

# Efficacy of laparoscopic ultrasonography in laparoscopic resection of insulinoma

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## ABSTRACT

Insulinoma is the most common functioning islet cell tumor of the pancreas, with an annual incidence of 4 cases/1 million individuals. It is treated by surgical methods. Open surgery was once considered the standard approach for the treatment of insulinoma. However, the procedure is traumatic and requires a large incision, which does not satisfy the growing expectations of minimally invasive management of small-sized tumors. Insulinomas are usually benign solitary tumors and mostly occur sporadically, which makes them suitable candidates for laparoscopic management. The potential advantages of laparoscopic management of insulinoma over open surgery include shorter duration of hospitalization, quicker recovery, and better cosmetic effect. However, because of the small tumor size as well as the depth and uncertainty of the location of the tumor, laparoscopic localization of the lesion without tactile sensation is difficult. Laparoscopic ultrasonography can detect about 90% of insulinomas, and its sensitivity is comparable to that of manual palpation along with intraoperative ultrasonography during open surgery; thus, it ensures the feasibility of laparoscopic management of insulinoma and reinforces its advantage as a minimally invasive procedure. Laparoscopic ultrasonography is vital for the localization of insulinomas and characterization of the surrounding pancreatic structure and should, therefore, be considered an integral part of the laparoscopic management of insulinoma.

**Key words:** Complications, insulinoma, laparoscopic surgery, laparoscopic ultrasonography, pancreas

## INTRODUCTION

Insulinoma is a type of neuroendocrine tumor of the pancreas, which leads to oversecretion of insulin and, consequently, hypoglycemia. Although the occurrence of insulinoma is rare, and its annual incidence is estimated to be 4 cases/1 million individuals, it is the most frequently encountered functioning islet cell

tumor of the pancreas. The presence of insulinoma is indicated by the presentation of Whipple’s triad, a combination of three criteria including fasting-induced hypoglycemic symptoms, blood glucose (BG) levels lower than normal at onset of symptoms (<3.0 mmol/L), and relief of symptoms after the

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**How to cite this article:** Wu M, Wang H, Zhang X, Gao F, Liu P, Yu B, et al. Efficacy of laparoscopic ultrasonography in laparoscopic resection of insulinoma. *Endosc Ultrasound* 2017;6:149-55.

### Access this article online

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DOI:

10.4103/2303-9027.194703

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**Received:** 2016-03-30; **Accepted:** 2016-06-14

administration of glucose; these symptoms are also the criteria for diagnosis of insulinomas. Insulinomas are usually benign solitary tumors and mostly occur sporadically. However, the occasional occurrence of these tumors in association with multiple endocrine neoplasia-1 (MEN-1) should not be overlooked.<sup>[1]</sup> Although the locations of most insulinomas are evenly distributed among the pancreatic head, body, and tail, about 3% of the tumors occur in the adjacent abdominal portions, such as the duodenum, splenic hilum, and gastrocolic ligaments.<sup>[2]</sup> Surgery is the most promising curative approach for insulinomas, especially the benign, solitary, sporadic type.<sup>[3]</sup> In this article, we review laparoscopic methods for the treatment of insulinoma, with an emphasis on the efficacy of intraoperative laparoscopic ultrasonography, which should be considered an integral part of laparoscopic resection of insulinoma.

## PHYSIOLOGY AND SYMPTOMS

Hyperinsulinemia caused by insulinoma results in the intermittent occurrence of hypoglycemic episodes. The resultant hypoglycemia causes sympathetic activation of the autonomous nervous system and energy deficiency of the brain cells.

The decrease of glucose levels to 2.8–3.0 mmol/L causes an increase in the secretion of glucotropic hormones, including glucagon, epinephrine, norepinephrine, and glucocorticoids. The oversecretion of epinephrine and norepinephrine leads to symptoms of sympathetic activation, including sweating, hunger, palpitation, pallor, and cold extremities.

Since glucose is the major source of energy to the brain cells, the hypoglycemic condition induced by the decrease of glucose levels to 2.5–2.8 mmol/L causes the successive inhibition of activity of the cortex, subcortical nerve centers, and medulla oblongata. The initial neurological symptoms of inhibition of cortical activity include dizziness, drowsiness, changes in vision, gait disturbance, and mental symptoms. While the inhibition of subcortical activity leads to convulsions and pyramidal signs, the inhibition of activity of the medulla oblongata leads to coma and areflexia.

