American Journal of Cancer Prevention, 2016, Vol. 4, No. 1, 8-12
Available online at http://pubs.sciepub.com/ajcp/4/1/2

DOI:10.12691/ajcp-4-1-2

Diagnosis and Surgical Treatment of Insulinoma in Sixteen Cases

Cheng Wei[1], Xu Xuesong[2], Gong Jianping[2,*]

[1]Surgery Department, Chongqing Yubei District Tranditional Chinese Medicine Hospital, Chongqing, China
[2]Heptobiliary Surgery Department, Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
*Corresponding author: gongjianping11@126.com

Abstract **Backgroud:** Insulinoma is a rare tumor derived from B cells of pancreas islets, while recently, according to some researches, the incidence of insulinoma is increasing. It is believed that much more attention should be attached to the diagnosis and treatment of insulinoma. The goal of this retrospective study was to analyze the strategy for the surgical management of insulinomas. **Methods:** From May 2001 to October 2010, the medical records of 16 patients with insulinomas were included in our studied. We confirmed the diagnosis accoringd to a series of biochemical tests. Then all tumors were localized precisely by imaging techniques combined with intraoperative palpation. Except 4 patients who denied surgical treatment, all these patients was accepted follow-up after operation. **Result:** 11 patients with benign lesions underwent open surgical. 1 patient with malignant insulinomas underwent pancreaticoduodenectomy. The mean hospital stay was 17.0 ± 6.0 days after after the open procedures. 14 complications occurred in 7 patients following resection. On follow-up, 92% of the patients were free from symptoms, and surgical cure was achieved in 95% of the patients with benign insulinomas. **Conclusion:** The choice of the surgical strategy for the treatment of pancreatic insulinomas depends on size and location of the tumor and the risk of malignancy. The optimal surgical procedure is key to prevent postoperative complications.

Keywords: *insulinoma, whipple triad, blood glucose lever, localization diagnosis, treatment*

Cite This Article: Cheng Wei, Xu Xuesong, and Gong Jianping, "Diagnosis and Surgical Treatment of Insulinoma in Sixteen Cases." *American Journal of Cancer Prevention*, vol. 4, no. 1 (2016): 8-12. doi: 10.12691/ajcp-4-1-2.

1. Introduction

Insulinoma is a rare tumor derived from B cells of pancreas islets, but it is the most common neoplasm of the endocrine pancreas. Pancreatic neuroendocrine tumors (PNETs) are uncommon neuroendocrine neoplasms with reported incidence of <1 per 100,000 persons per year in population-based studies from Europe and Asia. Recently, Halfdanarson et al. [1] reported an annual incidence of 2.2 in 1,000,000 for PNETs covering a period of 27 years. Meanwhile,in 2011,according to the research of Zhao [2], the incidence of insulinoma was 4 per 1000000. Insulinoma accounts for the majority of functioning PNETs (range 46%-85%). Zhou [3] reported that it accounts for almost three forth(70%-75%) of the number of tumor derived from pancreatic islet cell. Rarely, 5-10% insulinoma may be associated with the syndrome of multiple endocrine neoplasia type 1 (MEN-1). [4,5] According to reports, <10% of insulinomas are malignant. Muro S [6] reported that the diameter of most malignant insulinomas is beyond 3cm with a liver or adjacent tissue metastasis. The 10-year survival rate is estimated at 91 and 29% for benign and malignant insulinomas, respectively. Surgical resection is preferred for insulinomas and achieved cure in more than 90% of the patients. Surgical procedures include tumor enucleation, partial or total pancreatic resection, and pancreatoduodenectomy (Whipple's operation). If malignancy is suspected, metastatic tumor resection and/or lymph node dissection is mandatory. In recent years, laparoscopic resection of pancreatic insulinomas has been performed successfully and provides patients with the benefits of minimally invasive surgery. However, only a few authors have reported the management strategy of insulinoma resection. The goal of this retrospective study was to assess feasibility, safety, and outcome of different surgical approaches and to analyze the surgical strategy of insulinoma management.

