Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Analysis of a series for surgical management of insulinomas in central China

Shishi Qiao (gandanwaike@zzu.edu.cn)
Zhengzhou University First Affiliated Hospital https://orcid.org/0000-0001-8979-1985

Hao Liu
Zhengzhou University First Affiliated Hospital

Xin Hu
the second affiliated hospital of Henan university of science and technology

Minghao Dong
Sanmenxia central hospital

Liangjie Feng
Zhengzhou University First Affiliated Hospital

Guokun Zhang
Zhengzhou University First Affiliated Hospital

Yingxuan Zhang
Zhengzhou University First Affiliated Hospital

Yufei Gu
Zhengzhou University First Affiliated Hospital

Yongfu Zhao
Zhengzhou University First Affiliated Hospital

Research Article

Keywords: insulinoma, pancreatic tumor, surgery

Posted Date: February 18th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-232699/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Analysis of a series for surgical management of insulinomas in central China

Running title: Surgical management of insulinomas

Shishi Qiao[1], Hao Liu[1], Xin Hu[2], Minghao Dong[3], Liangjie Feng[1], Guokun Zhang[1], Yingxuan Zhang[1], Yufei Gu[1], Yongfu Zhao[1*]

1 Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University, No.1, Jianshe East Road, Zhengzhou city, Henan 450000 P.R. China.

2 Department of General Surgery, The Second Affiliated Hospital of Henan University of Science and Technology, No.80, Jinguyuan Road, Luoyang city, Henan 471003 P.R. China.

3 Department of Hepatobiliary and Pancreatic Surgery, Sanmenxia Central Hospital, No.80, Jinguyuan Road, Luoyang city, Henan 472100 P.R. China.

Corresponding author: Yongfu Zhao,
Department of Hepatobiliary and Pancreatic Surgery
The First Affiliated Hospital of Zhengzhou University
No.1, Jianshe East Road, Zhengzhou city, Henan 450000 P.R. China.
Email: gandanwaike@zzu.edu.cn

Abstract

The aims of this study were to summarize the characteristics of insulinoma in central China and to present our experience with surgical management in the Department of Hepatobiliary and Pancreatic Surgery of The First Affiliated Hospital of Zhengzhou University. 617 patients were enrolled in this retrospective analysis, including 89 cases of insulinoma and 528 cases of other pancreatic tumors. All patients had been confirmed by histopathology reports and underwent surgical treatment. Medical data and operative notes were incorporated into the database. Among the 617 patients, 4 died during the perioperative period. In the insulinoma group, no deaths occurred. The average size of the insulinoma tumor was 1.4±0.8 cm. The ratio of open surgical procedure (57) to laparoscopic resection (32) was 1.8/1. The mean interoperation blood loss was significantly lower in the laparoscopic group (LA) (mean 35.2±17.4ml, range from 10 to 170ml) than that in the open surgical (OA) group (mean 64.7±38.6ml, range from 25 to 400ml). The mean postoperative hospital stay was also lower in the LA group (mean 8.1 ± 3.2days, range from 5 to 20 days) than that in the OA group (Mean 13.1±8.2days, range from 9 to 60 days). There was no significant difference for postoperative complications between the two groups (LA:37.5% vs OA:40.3%). The rate of clinically significant postoperative-pancreatic-fistula (POPF) was 21.3 %, and there was only one case of C-degree-POPF. The average length of postoperative-gastrointestinal function recovery was 2.8 ± 0.9 days. And the average length of blood glucose fluctuation was 18±7.2 days. During the follow-up, 2 cases were found to be hypoglycemic again, and the rate of significant weight loss was 57.3% (51/89). Insulinoma was rare among patients who underwent surgical treatment at the Department. Their cases were benign, and their treatment was unproblematic. However, there was a small group of cases that could be associated with problematic clinical situations, and, therefore, treatment of patients with insulinoma should be conducted at specialist centers. Correct diagnostic and therapeutic management, involving close cooperation between multiple medical specialists, results in completely curing most patients.

