson Imaging 2017; 46:1648-55.
56. Khashab MA, Yong E, Lennon AM et al. EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. Gastrointest Endosc 2011;73:691-6. doi: 10.1016/j.gie.2010.08.030. Epub 2010 Nov 10.
57. Wei J, Liu X, Wu J et al. Diagnosis and surgical management of insulinomas in 33 consecutive patients at a single institution. Langenbecks Arch Surg 2016;401:1019-25. Epub 2016 Aug 19.
58. Balci NC, Semelka RC. Radiologic features of cystic, endocrine and other pancreatic neoplasms. Eur J Radiol 2001;38:113-9.
59. Noone TC, Hosey J, Firat Z, Semelka RC. Imaging and localization of islet-cell tumours of the pancreas on CT and MRI. Best Pract Res Clin Endocrinol Metab 2005;19:195-211.
60. McAuley G, Delaney H, Colville J et al. Multimodality preoperative imaging of pancreatic insulinomas. Clin Radiol 2005;60:1039-50.
61. Ueda K, Ito T, Kawabe K et al. Should the Selective Arterial Secretagogue Injection Test for Insulinoma Localization Be Evaluated at 60 or 120 Seconds? Intern Med 2017;56:2985-91. doi: 10.2169/internalmedicine.9107-17. Epub 2017 Sep 25. PubMed PMID: 28943589; PubMed Central PMCID: PMC5725851.
62. Millan VG, Urosa CL, Molitch ME et al. Localization of occult insulinoma by super-selective pancreatic venous sampling for insulin assay through percutaneous transhepatic catheterization. Diabetes 1979; 28:249-51.
63. Kinoshita Y, Nonaka H, Suzuki S et al. Accurate localization of insulinoma using percutaneous transhepatic portal venous sampling--usefulness of simultaneous measurement of plasma insulin and glucagon levels. Clin Endocrinol (Oxf) 1985; 23:587-93.
64. Sotoudehmanesh R, Hedayat A, Shirazian N et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. Endocrine 2007; 31:238-41.
65. Abboud B, Boujaoude J. Occult sporadic insulinoma: localization and surgical strategy. World J Gastroenterol 2008;14:657-65.

66. Atiq M, Bhutani MS, Bektas M et al. EUS-FNA for pancreatic neuroendocrine tumors: a tertiary cancer center experience. Dig Dis Sci 2012; 57:791-800.
67. Zografos GN, Stathopoulou A, Mitropapas G et al. Preoperative imaging and localization of small sized insulinoma with EUS-guided fine needle tattoing: a case report. Hormones (Athens) 2005; 4:111-6.
68. Mirallie E, Pattou F, Malvaux P et al. [Value of endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localization of insulinomas and gastrinomas. Experience of 54 cases]. Gastroenterol Clin Biol 2002; 26:360-6.
69. Kisker O, Bartsch D, Weinel RJ et al. The value of somatostatin-receptor scintigraphy in newly diagnosed endocrine gastroenteropancreatic tumors. J Am Coll Surg 1997; 184:487-92.
70. Luo Y, Pan Q, Yao S 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.
71. Christ E, Wild D, Forrer F et al. Glucagon-like peptide-1 receptor imaging for localization of insulinomas. J Clin Endocrinol Metab 2009; 94:4398-405.
72. Wild D, Christ E, Caplin ME et al. Glucagon-like peptide-1 versus somatostatin receptor targeting reveals 2 distinct forms of malignant insulinomas. J Nucl Med 2011; 52:1073-8.
73. Antwi K, Fani M, Heye T 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.
74. Christ E, Wild D, Ederer S et al. Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: a prospective multicentre imaging study. Lancet Diabetes Endocrinol 2013; 1:115-22.
75. Norton JA. Intraoperative methods to stage and localize pancreatic and duodenal tumors. Ann Oncol 1999; 10 (Suppl 4):182-4.
76. Ravi K, Britton BJ. Surgical approach to insulinomas: are pre-operative localisation tests necessary? Ann R Coll Surg Engl 2007; 89:212-7.
77. Pasieka JL, McLeod MK, Thompson NW et al. Surgical approach to insulinomas. Assessing the need for preoperative localization. Arch Surg 1992; 127:442-7.
78. Gill GV, Rauf O, McFarlane IA. Diazoxide treatment for insulinoma: a national UK survey. Postgrad Med J 1997; 73:640-1.
79. Hirshberg B, Cochran C, Skarulis MC et al. Malignant insulinoma: spectrum of unusual clinical features. Cancer 2005; 104:264-72.
80. Goode PN, Farndon JR, Anderson J et al. Diazoxide in the management of patients with insulinoma. World J Surg 1986; 10:586-92.