2. Patients and Methods

From May 2001 to October 2010, the data of 16 patients with pancreatic insulinomas were retrospectively collected for the present study. These patients included 7 men and 9 women with a mean age of 57 ± 6 (range 44-78) years who underwent surgical treatment at the Second Affiliated Hospital of Chongqing Medical University. All patients presented with hypoglycemia that developed after fasting or exertion and improved after glucose intake.

The diagnosis was confirmed with a 75-gram oral glucose tolerance test and determination of serum insulin, proinsulin, and C peptide levels every 6h. Preoperative localization was performed, including transabdominal ultrasonography, computed tomography, magnetic resonance

imaging, selective arteriography. Furthermore, intraoperative frozen-section examination were also performed routinely. Except 4 patients who denied surgical treatment, all these patients was accepted follow-up after operation(median follow-up period was 37 (range 6–61) months). The location sensitivity of different methods, the proportion of tumors located in different parts of the pancreas, the sides of tumors were counted to value the diagnostic reliability of different methods. Operation time, blood loss, hospital stay time and incidence of complications were counted to value the reliability of surgical treatment.All these results are expressed as mean values ± SD. Independent sample t test and ANOVA were used to compare quantitative variables. Significance was defined as $p < 0.05$.

3. Results

3.1. Localization of the Lesion

All patients underwent at least one of the above-mentioned imaging procedures to localize the lesions. The sensitivity was 82% for computed tomography (n=9), 42% for ultrasonography (n=5), 67% for selective arteriography (n=8), 86% for magnetic resonance imaging (n=10), and 92% for intraoperative utrasonography (n=11). All tumors were precisely located according to previously mentioned imaging techniques. Five lesions (31%) were localized in the head, one (6%) in the uncinate process, four (25%) in the neck, six (38%) in the body, and one (6%) in the tail of the pancreas. Mean sizes of the lesions were 15.7, 17.4, 14.2, 16.9, and 15.1 mm in head, uncinate process, neck, body, and tail of the pancreas, respectively.

3.2. Surgical Management

Table 1 summarizes the surgical features of the patients with benign insulinomas. The surgical procedures were performed in 11 patients. Successful resection was performed in all of the eleven patients, 9 patients underwent tumor enucleation, and 2 patient underwent spleen-preserving distal pancreatectomy. The mean hospital stay was 17.0 ± 6.0 days after the surgical procedures. One patients with malignant insulinomas underwent successful pancreaticduodenectomy. Pancreaticoduodenectomy needed longer operating times and hospital stays and caused greater blood loss as compared with the other surgical procedures.

Table 1. Surgical features of 12 patients with benign insulinomas

Surgical procedure	n	Tumor size mm	Operation time min	Blood loss ml	Hospital stay days
Enucleation	8	14.8±2.7	135±23	115±46	17.0±4.0
Distal pancreatectomy	3	15.6±3.0	187±34	246±59	19.0±5.3
Pancreaticoduodenectomy	1	18.7	245	550	21

3.3. Morbidity

There were no operative deaths. Fourteen complications occurred in 7 patients following resection (Table 2). The most common complications were pancreatic fistulas, delayed gastric emptying, and infections. Other complications included intra-abdominal collection (n=2), pleural effusion (n=2), pancreatic pseudocyst (n=1), bleeding (n=1), and diabetes (n=1). Two patients required reoperation during the early postoperative period: 1 for intra-abdominal bleeding and 1 for severe pancreatic fistula. Five low-output pancreatic fistulas spontaneously healed after 6 weeks. One patient who underwent pancreatectomy developed late diabetes.