Key words: insulinoma, pancreatic tumor, surgery

Background

Insulinoma is the most common functional neuroendocrine tumor of the pancreas [1], although its incidence in central China is rarely reported. Henan Province has a population greater than 130 million people, and more than 15,000 inpatients with various of health issues are cared for at The First Affiliated Hospital of Zhengzhou University each day. Here we aim to launch a retrospective analysis to study the characteristics of patients with insulinoma treated at the Department of Hepatobiliary and Pancreatic Surgery of The First Affiliated Hospital of Zhengzhou University between 2009 and 2019.

Materials and Methods

Subjects

617 patients were recruited into this retrospective study, including 89 cases of insulinoma and 528 cases of other tumors. The mean age was 54.7±12.1 years old, ranging from 13 to 78 years old. The ratio of males to females was 1/1.4. All data was obtained from the hospital's medical records, surgical protocols and pathology reports. All surgical procedures were finished by the Department of Hepatobiliary and Pancreatic Surgery of the First Affiliated Hospital of Zhengzhou University from 2009 to 2019. Clinical characteristics are summarized in Table 1.

Methods

All insulinoma patients were admitted with typical symptoms, such as hypoglycemia or other nervous signs (Whipple's triad). As a rule, the value of serum insulin and glucose were to be assayed, and other provocation tests, such as the hunger test and exercise test were performed before diagnosis. Notably, preoperative contrast enhanced CT scan and intra-operative ultrasound scan were regular in every case. According to the location of the tumor, several surgical procedures were selected whether by laparoscopic or open surgery, including tumor enucleation, radiofrequency ablation, spleen-preserving distal pancreatectomy, distal pancreatectomy, pancreaticoduodenectomy, and central pancreatectomy. All cases were confirmed by

pathological diagnosis after surgery. The different procedures are summarized in Table 2.

For other pancreatic tumor, all data were restricted from those who received radical resection. Palliative surgeries, such as choledochojejunostomy, were excluded. Of course, all cases were also confirmed by pathological diagnosis (Table 1).

Patient follow-up was conducted for determination of survival and recurrence through review of our medical records, postal follow-up, and via telephone contact.

Quantitative data were summarized as means and standard deviations, analyzed using the t-test, $\chi 2$-test, and one-way ANOVA. All statistical analysis was performed with SPSS for MAC, version 21.0 (SPSS, Inc, Chicago, IL, USA). $P<0.05$ was considered statistically significant.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Human Research Committee of The First Affiliated Hospital of Zhengzhou University.

Results

Among all patients, there were 4 deaths in the perioperative period, 3 for adenocarcinoma and 1 for neuroendocrine carcinoma. No deaths occurred in the insulinoma group. The longest operation time （350 minutes） belonged to pancreaticoduodenectomy. The average size of the insulinoma tumor was 1.4±0.8 cm. The ratio of open surgical procedure (OA)vs. laparoscopic resection (LA) was 1.8/1 (57/32). The rate of conversion from LA to open surgery was 13.4%. The mean interoperation blood loss was significantly lower in the LA group (mean 35.2±17.4ml, range from 10 to 90 ml) than that in the OA group (mean 64.7±38.6ml, range from 25 to 400 ml). The greatest intraoperative blood loss (400ml) occurred in one case of distal pancreatectomy and, because of the splenic vein bleeding, ended in the conversion from laparoscopic to open operation. The mean postoperative hospital stay was lower in the LA group (mean 8.1 ± 3.2days, range from 5 to 20 days) than in the OA group (mean 13.1 ± 8.2days, range from 9 to 60 days). There were no significant differences for postoperative complications between the two groups (LA 37.5% vs. OA 40.3%). The rate of clinically significant postoperative-pancreatic-fistula (POPF) was 21.3 %. There was only 1 case of C-degree-POPF which developed into a pancreatic pseudocyst and

the patient underwent another -operation six months later. The overall average length of postoperative oral intake time was 2.8 ± 0.9 days, with no significant difference between the two groups(LA 2.5 ± 0.8, OA3.1 ± 0.7 days). Within one week after the operation, 60.1% (54/89) of patients had a peak level of blood glucose over 10mmol/L. The total average length of blood glucose fluctuation was 19.7 ± 5.6 days. During the follow-up, 2 cases were found to be hypoglycemic again, and the rate of significant weight loss was 57.3% (51/89).