Insulinoma is characterized by the presentation of Whipple's triad, and patients with insulinoma suffer intermittent episodes of a combination of the above-mentioned sympathetic and neurological

symptoms. The diversity of symptoms often leads to misdiagnosis, especially in China. Insulinoma is often misdiagnosed as epilepsy, psychosis, cerebrovascular disease, or hysteria.<sup>[4]</sup> Persistent hypoglycemic damage to the brain is irreversible and results in neurological sequelae. Therefore, early diagnosis and treatment are vital for the good prognosis of this disease.

## QUALITATIVE DIAGNOSIS

The presentation of Whipple's triad confirms the relationship between the symptoms and hypoglycemia. In addition, the presence of insulinomas is further confirmed by the presence of high serum concentrations of insulin during a hypoglycemic episode, which can be induced by a 72-h fasting test. It is vital that the concentrations of plasma glucose, insulin, and c-peptides are all evaluated simultaneously.

Plasma glucose levels <2.8 mmol/L, insulin levels  $\geq 36$  pmol/L, and c-peptide concentrations >300 pmol/L should be considered indicative of the presence of insulinoma; immunoreactive insulin/BG level >0.3 is another preferential indicator of insulinoma.<sup>[5]</sup> Conditions such as nesidioblastosis, sulfonyleurea-induced hypoglycemia, and insulin autoimmune hypoglycemia should be ruled out since they share similar associations with hyperinsulinemia as insulinoma.

## PREOPERATIVE LOCALIZATION METHODS

About 97% of insulinomas are regionalized in the pancreas, where they are evenly distributed in the head, body, and tail regions of the pancreas, in terms of occurrence. About 90% of insulinomas are solitary tumors. They are typically small, with an average size of 1.0–1.5 cm, and are <2 cm in size in 90% of the cases.<sup>[3]</sup> Although these tumors are usually richly supplied by blood, insulinomas with less blood supply or cystic degeneration are not uncommon.

Laboratory examination is adequate to establish the diagnosis of insulinoma. The major role of preoperative imaging is the localization of tumors along with the evaluation of their size, extent, relationship with the adjacent structures, and lymph node metastases, to help surgeons better decide the appropriate method for surgical treatment. Several imaging techniques with varied efficacies are now applied in the preoperative localization of insulinomas.

### *Transabdominal ultrasonography*

Insulinomas present as solitary hypoechoic circular nodules with rich intralésion vascularization on ultrasonographic images. The pancreas is anatomically located deep within the abdomen, and it is susceptible to disturbance because of intestinal gas. The average sensitivity of transabdominal ultrasonography ranges from 9.6% to 33%.<sup>[6-8]</sup> It is an economical, convenient, and noninvasive diagnostic modality and, therefore, still used as a routine method for clinical examination. Although contrast-enhanced ultrasonography with SF<sub>6</sub> is reported to have a much higher sensitivity (92.31%) than the conventional technique,<sup>[9]</sup> it is not widely used.

### *Computer tomography*

Since most solitary insulinomas are small in size (<2 cm), they do not cause morphological changes to the pancreas.<sup>[3]</sup> The precontrast attenuation values of insulinomas are similar to those of normal pancreatic tissue, which is remarkably enhanced during the arterial phase. Enhanced computer tomography (CT) has a relatively high sensitivity (33%–60%) for the diagnosis of insulinomas.<sup>[6-8,10]</sup> Although CT imaging findings can help exclude metastatic diseases, tumors <1 cm are not easily detected by CT. Arteriography performed in conjunction with CT can detect lesions as small as 1.0 cm × 0.8 cm.<sup>[11]</sup> Recent advances in CT equipment have enabled the detection of insulinomas with greater efficacy. The sensitivity of dual-phase thin-section multidetector CT scanner was reported to be 94%, which is much higher compared to that of conventional CT scanners.<sup>[12]</sup> Thus, CT is the diagnostic modality of choice for patients with insulinomas.

### *Magnetic resonance imaging*

Insulinomas present low T1-weighted image (T1WI) and high T2-WI (T2WI) signal intensities on magnetic resonance imaging (MRI). The T2WI sequence provides a better contrast of tumor to normal pancreatic tissue and is, therefore, better than the T1WI sequence for the diagnosis of insulinomas. These tumors are visualized as circular nodules with sharp margins on MRI. Enhanced T2WI fat-suppression sequence is the most optimal imaging protocol for insulinomas. The high-intensity signal of the adjacent fat tissue is converted into a low-intensity signal by the fat-suppression technique, which not only provides a much better contrast than conventional MRI but also aids the detection of smaller lesions. The diagnostic sensitivity of MRI for insulinomas ranges from 15% to 75%.<sup>[6,8]</sup>