Table 2. Postoperative complications in patients with insulinomas

Surgical procedure	*Pancreatic fistula*	*Delayed gastric emptying*	*Infections*	*Other complications*
Enucleation	3		1	Pleural effusion(1) Intra-abdominal collection(2)
Distal pancreatectomy	1			Pancreatic pseudocyst(1), Pleural effusion(1)
Pancreaticoduodenectomy	1	1		Bleeding (1), Diabetes(1)
Total	5	1	1	7

3.4. Follow-Up

Follow-up data were obtained from patient records supplemented by telephone. The patients were considered cured postoperatively, if symptoms disappeared and serum hormone levels were normal and remained so for at least 6 months. No patients had been lost to follow-up, and 1 patient died of the malignant insulinoma 2 years after primary operation. During the median follow-up period of 37 (range 6–61) months, 9 patients (81%) were free from symptoms. Surgical cure was achieved in all of the patients with benign insulinomas.

4. Discussions

Insulinoma is a rare tumor derived from B cells of pancreas islet, but it is the most common neoplasm of the endocrine pancreas. Insulinoma takes majority of pancreatic islet cells, others gastrinoma, and rare functional tumors, VIPoma, glucagonoma, carcinoids (serotonin), somatostatinoma, and exceedingly rare neoplasms like PPoma, adrenocorticotropic hormone (ACTH) oma, growth hormone releasing factor (GRF)oma, calcitonin-producing tumors, parathryroid hormone-related peptide-producing tumors, and others [7,8,9].

4.1. Qualitative Diagnosis of Insulinoma

In our research, all these cases included presented hypoglycemia that developed after fasting or exertion and improved after glucose intake, it is believed that the the so-called syndrome, which is titled as Whipple triad or symptoms of hypoglycemia is a reliable diagnostic clinical manifestation. Except the clinical manifestation, according to some lab test proceeded in our research to confirm their diagnosis, such as 75-gram oral glucose tolerance test , determination of serum insulin, proinsulin, and C peptide

levels every 6h, we believe that pathognomonic finding is an inappropriately high (>5 mU/mL) level of serum insulin during symptomatic hypoglycemia. A diagnostic ratio of blood insulin (in microunit per milliliter) to glucose (in milligram per deciliter) of greater than 0.4 or C peptide level higher than 2 nmol/L has proved valuable in diagnosis.

Some results derived from other groups seem to also support our conclusion. Hu indicated that although the Whipple's triplet syndrome is not the specific clinical manifestations of insulinoma, easily confused with a lot of mental diseases, it is a reasonable evidence of prime diagnosis of insulinoma [10]. In the survey of Zhang [11], including a group of 45 patients with insulinoma, they supposed that associated with the Whipple's triplet syndrome, most of patients can be diagnosed as insulinoma with the result of laboratory examination which includes the level of serum insulin over 43 pmol/L, the ratio of blood insulin (in microunit per milliliter) to glucose (in milligram per deciliter) of beyond 0.3 and the C peptide level over 200 pmol/L. Except above examinations, Han [12] supposed that a series of plasma glucose-related indexes are also helpful to diagnose insulinoma, including HbA1c, oral glucose tolerance test(OGTT) and continuous glucose monitoring.

4.2. Localization

Insulinomas are small in most cases, and are difficult to detect during surgery. Compared with the qualitative diagnosis, the localization is much more far-reaching for operation of insulinoma.

4.2.1. Preoperative Localization

The meaning of preoperative localization is truly significant, because it can help operators confirm the location and the metastasis status of tumor, plan the appropriate surgical program and reduce the complications effectively [13]. The initial imaging technique used to localize insulinoma and stage the disease is a high-quality spiral or multi-detector three-dimensional computed tomography (CT) scan.