The detailed data is shown in Table 2, which includes operative-related complications, overall morbidity, pancreatic fistula (PF), intra-abdominal abscess/ infection, postoperative hemorrhage, reoperation, length of postoperative gastrointestinal function recovery, length of mean hospital stay, weight lost, length of blood glucose fluctuation and recurrence of hypoglycemia.

Discussion

Insulinoma is the most common functional neuroendocrine tumor of the pancreas [2] and its incidence is 0.396 per 100,000 person-years [1,3-5], accounting for 1~2% of all pancreatic neoplasms [6]. Surgical resection is the only effective treatment for pancreatic insulinomas [7-11], and results in curing almost 95% of patients. However, some cases present problematic clinical situations, so clinical observation, monitoring and investigation are important aspects of the surgical treatment [12]. Each year, our center accepts 10 cases of insulinoma and more than 300 cases of other pancreatic tumors. Each of these patients presents a different situation, and it is most important to select suitable surgical procedures on a case by case basis

Generally, the number and location of tumors are the most important factors to a treatment plan [9,11,13]. From multiphase dynamic CT enhanced scan to one stop perfusion enhanced scan, pre-operation image examination was routinely performed on every patient, and included MRI and ultrasonic examination. On occasion endoscopic ultrasonic was adopted [14], since EUS has been confirmed as the most sensitive preoperative technique for insulinomas [15,16]. Still, in a few patients, tumors were unable to be located exactly. Thus, in all cases, the whole pancreas should be evaluated with intraoperative ultrasonography because none of the current preoperative diagnostic methods are as sensitive as manual palpation of the pancreas and intraoperative ultrasonography [17,18]. In some insulinoma cases, the discovery in

pancreatic surgery and bimanual palpation of the whole pancreas are important [8]. We had 8 cases where new nodes were found during in exploratory surgery, which depended on palpation combined with ultrasonic investigation. Thus, we consider that palpation and ultrasonic scan in-operation is irreplaceable.

For tumors with a well-known location, enucleation is the most popular procedure. In this investigation, there were 41 patients who underwent tumor enucleation, 27 cases of open operation and 14 of laparoscopic operation. According to statistics, more than 80% of the insulinoma diameters were less than 2 cm [19], lending to the determination that these could be resected entirely laparoscopically. As instrumentation improved over time, we performed tumor enucleation increasingly through laparoscopy. Compared with open operation, there were no statistical differences in operation time or bleeding volume.

In addition to enucleation, we can perform distal pancreatectomy or spleen-preserving distal pancreatectomy by laparoscopic procedure, even for some tumors adjacent to spleen vessels which previously required resection by open operation. Considering the overall minimal disturbance to the gastrointestinal tract and faster recovery in function and postoperative oral intake, we consider the laparoscopic procedure as feasible, safe, and effective [20,21]. Furthermore, it can also reduce post-surgical pain and analgesic requirements [22].

However, some tumors remain difficult to address, especially some located in the head or sulcus of the pancreas. Of course, location in the neck is also difficult, especially when it invades the tubes or vessels. We had 3 cases of pancreaticoduodenectomy and 2 cases of central pancreatectomy.

We had 3 cases where the patient, due to advanced age or physical conditions, underwent laparoscopic-assisted radio-frequency ablation. None of these cases suffered hypoglycemic symptom relapse during the follow-up period, and we can suggest that RFA is a wise alternative compared with palliative treatment [23,24].

With the continuing development of technologies and instrumentation, procedures increasingly are being performed laparoscopically. Among our 89 cases of insulinoma, 32 cases were performed laparoscopically. The ratio of open surgical procedure vs. laparoscopic resection was 1.8/1 (57/32). Our data showed that there was no difference in the postoperative gastrointestinal function recovery time between the LA group and the OA group (2.5 ± 0.8 days versus 3.1 ± 0.7 days, respectively; $P < 0.001$). However,

laparoscopic resection was distinctly superior to open procedure when considering intra-operation blood loss and length of mean hospital stay.