81. Cohen MS, Bower RH, Fidler SM et al. Inhibition of insulin release by diphenylhydantoin and diazoxide in a patient with benign insulinoma. Lancet 1973; 1:40-1.
82. Moris D, Ntanasis-Stathopoulos I, Tsilimigras DI et al. Update on surgical management of small bowel neuroendocrine tumors. Anticancer Res 2018;38:1267-78.
83. Jensen RT. Presence of somatostatin receptors on gastro-enteropancreatic endocrine tumors (GEPs): Impact on clinical management with somatostatin receptor imaging and other uses of somatostatin analogues. In: Lamberts SWJ (Ed): Octreotide: The Next Decade. Bristol, UK, Bioscientific, 1999, p 149.
84. Krenning EP, Kwekkeboom DJ, Oei HY et al. Somatostatin-receptor scintigraphy in gastroenteropancreatic tumors. An overview of European results. Ann N Y Acad Sci 1994; 733:416-24.
85. Reubi JC, Laissue J, Waser B et al. Expression of somatostatin receptors in normal, inflamed, and neoplastic human gastrointestinal tissues. Ann N Y Acad Sci 1994; 733:122-37.
86. Gillis JC, Noble S, Goa KL. Octreotide long-acting release (LAR). A review of its pharmacological properties and therapeutic use in the management of acromegaly. Drugs 1997; 53:681-99.
87. Lamberts SW, van der Lely AJ, de Herder WW et al. Octreotide. N Engl J Med 996; 334:246- 54.
88. Maton PN, Gardner JD, Jensen RT. Use of long-acting somatostatin analog SMS 201-995 in patients with pancreatic islet cell tumors. Dig Dis Sci 1989; 34 (3 Suppl):28S-39S.
89. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology 2008; 135:1469-92.
90. Vezzosi D, Bennet A, Rochaix P et al. Octreotide in insulinoma patients: efficacy on hypoglycemia, relationships with Octreoscan scintigraphy and immunostaining with anti-sst2A and anti-sst5 antibodies. Eur J Endocrinol 2005; 152:757-67.
91. Arnold R, Simon B, Wied M.Treatment of neuroendocrine GEP tumours with somatostatin analogues: a review. Digestion 2000; 62 (Suppl 1):84-91.
92. Kulke MH, Bergsland EK, Yao JC. Glycemic control in patients with insulinoma treated with everolimus. N Engl J Med 2009; 360:195-7.
93. Cuesta Hernandez M, Gomez Hoyos E, Marcuello Foncillas C et al. Advanced malignant insulinoma. Everolimus response and toxicity. Endocrinol Nutr 2014; 61:e1-3.
94. Asayama M, Yamada-Murano T, Hara H et al. Everolimus dramatically improves glycemic control in unresectable metastatic insulinoma: a case report. Jpn J Clin Oncol 2014; 44:186-90.
95. Matej A, Bujwid H, Wronski J. Glycemic control in patients with insulinoma. Hormones (Athens) 2016; 15:489-99.
96. Yanagiya S, Cho KY, Nakamura A et al. The Effect of Everolimus on Refractory Hypoglycemia in a Patient with Inoperable Metastatic Insulinoma Evaluated by Continuous Glucose Monitoring. Intern Med 2018; 57:2527-31.
97. Fiebrich HB, Siemerink EJ, Brouwers AH et al. Everolimus induces rapid plasma glucose normalization in insulinoma patients by effects on tumor as well as normal tissues. Oncologist 2011; 16:783-7.
98. Ito T, Igarashi H, Jensen RT. Therapy of metastatic pancreatic neuroendocrine tumors (pNETs): recent insights and advances. J Gastroenterol 2012; 47:941-60.

99. Bernard V, Lombard-Bohas C, Taquet MC et al. Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia. Eur J Endocrinol 2013; 168:665-74.
100. Chen J, Wang C, Han J et al. Therapeutic effect of sunitinib malate and its influence on blood glucose concentrations in a patient with metastatic insulinoma. Expert Rev Anticancer Ther 2013; 13:737-43.
101. Limmer S, Huppert PE, Juette V et al. Radiofrequency ablation of solitary pancreatic insulinoma in a patient with episodes of severe hypoglycemia. Eur J Gastroenterol Hepatol 2009; 21:1097-101.
102. Levy MJ, Thompson GB, Topazian MD et al. US-guided ethanol ablation of insulinomas: a new treatment option. Gastrointest Endosc 2012; 75:200-6.
103. Huscher CG, Mingoli A, Sgarzini G et al. Image-guided robotic radiosurgery (CyberKnife) for pancreatic insulinoma: is laparoscopy becoming old? Surg Innov 2012; 19:NP14-7.
104. Papamichail M, Ali A, Pizanias M et al. Irreversible electroporation for the treatment of pancreatic neuroendocrine tumors. Korean J Hepatobiliary Pancreat Surg 2016; 20:116-20.