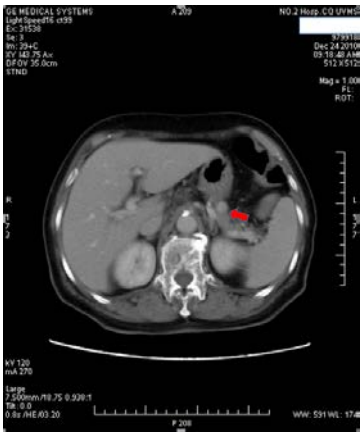

Figure 1. These pictures are the part of CT test result of our patients. According to our research, most of insulinomas are typically hyperenhancing(marked by red arrow) and are usually best seen on CT scans obtained during the arterial phase, espacially for those larger than 1.5cm

CT is atraumatic and convenient for preoperative examination, and is useful in assessing size and location of the primary tumor, peripancreatic lymph node involvement, and the presence or absence of liver metastases (Figure 1, Figure 2, Figure 3). In our research, the sensitivity of CT was 82%(n=9), this value was the second highest in all imaging technologies used in our patients. Considering its sensitivity and universality, we believe that CT is initial localization procedure for preoperative location of most insulinoma. A retrospective study showed that 63% of insulinomas could be detected by multiphasic spiral CT prospectively, and 83% of the lesions could be seen in retrospect. [14,15] While according to survey of Hu,with a sensitivity of 64%, almost all the insulinoma detected by CT is large than 1.5cm [10]. This result remand us that CT is not suitable for the location diagnosis of insulinoma whose diameter is beyond 1.5cm.

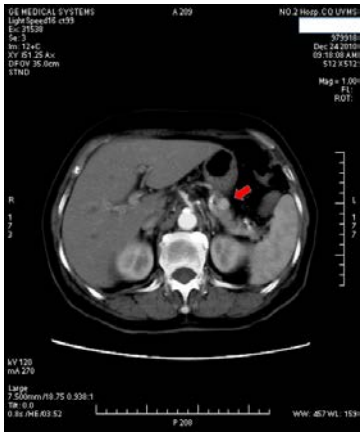

Figure 2. These pictures are the part of CT test result of our patients. According to our research, most of insulinomas are typically hyperenhancing(marked by red arrow) and are usually best seen on CT scans obtained during the arterial phase, espacially for those larger than 1.5cm

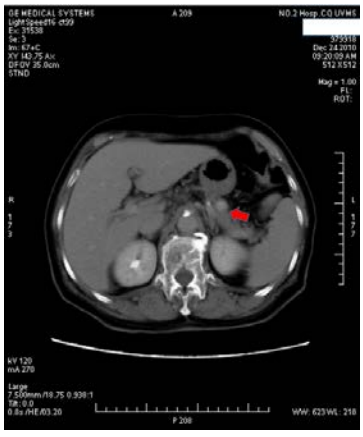

Figure 3. These pictures are the part of CT test result of our patients. According to our research, most of insulinomas are typically hyperenhancing(marked by red arrow) and are usually best seen on CT scans obtained during the arterial phase, espacially for those larger than 1.5cm

According to our research, MRI is demonstrated to be superior to other preoperative imaging techniques in identifying small pancreatic insulinomas whose sensitivity reached up to 86%(most highest in all the preoperative imaging technology), this result reminds us that MRI may replace CT as the initial imaging test. Ichikawa [16] reported that sensitivity of MRI ranges from 85% to 95%, in the detection of insulinomas and the determination of

the presence of metastases. An improvement in MRI technique is the use of diffusion weighted MRI (DWI) for abdominal imaging. [17] DWI is an MRI technique which detects changes in the molecular diffusion of water in biologic tissues. DWI may be a promising tool for detecting and localizing small insulinomas especially those with no hypervascular pattern [18].

Selective angiography is used for selective visualization of the arterial supply to the pancreas and peripancreatic regions. The accuracy of angiography was 67% in our research. With the advent of EUS, this test is much less commonly utilized.