However, laparoscopic operation is still a complicated procedure [25-28], requiring more study and improved techniques. We had 12 cases of LA converted to OA, similar to the conversion rates in the literature [27,22]. The most common (8 cases) reason was the inability to locate tumor successfully such as when the tumor was immersed in pancreatic head or due to lack of resolution in laparoscopic ultrasound. Other causes of conversion included excessive fatty tissue (1 case) a severe adhesion (1 case). Furthermore, the greatest danger was from intraoperation bleeding [11,10,29,30], and we had 2 cases with splenic vein bleeding, resulting in blood loss of 400 ml and procedure conversion.

Postoperative pancreatic fistula (POPF) is the most popular complication after pancreatic surgery [31]. Based on the criteria from the International Study Group of Pancreatic Fistula (ISGPF) [32], we defined a clinically significant POPF as grade B that required nonoperative intervention and grade C [33]. In our procedure, the clinically significant rate of POPF for insulinoma was 21.3 %.

We had 3 patients who underwent pancreaticoduodenectomy and without POPF. But 2 cases underwent central pancreatectomy, resulting in 1 case of POPF. In addition, we had 3 cases involving radiofrequency ablation, finished by laparoscopically, resulting in 1 case of POPF. As for POPF, there were no difference between enucleation (24.3 %; 10/41) and resection (17.8 %; 8/45) ($p = 0.45$). Similarly, there were no difference between open operation (15.7%; 9/57) and laparoscopic operation (31.2 %; 10/32) ($p = 0.88$). However, as shown in Table 2, for laparoscopic procedures, there existed a high rate for POPF with enucleation compared to resection (42.8% [6/14] vs. 20.0 % [3/15]) ($p = 0.18$).

It has been reported that the rates of POPF for pancreatic neuroendocrine tumors (PNET) range from 17 to 39 % [34,35,9]. In our procedure, the rate was obviously lower, possibly because the majority of cases were functional insulinomas. Comparatively, non-functional PNET and inherited diseases will have higher rates of POPF, such as VHL or MEN-1 [36,15],in part because they have increased abnormal pancreatic parenchyma [37-40]. Other reports suggest that PNET is a risk factor for developing POPF, when compared to procedures for pancreatic adenocarcinoma or chronic pancreatitis [41,40].

All patients had a closed suction intra-operative drain placed at the pancreatic anastomosis, resection margin, or enucleation bed. The data did not change our guidelines, although there were some investigations that found an increased risk for POPF with enucleation compared to resection [42,33]. In fact, we considered the character of the pancreatic gland, whether soft or tough, more related to POPF [43-45]. Among patients who underwent surgical procedures, only 2 cases were found to be hypoglycemic again after more than 6 months. One was found 20 months after operation, while the other was found 31 months later. Generally, we considered symptomatic hypoglycemia 6 months after removal as recurrence[1]. A limitation in our study was the follow-up period; we were unable to compare to other research with our cumulative incidence of recurrence over only ten years. Service at el. followed 169 cases for more than 60 years, and confirmed the cumulative incidence of recurrence was 6% at 10 years and 8% at 20 years[1]. They also confirmed that, if a recurrence has not appeared within 20 years, subsequent recurrence is extremely unlikely [1].

However, hyperglycemia with a need for insulin therapy occurring during the first post-operative week is a common phenomenon [46,47]. In our group, 60.1% (54/89) of patients had a peak level of blood glucose over than 10 mmol/L, and the average median time for blood glucose level to return under 6.9 mmol/L was 19.7 ± 5.6 days. which is much longer than the data reported by Yu [46].