105. Doherty GM, Doppman JL, Shawker TH et al. Results of a prospective strategy to diagnose, localize, and resect insulinomas. Surgery 1991; 110:989-96; discussion 996-7.
106. Norton JA, Shawker TH, Doppman JL et al. Localization and surgical treatment of occult insulinomas. Ann Surg 1990; 212:615-20.
107. Kaplan EL, Lee CH. Recent advances in the diagnosis and treatment of insulinomas. Surg Clin North Am 1979; 59:119-29.
108. May GR, James EM, Johnson CM. The radiologist's role in acute endocrine problems. World J Surg 1982; 6:725-34.
109. Stamatakos M, Safioleas C, Tsaknaki S et al. Insulinoma: a rare neuroendocrine pancreatic tumor. Chirurgia (Bucur) 2009; 104:669-73.
110. Mehrabi A, Fisher L, Hafezi M et al. A systematic review of localization, surgical treatment options, and outcome of insulinoma. Pancreas 2014;43:673-86.
111. Beger HG, Gansauge F, Siech M et al. Duodenum-preserving total pancreatic head resection for cystic neoplastic lesions in the head of the pancreas. J Hepatobiliary Pancreat Surg 2008; 15:149-56.
112. Beger HG, Rau B, Gansauge F et al. Pancreatic cancer--low survival rates. Dtsch Arztebl Int 2008; 105:255-62.
113. Beger HG, Rau BM, Gansauge F et al. Duodenum-preserving subtotal and total pancreatic head resections for inflammatory and cystic neoplastic lesions of the pancreas. J Gastrointest Surg 2008; 12:1127-32.
114. Beger HG, Rau BM, Gansauge F et al. Duodenum-preserving total pancreatic head resection for cystic neoplasm: a limited but cancer-preventive procedure. Langenbecks Arch Surg 2008; 393:589-98.
115. Hackert T, Hinz U, Fritz S et al. Enucleation in pancreatic surgery: indications, technique, and outcome compared to standard pancreatic resections. Langenbecks Arch Surg 2011; 396:1197-203.
116. Sperti C, Pasquali C, Ferronato A et al. Median pancreatectomy for tumors of the neck and body of the pancreas. J Am Coll Surg 2000; 190:711-6.
117. Proye C. Surgery of insulinoma. Acta Chir Belg 1991; 91:82-7.
118. Finlayson E, Clark OH. Surgical treatment of insulinomas. Surg Clin North Am 2004; 84:775-85.
119. Hu MG, Xiao YH, Song DD et al. First experience of robotic spleen-preserving distal pancreatectomy in a child with insulinoma. World J Surg Oncol 2017; 15:199.
120. Ueda J, Nakamura Y, Aimoto T et al. Laparoscopic distal pancreatectomy preserving spleen and splenic vessels for pancreatic insulinoma. J Nippon Med Sch 2010; 77:175-80.
121. Sciuto A, Abete R, Reggio S et al. Laparoscopic spleen-preserving distal pancreatectomy for insulinoma: experience of a single center. Int J Surg 2014; 12 (Suppl 1):S152-5.
122. D'Ambrosio G, Quaresima S, Balla A et al. Spleen preserving laparoscopic distal pancreatectomy for treatment of pancreatic lesions. Ann Ital Chir 2015; 86:273-8.
123. Hirono S, Tani M, Kawai M et al. Treatment strategy for intraductal papillary mucinous neoplasm of the pancreas based on malignant predictive factors. Arch Surg 2009; 144:345-9;discussion 349-50.
124. Machado MC, da Cunha JE, Jukemura J et al. Insulinoma: diagnostic strategies and surgical treatment. A 22-year experience. Hepatogastroenterology 2001; 48:854-8.
125. Gagner M, Pomp A, Herrera MF. Early experience with laparoscopic resections of islet cell tumors. Surgery 1996;120:1051-4.
126. Sa Cunha A. Laparoscopic versus open approach for solitary insulinoma. Surg Endosc 2001;21:103-8.
127. Gumbs AA, Gres P, Madureira F et al. Laparoscopic vs open resection of pancreatic endocrine neoplasms: single institution's experience over 14 years. Langenbecks Arch Surg 2008;393:391-5.
128. Belfiori G, Wiese D, Partelli S et al. Minimally Invasive Versus Open Treatment for Benign sporadic Insulinoma Comparison of Short-Term and Long-Term Outcomes. World J Surg 2018; 42:3223-30.
129. Liu H, Peng C, Zhang S et al. Strategy for the surgical management of insulinomas: analysis of 52 cases. Dig Surg 2007; 24:463-70.