Except above imaging technologies used in our research to locate insulinoma preoperation, some other technologies are supported by other teams in location of insulinoma, especially Endoscopic ultrasonography(EUS) and PET-CT. A recent single-centre prospective study showed that a sensitivity of EUS was 93% and a specificity was 95% in localization of intra-pancreatic lesions. [19] Sotoudehmanesh R et al. [20] reported the sensitivity of endoscopic ultrasonography for detection of lesions in pancreatic head, body and tail was 92.6%, 78.9%, and 40.0%, respectively. Recently, some scholars released that combined utilization of multiple imaging techniques is superior to any single imaging examination, especially associated with the use of PET-CT, which is achieved a sensitivity above 90% [21]. Sharma P [22] believed that 111In-labeled glucagon-like peptide 1 receptor agonist is prior to traditional imaging technologies in detection of insulinoma. Wild [23] reported that ^{68}Ga-exendin-4 PET-CT has an advantages in detection of insulinoma, especially for tumors whose diameter is less than 1cm. But considering the high expense, PET-CT could not be regarded as the routine method for diagnosis of insulinoma.

4.2.2. Intraoperative Localization

Manual localization is basic but blindest, the accuracy is depending on the size and position of tumor with experience of operator. Therefore, localization for tumors may failure in many cases. The tumor excision was predominantly done by extensive pancreatic resection. The most common complication following extensive pancreatic resections was acute pancreatitis, while after enucleation pancreatic fistula occurred more frequently.

Accroding to our research, intraoperative ultrasound (IOUS) is predominant for intraoperative localization, whose sensitivity reached 92% in patients with insulinomas. the IOUS demonstrates the relevant anatomy, defining the relationship of the tumor to the pancreatic, bile duct and adjacent splenic or superior mesenteric vessels, preventing injuries to these tissues, so we believe that IOUS is capable to identify suspected multiple lesions and latent insulinoma. What's more, exact IOUS is beneficial to the distinct the tumor and normal pancreatic parenchyma. Geng [24] reported that IOUS or Laparoscopic IOUS can also help operators reduce the incidence of pancreatic fistula. Okabayashi [25] also agreed that united application of IOUS and other preoperation imaging examinations is helpful to the exact diagnose of insulinoma. Intraoperative localization techniques, which include both careful surgical palpation of the pancreas and the use of IOUS, remain the most reliable way to localize insulinomas and determine the indicated surgical procedure.

4.3. Therapy for Linsulinoma

4.3.1. Surgical treatment

Surgery is the only treatment-modality with the potential to cure patients with insulinoma. Conluded from our research, with the least operation time(17.0±4.0day), blood loss (115±46ml) and hospital stay days(135±23day), Enucleation is our initial procedure for benign insulinoma, particularly they are small and surficial. While the tumor is large and deep in the neck, body, or tail of pancreatic parenchyma and is anatomically unsuitable for enucleation, resection of the distal pancreas is a safe and effective alternative.

Tumors that are hard, cause puckering of surrounding soft tissue appear to be infiltrating, or causing distal dilatation of the pancreatic duct raise serious suspicion of malignancy. [26] These tumors are usually single and large, averaging 6 cm in diameter. Aggressive attempts at resection (such as pancreaticoduodenectpmy)were recommended as these tumors are much less virulent than their malignant ductal exocrine counterparts. What's more, Ten-year survival of 29% has been reported in malignant insulinoma.[27] Based on above reasons, when malignant insulinoma is highly suspected, we should as far as possible achieve complete excision of primary tumor and metastasis.

Complications related to the pancreatic dissection include fistula, pseudocyst, acute pancreatitis and abscess. The most common one is pancreatic fistula, in our patients, it would be cured in 6 weeks by free drainage and supporting therapy, except those severe pancreatic fistula. Our follow-up showed that 9 patients diagnosed as benign insulinomas (81%) were free from symptoms, during the median follow-up period of 37 (range 6–61) months. Meanwhile, at the end of the follow-up, surgical cure was achieved in all of the patients with benign insulinomas (n=11). So we believes that good effect could be obtained after enucleation or distal pancreatectomy. Another case was confirmed to be malignant insulinoma with lymph node metastasis after pancreaticoduodenectomy, also achieved relative good results(achieved a 2-years survive period after pancreaticoduodenectomy), indicating that the targeted tumor resection is an effective means of treating insulinoma.