During the follow-up period, we noticed that 57.3% (51/89) of patients had significant weight loss. 3 months after surgery, 51 patients had a body weight decrease of more than 5 kg, and the average percent of weight loss was greater than 8%. Many factors possibly contributed to the postoperative weight loss [48], such as decreased food intake, elimination of hyperinsulinemia and surgical trauma. Similar to our results, Hongmei et al. reported significant weight loss after surgery for a group of patients with insulinoma [49]. Their statistics showed than patients with high BMI (median BMI = 26.0 kg/m2) had a significant weight loss of 11.5 kg and %WL of 15.0% 3 months after surgery. furthermore, they maintained a steady weight change from 3 months after surgery to 1-3 years after operation.

Conclusion

In conclusion, insulinoma is a very rare, but important disease. Accurate information about its natural history remains limited. Without doubt, surgical treatment is the most

important method in curing insulinoma, but due to the different body conditions and different tumor locations, exact surgical techniques should be selected on a case by case basis. Because of the retrospective character of this study, additional research is required.

Acknowledgments

All patients signed written informed consents and agreed to publish this report.

Funding:

No receiving funding

Authors' contributions

SQ, XH and YZ conceived and designed the experiments. SQ, MD, GZ, HL, and YG collected and analyzed the data. SQ and YZ interpreted the results and wrote the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research and to guarantee for the accuracy and integrity of any part of the work.

Ethics approval and consent to participate

This study was performed in accordance with standard guidelines and was approved by the Ethics Committee of The First Affiliated Hospital, Zhengzhou University (Approval No: 2016004). All patients provided written informed consent prior to the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Table 1. Clinical data of 617 patients who underwent pancreatic surgery in The First Affiliated Hospital of Zhengzhou University

HISTO-PATHO-LOGICAL	MEDIAN AGE (YEARS) ± S D	RANGE (YEARS)	MALE/ FEMALE RATIO	TUMOR LOCATION			TUMOR SIZE	PROCEDURE			DEATH
				UNCINATE	NECK	BODY /TAIL		LA	OA	CONVERT	
PIs	45±13.8	13~74	1/1.8	6	14	69	1.4±0.8	32	57	13.4%	0
PDAC	56±14.6	27~76	1/1.2	174	27	124	2.8±1.7	94	231	15.7%	3
IT	40±10.1	25~60	1/0.4	2	2	6	3.5±3.2	1	9	20.0%	0
NET	48±11.2	26~71	1/0.8	3	4	25	2.7±1.1	13	30	11.6%	0
NEC	39±10.7	30~64	1/0.9	2	5	31	4.5±1.2	7	31	13.1%	1
IPMN	68±12.1	50~78	1/0.6	22	3	7	1.5±2.2	14	18	6.2%	0
MCN	48±5.4	40~56	0/35	0	2	23	2.4±0.8	10	25	8.5%	0
SCN	63±10.7	48~74	1/4.0	0	2	8	8.4±5.6	4	6	0%	0
GIST	61±14.6	31~72	1/1.0	0	2	4	4.2±2.6	1	5	0%	0
SPT	25±11.8	18~45	1:3.4	4	3	15	9.34±2.7	8	14	4.5%	0
SFT	35±8.9	25~64	1/1.3	1	1	5	2.2±1.3	2	5	0%	0

PIs—pancreatic insulinoma, NEC—neuroendocrine carcinoma, NET—neuroendocrine tumor, GIST – gastrointestinal stroma tumor,
PDAC—pancreatic ductal adenocarcinoma, IPMN – intraductal papillary mucinous neoplasm, SFT – solitary fibrous tumor,
MCN – mucinous cystic neoplasms, SCN – serous cystic neoplasms, SPT – solid papillary tumor, IT— inflammatory