130. Isla A, Arbuckle JD, Kekis PB et al. Laparoscopic management of insulinomas. Br J Surg 2009; 96:185-90.
131. Grover AC, Skarulis M, Alexander HR et al. A prospective evaluation of laparoscopic exploration with intraoperative ultrasound as a technique for localizing sporadic insulinomas. Surgery 2005; 138:1003-8; discussion 1008.
132. Berends FJ, Cuesta MA, Kazemier G et al. Laparoscopic detection and resection of insulinomas. Surgery 2000; 128:386-91.
133. Gagner M PA. Laparoscopic pancreatic resection: is it worthwhile? J Gastrointest Surg 1997;1:20-6.
134. Sussman LA. Laparoscopic excision of distal pancreas

including insulinoma. Aust NZ J Surg 1996;66:414-6.

135. Nakamura Y, Matsushita A, Katsuno A et al. Clinical outcomes of 15 consecutive patients who underwent laparoscopic insulinoma resection: The usefulness of monitoring intraoperative blood insulin during laparoscopic pancreatectomy. Asian J Endosc Surg 2015;8:303-9.
136. Villacreses DE, Stauffer JA, Horacio J et al. Laparoscopic central pancreatectomy for insulinoma J Visc Surg 2016; 153:473-4.
137. Aggeli C, Nixon AM, Karoumpalis I et al. Laparoscopic surgery for pancreatic insulinomas: an update. Hormones (Athens) 2016; 15:157-69.
138. Fernandez-Cruz L, Blanco L, Cosa R et al. Is laparoscopic resection adequate in patients with neuroendocrine pancreatic tumors? World J.Surg. 2008; 32:904-17.
139. Park AE, Heniford BT. Therapeutic laparoscopy of the pancreas. Ann Surg 2002;236:149-58.
140. Choi SH, Kang CM, Lee WJ et al. Robot-assisted spleen-preserving laparoscopic distal pancreatectomy. Ann Surg Oncol 2011; 18:3623.
141. Addeo P, Marzano E, Nobili C et al. Robotic central pancreatectomy with stented pancreaticogastrostomy: operative details. Int J Med Robot 2011; 7:293-7.
142. Kooby DA, Gillespie T, Bentrem D et al. Left-sided pancreatectomy: a multicenter comparison of laparoscopic and open approaches. Ann Surg 2008; 248:438-46.
143. Luo Y, Liu R, Hu MG et al. Laparoscopic surgery for pancreatic insulinomas: a single-institution experience of 29 cases. J Gastrointest Surg 2009; 13:945-50.
144. Falconi M, Zerbi A, Crippa S et al. Parenchyma-preserving resections for small nonfunctioning pancreatic endocrine tumors. Ann Surg Oncol 2010; 17:1621-7.
145. Shin JJ, Gorden P, Libutti SK. Insulinoma: pathophysiology, localization and management. Future Oncol 2010; 6:229-37.
146. Crippa S, Zerbi A, Boninsegna L et al. Surgical management of insulinomas: short- and long-term outcomes after enucleations and pancreatic resections. Arch Surg 2012; 147:261-6.
147. Gonzalez-Gonzalez A, Recio-Cordova JM. Liver metastases 9 years after removal of a malignant insulinoma which was initially considered benign. JOP 2006; 7:226-29.
148. Jonkers YM, Claessen SM, Perren A et al. Chromosomal instability predicts metastatic disease in patients with insulinomas. Endocr Relat Cancer 2005; 12:435-47.
149. Sarmiento JM, Que FG, Grant CS, Thompson GB, Farnell MB, Nagorney DM. Concurrent resections of pancreatic islet cell cancers with synchronous hepatic metastases: outcomes of an aggressive approach. Surgery 2002;132:976-82.
150. Danforth DN, Jr., Gorden P, Brennan MF. Metastatic insulin-secreting carcinoma of the pancreas: clinical course and the role of surgery. Surgery 1984; 96:1027-37.
151. Hesdorffer CS, Stoopler M, Javtch J. Aggressive insulinoma with bone metastases. Am J Clin Oncol 1987;12:498-501.
152. Rothmund M, Angelini L, Brunt LM et al. Surgery for benign insulinoma: an international review.World J Surg 1990; 14:393-8; discussion 398-9.
153. Karatas F, Sahin S, Aytekin A et al. Durable complete response with a short course of streptozotocin plus doxorubicin combination in malignant metastatic insulinoma. J Cancer Res Ther 2018; 14:1149-51.
154. Galbut DL, Markowitz AM. Insulinoma: diagnosis, surgical management and long-term follow-up. Review of 41 cases. Am J Surg 1980; 139:682-90.
155. Chiruvella A, Kooby DA. Surgical Management of Pancreatic Neuroendocrine Tumors. Surg Oncol Clin N Am 2016; 25:401-21.