4.3.2. Non-surgical Treatment

Although surgery is the initial treatment for insulinoma, considering the situation that patients may have a variety of operation contraindications, Levy [28] supposed that repeated low-dose ethanol ablation induced by ultrasound endoscope is a optional treatment. Fiebrich [29] hold that oral everoilimus can reduce the volume of tumor through decreasing the secretion of insulin or insulingen. Arianeb M [30] put forward 2 main distinct parts of medical treatment to control the hyperglycemic disorder. On one hand, utilizing diazoxide to relieve the neuroglycopenic symptoms. On the other, applying streptozotocin intravenously to control the hyperglycemic disorder by inhibiting the biosynthesis of insulin in β cell.

5. Operation Highlights

Firstly, it is particularly important that normalize the blood glucose during preoperative period. The choice of surgical procedures should be decided under the features of insulinoma. Espana G [31] reported that atypical resection, such as enucleation, should be performed for insulinoma that are benign, small and located in the body or tail of pancreas. Contrarily, Okabayashi T [25] supposed that radical resection should be performed for insulinoma that multiple, not well-capsulated, large than 4 cm and located or near the main pancreatic duct. Meanwhile, for patients with malignant insulinoma, aggressive surgery is recommended, such as Pancreaticoduodenectomy, because of its relative low grade of malignancy. Some research showed that the laparoscopic surgery is demonstrated to be safe for insulinomas which are accurately located in the body or tail of pancreas. Pancreatic leak for laparoscopic surgery is reported to happen in 8 percent to 50 percent of patients, whereas 24 to 58 percent for laparotomy insulinoma resection. The complications morbidity has no significant difference with surgical resection. In the future, the laparoscopic surgery may play much more important role in the surgical treatment of insulinoma.

References

[1] Halfdanarson TR, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol*, 19(10). 1727-1733. 2008.

[2] Zhao YP, Zhan TP, et al. Surgical management of patients with insulinomas: Result of 292 cases in a single institution[J]. *J Surg Oncol*, 103(2). 169-174. 2011.

[3] Zhou JS, Jiang Y, Wu BQ, et al. Diagnose and treatment experience about 10 Cases of Insulinoma. *Journal of Hepatopancreatobilaary Surgery*, 22. 500-501. 2010.

[4] Alexakis N, Neoptolemos JP. Pancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol* 22(1). 183-205. 2008.

[5] De Herder WW, Niederle B, Scoazec JY, et al. Well-differentiated pancreatic tumor/carcinoma: insulinoma. *Neuroendocrinology*, 84(3). 183-188. 2006.

[6] Muro S, Nasu J, Harada R, et al. Prompt resolution of hypoglycemia by hepatic transarterial embolization for malignant insulinoma with multiple liver metastasis[J]. *Acta Med Okayama*, 68(5). 303-306. 2014.

[7] Garbrecht N, Anlauf M, Schmitt A, et al. Somatostatin-producing neuroendocrine tumors of the duodenum and pancreas: incidence, types, biological behavior, association with inherited syndromes, and functional activity. *Endocr Relat Cancer*, 15(1). 229-241. 2008

[8] O'Toole D, Salazar R, Falconi M, et al. Rare functioning pancreatic endocrine tumors. *Neuroendocrinology*, 84(3). 189-195. 2006

[9] Ehehalt F, Saeger HD, Schmidt CM, et al. Neuroendocrine tumors of the pancreas. *Oncologist*, 14(5). 456-467. 2009

[10] Hu WY, Guo WD, KongJ, et al. Diagnose and treatment of Insulinoma. *Journal of Abdominal, Surgery*, 27(3). 200-202. 2014.

[11] Zhang N, Qiu XG. Surgical diagnosis and treatment of insulinoma. *International Journal of Surgery*, 42(3). 174-176. 2015.