Table 2 . Clinical feature of patients with insulinoma

Procedure		Open Operation					Laparoscopic Operation				Total
		EN	DP	SPDP	PD	CP	EN	DP	SPDP	RA	
Number		27	16	9	3	2	14	11	4	3	89
length of operation time (minutes)		30~120	40~120	60~120	240~350	160~240	50~120	60~240	120~240	30~60	30~350
Intra-operation blood lost (ml)	Range	25~97	35~400	30~120	60~240	50~140	20~70	20~100	25~170	10~15	10~400
	SD	64.7±38.6					35.2±17.4				47.8±25.4
length of mean hospital stay (days)	Range	9~15	10~60	8~24	12~24	10~20	6~14	7~20	7~18	5~20	5~60
	SD	13.1±8.2					8.1±3.2				9.4±6.2
Gastrointestinal function Recovery(days)	Range	1~5	2~4	2~5	2~5	2~4	1~4	2~5	2~5	1~3	1~5
	SD	3.1±0.7					2.5±0.8				2.8±0.9
abdominal abscess /infection		3	2	1	1	1	0	0	0	0	8
postoperative hemorrhage		0	1	1	1	0	0	0	0	0	3
pancreatic fistula A-, B- degree		0	0	0	3	0	0	0	0	2	5
pancreatic fistula B+ degree		4	2	1	0	1	6	2	1	1	21.3%
pancreatic fistula C- degree		0	1	0	0	0	0	0	0	0	
total postoperative complications		40.3%					37.5%				39.3%
weight lost >5kg in 3 month		11	9	5	3	2	10	7	3	1	57.3%
Blood glucose Fluctuate (days)	Range	12~20	10~25	9~21	13~25	21~28	13~19	13~27	10~16	11~19	9~28
	SD	20.7±7.8					16.8±8.6				18.3±7.2
Symptom recurrence hypoglycemia		1	0	0	0	0	1	0	0	0	2

LA=Laparoscopic Operation; OA=Open Operation; RA=Radiofrequency Ablation; EN=enucleation; DP=distal pancreatectomy; PD=pancreaticoduodenectomy; CP=central pancreatectomy SPDP=spleen-preserving distal pancreatectomy;

POPF was defined analogous to the ISGPF criteria. Grade A POPF is defined as an asymptomatic elevation of pancreatic enzymes in the drainage without requiring a specific treatment. Grade B POPF is mostly associated with an abdominal infection. A specific treatment or persistent drainage over 3 weeks can be required. Grade C POPF a severe change of the clinical management or deviation from the normal clinical pathway occurs (e.g. reoperation, intensive care unit, death).

References:

[1] Service FJ1 MM, O'Brien PC, Ballard DJ. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc. 1991:711-9.
[2] Li X, Zhang F, Chen H, Yu H, Zhou J, Li M, et al. Diagnosis of insulinoma using the ratios of serum concentrations of insulin and C-peptide to glucose during a 5-hour oral glucose tolerance test. Endocr J. 2017;64:49-57.
[3] Kavlie H, White TT. Pancreatic islet beta cell tumors and hyperplasia: experience in 14 Seattle hospitals. Ann Surg. 1972;175:326-35.
[4] Cullen RM, Ong CE. Insulinoma in Auckland 1970-1985. N Z Med J. 1987;100:560-2.
[5] Czupryniak L, Strzelczyk J, Drzewoski J. Diagnostic difficulties in long-standing insulinoma with near-normal plasma insulin levels. J Endocrinol Invest. 2005;28:170-4.
[6] Sotoudehmanesh R, Hedayat A, Shirazian N, Shahraeeni S, Ainechi S, Zeinali F, et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. Endocrine. 2007;31:238-41.
[7] Grygiel K, Szmidt J, Jelenska M, Pawlak K. Surgical treatment of hyperinsulinism during the course of pancreatic cancer (insulinoma) - one center experience. Pol Przegl Chir. 2012;84:31-6.
[8] Bonato FT, Coelho JC, Petruzzielo A, Matias JE, Ferreira GA. Surgical treatment of pancreatic insulinomas. Arq Bras Cir Dig. 2012;25:101-4.
[9] Zhao YP, Zhan HX, Zhang TP, Cong L, Dai MH, Liao Q, et al. Surgical management of patients with insulinomas: Result of 292 cases in a single institution. J Surg Oncol. 2011;103:169-74.
[10] Sabaretnam M, Chand G, Mishra A. Pancreatic insulinoma: a surgical experience. World J Surg. 2010;34:2266.
[11] Liu H, Peng C, Zhang S, Wu Y, Fang H, Sheng H, et al. Strategy for the Surgical Management of Insulinomas: Analysis of 52 Cases. Digestive Surgery. 2007;24:463-70.
[12] Durczynski A, Hogendorf P, Szymanski D, Izdebski W, Kaczka A, Durko L, et al. Insulinoma--rare, but important clinical problem. Analysis of a series of 530 patients who underwent surgical treatment for the pancreatic tumor. Pol Przegl Chir. 2015;86:505-10.
[13] Fernandez-Cruz L, Cesar-Borges G. Laparoscopic strategies for resection of insulinomas. J Gastrointest Surg. 2006;10:752-60.
[14] Kann PH, Rothmund M, Zielke A. Endoscopic ultrasound imaging of insulinomas: limitations and clinical relevance. Exp Clin Endocrinol Diabetes. 2005;113:471-4.
[15] Bartsch DK, Albers M, Knoop R, Kann PH, Fendrich V, Waldmann J. Enucleation and limited pancreatic resection provide long-term cure for