### *Endoscopic ultrasonography*

Endoscopic ultrasonography (EUS) is a combination of the best features of ultrasonography and endoscopy. Ultrasonic probes can acquire images of the pancreas at close range through the stomach or duodenal cavity. The higher resolution and closer range of image acquisition guarantee better visualization of the pancreatic tissue. The sensitivity of EUS for the detection of insulinomas ranges from 65% to 100%.<sup>[6-8,10]</sup> Téllez-Ávila *et al.* reported in a study on the comparison of the efficacies of CT and EUS in the detection of insulinomas that the sensitivity and accuracy of EUS were 100% and 95.4%, while those of CT were 60% and 68%, respectively.<sup>[10]</sup> The sensitivity of EUS is dependent on the location of insulinomas. It is more sensitive for the detection of tumors located in the head region of the pancreas. The rates of detection of lesions located in the pancreatic head and body are reported to be much higher compared to those of lesions located in the pancreatic tail (80%–100% *vs.* 37%–60%).<sup>[13]</sup>

### *Digital subtraction angiography*

Since insulinomas usually have a rich blood supply, hypertrophic tumor vessels and tumor signals are visualized on digital subtraction angiography (DSA) images. The sensitivity of DSA for the detection of insulinomas ranges from 33% to 84.6%.<sup>[6]</sup> However, the application of this method for the diagnosis of insulinomas was discontinued because of its relatively high false-positive rates.

### *Intra-arterial calcium-stimulated venous sampling*

Intra-arterial calcium-stimulated venous sampling (ASVS) is a reliable method for the preoperative localization of insulinomas, especially in cases where noninvasive procedures have failed to localize the lesions. This technique was first described by Doppman *et al.* in 1991.<sup>[14]</sup> Catheters are inserted through a femoral venous puncture to evaluate blood insulin levels in the right hepatic vein. A fundamental value of insulin level is noted. Following this, the gastroduodenal, superior mesenteric, splenic, and hepatic arteries are selectively cannulated in turn. Calcium gluconate is rapidly injected into the above-mentioned arteries. Blood insulin levels are evaluated at 30, 60, and 120 s after the injection of calcium gluconate through the hepatic vein. A peak insulin level twice the fundamental value is considered being indicative of positive result. Calcium ions stimulate the insulinomas to rapidly secrete insulin, and consequently, the lesions can be regionalized in

the pancreatic head, body, or tail, each of which is supplied by their corresponding arteries. The sensitivity of ASVS for the detection of insulinomas ranges from 87.5% to 95%,<sup>[15]</sup> which is much higher compared to the sensitivities of other preoperative localization techniques. However, in addition to being expensive, ASVS is a traumatic experience. It, therefore, requires a high level of technology and is considered as the modality of the second choice for the preoperative localization of insulinomas.

#### *Percutaneous transhepatic portal catheterization sampling*

The sensitivity of percutaneous transhepatic portal catheterization sampling for the detection of insulinomas is reported to be around 88%.<sup>[16]</sup> It is a traumatic and expensive diagnostic modality, with lower sensitivity than ASVS, leading to it being replaced by the latter.

Altogether, clinical examination by transabdominal ultrasonography, CT, or MRI is the first step in the preoperative localization of insulinomas. In case of failure of these diagnostic modalities, EUS should be performed. In case of failure of the above-mentioned nontraumatic procedures, ASVS should be considered for the localization of insulinomas. However, in the absence of the MEN-1 syndrome, the reliability of intraoperative diagnosis renders these preoperative localization modalities insignificant.<sup>[17]</sup>

### **SURGICAL MANAGEMENT OF INSULINOMA**

Insulinoma is treated surgically using open or laparoscopic surgical procedures. Open surgery was once considered as the standard approach for the treatment of insulinomas. The sensitivity of palpation in conjunction with intraoperative ultrasonography for the detection of insulinomas can be as high as 100%.<sup>[7,8,16-19]</sup> However, open surgery is a traumatic procedure and requires a large incision, which cannot satisfy the growing expectations of minimally invasive management of small-sized tumors.