[12] Han JF, Zhang F, Bao YQ, et al. Clinical significance of glycometabolism-related indexes for diagnosis of insulinoma. Chinese Medical Journal, 90(16). 1093-1096. 2010.

[13] Sun WY, Guo DW, Jiang XF, et al. Application experience about the role of ultrasound localization in surgical treatment of insulinoma. *Journal of Modern Oncology*, 19(8). 1605-1607. 2011.

[14] Long X, Li Y, Wang X, Ouyang Y, et al. Retrospective analysis of preoperative localization of insulinomas on CT. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*, 34(2). 165-171. 2009.

[15] Fidler JL, Fletcher JG, Reading CC, et al. Preoperative detection of pancreatic insulinomas on multiphasic helical CT. *AJR Am J Roentgenol*, 181(3). 775-780. 2003.

[16] Ichikawa T, Peterson MS, Federle MP, et al. Islet cell tumor of the pancreas: biphasic CT versus MR imaging in tumor detection. *Radiology* , 216(1). 163-171. 2000.

[17] Erturk SM, Ichikawa T, Motosugi U, et al. Diffusion-weighted MR imaging in the evaluation of pancreatic exocrine function before and after secretin stimulation. *Am J Gastroenterol*, 101(1). 133-136. 2006.

[18] Anaye A, Mathieu A, Closset J, et al. Successful preoperative localization of a small pancreatic insulinoma by diffusion-weighted MRI. *JOP* , 10(5). 528-531. 2009.

[19] Anderson MA, Carpenter S, Thompson NW, et al. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. *Am J Gastroenterol* , 95(9). 2271-2277. 2000.

[20] Sotoudehmanesh R, Hedayat A, Shirazian N, et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. *Endocrine* , 31(3). 238-241. 2007.

[21] Wu HS, Zhang JJ, Xiong JQ, et al. Diagnosis and treatment analysis and clinical features of nonfunctional insulinoma. *Chinese Journal of General Surgery*, 18(8). 843-846. 2009.

[22] Sharma P, Singh H, Bal C, et al. PET/CT imaging of neuroendocrine tumor with (68) Gallium-Labeled somatostatin analogues: an overview and single institution experience from India[J]. *Indian J Med*, 29(1). 2-12. 2014.

[23] Wild D, Wicki A, Mansi R, et al. Exendin-4-based radiopharmaceuticals for glucagon-like peptide 1 receptor PET/CT and SPECT/CT[J]. *J Nucl Med*, 51(7). 1059-1067. 2010.

[24] Geng C, Ma SZ, Wang XY, et al. Accurate rescetion of functional insulinoma. *Chinese Journal of General Surgery*, 22(3). 329-332. 2013.

[25] Okabayashi T, Shima Y, Sumiyoshi T, et al. Diagnosis and management of Insulinoma. *World J Gastroenterol*, 32. 176-178. 2013.

[26] Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc*, 66(7). 711-719. 1991

[27] Grant CS: Insulinoma. *Best Pract Res Clin Gastroenterol*, 19(5). 783-798. 2005.

[28] Levy MJ, Thompson GB, Topazian MD, et al. US-guided ethanol ablation of insulinoma: a new treatment option[J]. *N Engl J Med*, 360(2). 195-197. 2009.

[29] Fiebrich HB, Siemerink EJ, Brouwers AH, et al. Everolimus induced rapid plasma glucose Nomalization in insulinoma patients by effects on tumor as well as normal tissue[J]. *Oncologist*, 16(6). 783-787. 2011.

[30] Arianeb M, Lars F, Mohammadreza H, et al. a Systematic review of location ,surgical treatment option and outcome of insulinoma. *Pancreas*, 43. 675-686. 2014.

[31] Espana G, Velazquez FD, Bezaury P, et al. Pancreatic insulinoma: a surgical experience. *World J Surg*, 7. 150-156. 2009.