insulinoma in multiple endocrine neoplasia type 1. Neuroendocrinology. 2013;98:290-8.
[16] McLean A. Endoscopic ultrasound in the detection of pancreatic islet cell tumours. Cancer Imaging. 2004;4:84-91.
[17] Lo CY, Lo CM, Fan ST. Role of laparoscopic ultrasonography in intraoperative localization of pancreatic insulinoma. Surg Endosc. 2000;14:1131-5.
[18] Ayav A, Bresler L, Brunaud L, Boissel P, Sfcl, Afce. Laparoscopic approach for solitary insulinoma: a multicentre study. Langenbecks Arch Surg. 2005;390:134-40.
[19] Mittendorf EA, Liu YC, McHenry CR. Giant insulinoma: case report and review of the literature. J Clin Endocrinol Metab. 2005;90:575-80.
[20] Tagaya N, Ishikawa K, Kubota K. Spleen-preserving laparoscopic distal pancreatectomy with conservation of the splenic artery and vein for a large insulinoma. Surg Endosc. 2002;16:217-8.
[21] Sciuto A, Abete R, Reggio S, Pirozzi F, Settembre A, Corcione F. Laparoscopic spleen-preserving distal pancreatectomy for insulinoma: experience of a single center. Int J Surg. 2014;12 Suppl 1:S152-5.
[22] Fernandez-Cruz L, Martinez I, Gilabert R, Cesar-Borges G, Astudillo E, Navarro S. Laparoscopic distal pancreatectomy combined with preservation of the spleen for cystic neoplasms of the pancreas. J Gastrointest Surg. 2004;8:493-501.
[23] Prochazka V, Hlavsa J, Andrasina T, Stary K, Muckova K, Kala Z, et al. Laparoscopic radiofrequency ablation of functioning pancreatic insulinoma: video case report. Surg Laparosc Endosc Percutan Tech. 2012;22:e312-5.
[24] Limmer S, Huppert PE, Juette V, Lenhart A, Welte M, Wietholtz H. Radiofrequency ablation of solitary pancreatic insulinoma in a patient with episodes of severe hypoglycemia. Eur J Gastroenterol Hepatol. 2009;21:1097-101.
[25] Roland CL, Lo C-Y, Miller BS, Holt S, Nwariaku FE. Surgical Approach and Perioperative Complications Determine Short-Term Outcomes in Patients with Insulinoma: Results of a Bi-Institutional Study. Annals of Surgical Oncology. 2008;15:3532-7.
[26] Karaliotas C, Sgourakis G. Laparoscopic versus open enucleation for solitary insulinoma in the body and tail of the pancreas. J Gastrointest Surg. 2009;13:1869.
[27] Su AP, Ke NW, Zhang Y, Liu XB, Hu WM, Tian BL, et al. Is laparoscopic approach for pancreatic insulinomas safe? Results of a systematic review and meta-analysis. J Surg Res. 2014;186:126-34.
[28] Kokudo T, Petermann D, Demartines N, Halkic N. Laparoscopic Pancreatic Enucleation With End-to-End Pancreatic Duct Reconstruction. Ann Surg Oncol. 2015;22:1190.