The first case of laparoscopic resection of insulinoma was reported in 1996.<sup>[20]</sup> The first case of laparoscopic surgery for insulinoma in China was reported in 2002.<sup>[17]</sup> Since then, the feasibility of laparoscopic surgery for insulinoma has been proven by several studies, which have also reported the advantages of the procedure, such as the lack of necessity for parietal incision

and relatively high levels of postoperative comfort. In addition, the intraoperative blood loss levels and duration of hospitalization with laparoscopic surgery are lower compared to those with open surgery.<sup>[21-36]</sup>

Laparoscopic management of insulinoma is now considered feasible and safe for benign solitary tumors located in the body or tail regions of the pancreas.<sup>[37-40]</sup> Because of their location adjacent to the main pancreatic duct and mesenteric vessels, insulinomas located in the head region of the pancreas often require open surgery. Tumor localization in the dorsal parts of the pancreas, as well as the presence of multiple adenomas and nesidioblastosis, is considered as contraindications for laparoscopic surgery.<sup>[17]</sup>

The rate of pancreatic complications with laparoscopic resection is comparable to that with open surgery. According to the results of a meta-analysis, which compared the complication rates between patients who underwent open resection of insulinoma at the Mayo Clinic and those who underwent laparoscopic resection of insulinoma, as reported in English journals published between 1996 and 2009, 27% of the patients of the laparoscopic surgery group developed pancreatic complications, which was more often than the patients of the open group (15%). Pancreatic complications observed among the patients of the open surgery group included fistulae (11%), abscesses (2%), and pseudocysts (2%), while those among the patients of the laparoscopic resection group included fistulae (24%) and peripancreatic abscesses (3%).<sup>[41]</sup> Another single-institution study involving 292 cases of surgical resection of insulinoma also reported pancreatic fistulae as the most frequently observed complication; however, no statistically significant differences were observed between open and laparoscopic surgery in terms of blood loss, operative time, or rate of complications.<sup>[17]</sup> This indicates that differences in surgical skills among surgeons from different institutes might affect the quality of surgery and influence the outcomes of comparison between the two surgical methods. The authors of both the above-mentioned studies emphasized the use of laparoscopic ultrasonography as an alternative to palpation to increase the safety of laparoscopic resection of insulinoma, especially during enucleation.<sup>[17,41]</sup>

Shorter duration of hospitalization, quicker recovery, and better cosmetic effects are the potential advantages of laparoscopic management of insulinoma over open

surgery. However, the issue with the former method is the difficulty in the laparoscopic localization of the lesion because of the loss of tactile sensation. A conversion rate of 30% to open surgery was reported in a multicenter study on laparoscopic approaches for the treatment of solitary insulinoma; inability to localize the tumor led to conversion in 63% of the patients, among whom, 85.7% had not undergone laparoscopic ultrasonography.<sup>[42]</sup> Laparoscopic ultrasonography is an ideal and essential aid for the laparoscopic resection of insulinoma.

## EFFICACY OF LAPAROSCOPIC ULTRASONOGRAPHY

The use of laparoscopic ultrasonography for the intraoperative detection of insulinomas was first reported in 1993.<sup>[43]</sup> Laparoscopic ultrasonography is of great benefit in the management of insulinoma because of its advantages in terms of localization of the tumor and characterization of important adjacent anatomical structures, which is of vital importance in choosing the appropriate surgical method for resection and avoiding complications.<sup>[44-46]</sup>

Although insulinomas (excluding MEN-1) are mostly benign and solitary, they sometimes prove difficult to localize intraoperatively, despite the preoperative imaging data, because of their small size as well as depth and uncertainty of location beneath the pancreatic surface.<sup>[47]</sup> Manual palpation along with intraoperative ultrasonography is considered as the most effective method for the localization of tumors during open surgery. Intraoperative localization of tumors is even more critical during laparoscopic resection because of the relative difficulty in exploration as well as the infeasibility of palpation. Laparoscopic ultrasonography combines the best features of laparoscopic exploration and intraoperative ultrasonography and is, therefore, the best method for the localization of insulinomas, especially the occult ones, as well as the prevention of conversion to open surgery despite accurate preoperative localization.<sup>[42,48]</sup> Benign insulinomas present as round hypoechoic nodules, mostly <2 cm in diameter, with clear margins. They also present abundant blood flow signals in color Doppler images. The detection rate of insulinomas with laparoscopic ultrasonography can be as high as 96.9%.<sup>[49]</sup>

In addition, important anatomical structures, such as the main pancreatic duct and major arteries, can be

clearly visualized intraoperatively with laparoscopic ultrasonography, which might help prevent any accidental injury that might cause pancreatic complications.

The choices of appropriate surgical strategy are ultimately dependent on the precise location of the insulinoma as well as the relative condition of the adjacent structures. Enucleation is favorable in cases of superficial tumors located away from the pancreatic duct. Distal pancreatectomy is preferred for insulinomas located deep within the body or tail regions of the pancreas. Insulinomas located deep within the head region of the pancreas often require conversion to open surgery because of their proximity to the main pancreatic duct and mesenteric vessels as well as the technical difficulties in the management of these tumors by laparoscopy alone.<sup>[50]</sup> Thus, laparoscopic ultrasonography is more preferable for the localization of insulinomas located in the pancreatic body and tail regions.<sup>[51]</sup>

Laparoscopic ultrasonography ensures the feasibility of laparoscopic resection of insulinoma and reinforces its strength as a minimally invasive procedure.<sup>[52,53]</sup>

## LAPAROSCOPIC ULTRASONOGRAPHY TECHNIQUE

Laparoscopic ultrasonography for the detection of insulinomas is performed by Color Doppler imaging at frequencies ranging from 5.0 to 9.0 MHz. After induction of general anesthesia, artificial pneumoperitoneum is normally applied. A laparoscope is inserted through a trocar placed at the umbilical incision. Two more ports are made at the right upper and middle quadrants of the abdominal wall, which will later be used for the operation of the laparoscopic ultrasonography probe. After a window is established on the gastrocolic ligament, pancreatic parenchyma is imaged by placing the probe directly over the gland. The pancreatic parenchyma is scanned thoroughly for lesions, and the pancreatic duct and peripancreatic vasculature are assessed for proximity and possible local invasion. Adequate mobilization of the pancreas is required to obtain more detailed images of the body and tail regions of the pancreas. The pancreatic head region is scanned using a laparoscopic Kocher maneuver. Enucleation or distal pancreatectomy may later be performed based on the location of the insulinoma.

## LOCALIZATION EFFICACY OF LAPAROSCOPIC ULTRASONOGRAPHY

The average sensitivity of laparoscopic ultrasonography is around 90%, which is comparable to that of manual palpation in conjunction with intraoperative ultrasonography. In an Institutional Review Board-approved study, Grover *et al.*<sup>[54]</sup> reported the successful localization of 85.7% of the tumors by laparoscopic ultrasonography and 87.5% of the tumors by preoperative diagnostic methods (50% by noninvasive preoperative diagnostic methods, 78.6% by invasive preoperative diagnostic methods). Clinical examination by CT, MRI, transabdominal ultrasonography, and ASVS was performed preoperatively, and the surgeons involved were blinded to the preoperative results. The authors suggested that laparoscopic ultrasonography was equivalent to ASVS in terms of efficacy of localization of tumors.

Despite the high efficacy of laparoscopic ultrasonography for the detection of insulinomas, preoperative localization is still necessary to choose an appropriate surgical method and prevent complications.<sup>[55,56]</sup> In this regard, EUS is recommended, especially for the laparoscopic treatment of insulinoma, because of its relatively high sensitivity for the detection of insulinomas located in the pancreatic head region, which complements the major drawback of laparoscopic ultrasonography.<sup>[6,8,57,58]</sup>

## LATEST DEVELOPMENTS IN ASSOCIATED SURGICAL TECHNIQUES

With the prosperity in laparoscopic ultrasonography, modified laparoscopic resection of insulinoma with better cosmetic effect has now become possible. Shibao *et al.*<sup>[59]</sup> reported the first case of insulinoma treated by reduced port surgery. In this case, three laparoscopic trocars were individually inserted into the abdominal cavity through a 2.5-cm umbilical incision. From the left subcostal region, another trocar (3-mm) was inserted leaving only 2 minor visible scars after the surgery. Better cosmetic effect was achieved. The feasibility of this surgical method has since been validated.

Laparoscopic ultrasonography with the aid of newly developed surgical technologies can achieve more accurate intraoperative tumor localization, which is important, especially to insulinomas located deep within the head region of the pancreas. Needle-guided

laparoscopic enucleation of insulinomas was reported to be a beneficial improvement of the laparoscopic management of small tumors located deep within the pancreatic head region.<sup>[60]</sup> A more precise enucleation of the lesion can be performed by the intraoperative insertion of an 18-gauge needle into the lesion under the guidance of laparoscopic ultrasonography, which solves the technical difficulties in the laparoscopic management of insulinomas located in this particular region.

## CONCLUSION

Laparoscopic resection of benign and solitary insulinomas is safe, feasible, and produces better cosmetic effect. Laparoscopic ultrasonography is highly sensitive for the intraoperative detection of insulinomas. In conjunction with an effective preoperative localization method, particularly preoperative EUS, laparoscopic ultrasonography can be used as an alternative to manual palpation for the localization of insulinomas.

### *Financial support and sponsorship*

Nil.

### *Conflicts of interest*

There are no conflicts of interest.

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