[29] Assalia A, Gagner M. Laparoscopic pancreatic surgery for islet cell tumors of the pancreas. World J Surg. 2004;28:1239-47.
[30] Lo CY, Chan WF, Lo CM, Fan ST, Tam PK. Surgical treatment of pancreatic insulinomas in the era of laparoscopy. Surg Endosc. 2004;18:297-302.
[31] Sheehan MK, Beck K, Creech S, Pickleman J, Aranha GV. Distal pancreatectomy: does the method of closure influence fistula formation? Am Surg. 2002;68:264-7; discussion 7-8.
[32] Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138:8-13.
[33] Inchauste SM, Lanier BJ, Libutti SK, Phan GQ, Nilubol N, Steinberg SM, et al. Rate of clinically significant postoperative pancreatic fistula in pancreatic neuroendocrine tumors. World J Surg. 2012;36:1517-26.
[34] Sa Cunha A, Beau C, Rault A, Catargi B, Collet D, Masson B. Laparoscopic versus open approach for solitary insulinoma. Surg Endosc. 2007;21:103-8.
[35] Hu M, Zhao G, Luo Y, Liu R. Laparoscopic versus open treatment for benign pancreatic insulinomas: an analysis of 89 cases. Surg Endosc. 2011;25:3831-7.
[36] Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97:2990-3011.
[37] Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol. 2005;19:753-81.
[38] Blansfield JA, Choyke L, Morita SY, Choyke PL, Pingpank JF, Alexander HR, et al. Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). Surgery. 2007;142:814-8; discussion 8 e1-2.
[39] Goudet P, Murat A, Binquet C, Cardot-Bauters C, Costa A, Ruszniewski P, et al. Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. World J Surg. 2010;34:249-55.
[40] van Beek DJ, Nell S, Verkooijen HM, Borel Rinkes IHM, Valk GD, Vriens MR. Surgery for multiple endocrine neoplasia type 1-related insulinoma: long-term outcomes in a large international cohort. British Journal of Surgery. 2020.
[41] Fendrich V, Merz MK, Waldmann J, Langer P, Heverhagen AE, Dietzel K, et al. Neuroendocrine pancreatic tumors are risk factors for pancreatic fistula after pancreatic surgery. Dig Surg. 2011;28:263-9.
[42] DiNorcia J, Lee MK, Reavey PL, Genkinger JM, Lee JA, Schrope BA, et al. One hundred thirty resections for pancreatic neuroendocrine tumor: evaluating the impact of minimally invasive and parenchyma-sparing techniques. J Gastrointest Surg. 2010;14:1536-46.
[43] DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ, et al. Assessment of complications after pancreatic surgery: A novel grading

system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg. 2006;244:931-7; discussion 7-9.
[44] Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. J Gastrointest Surg. 2004;8:951-9.
[45] Berger AC, Howard TJ, Kennedy EP, Sauter PK, Bower-Cherry M, Dutkevitch S, et al. Does type of pancreaticojejunostomy after pancreaticoduodenectomy decrease rate of pancreatic fistula? A randomized, prospective, dual-institution trial. J Am Coll Surg. 2009;208:738-47; discussion 47-9.
[46] Yu JC. [Continuous monitoring for blood glucose after surgery of insulinoma and the use of insulin]. Zhonghua Wai Ke Za Zhi. 1993;31:352-4.
[47] Li GL, Ge W, Lu RY. [Monitoring blood glucose level in patients with insulinoma during the postoperative period: 3 case reports]. Zhonghua Hu Li Za Zhi. 1997;32:575-7.
[48] House MG, Fong Y, Arnaoutakis DJ, Sharma R, Winston CB, Protic M, et al. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. J Gastrointest Surg. 2008;12:270-8.
[49] Dai H, Xu Q, Hong X, Wang X, Pang H, Wu W, et al. Surgery in overweight patients with insulinoma: effects on weight loss. Scand J Gastroenterol. 2017;52:1037-41.