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TOPIC HIGHLIGHT

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Pancreatic insulinomas: Laparoscopic management

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Abstract

Insulinomas are rare pancreatic neuroendocrine tumors that are most commonly benign, solitary, and intra-pancreatic. Uncontrolled insulin overproduction from the tumor produces neurological and adrenergic symptoms of hypoglycemia. Biochemical diagnosis is confirmed by the presence of Whipple's triad, along with corroborating measurements of blood glucose, insulin, proinsulin, C-peptide, β-hydroxybutyrate, and negative tests for hypoglycemic agents during a supervised fasting period. This is accompanied by accurate preoperative localization using both invasive and non-invasive imaging modalities. Following this, careful preoperative planning is required, with the ensuing procedure being preferably carried out laparoscopically. An integral part of the laparoscopic approach is the application of laparoscopic intraoperative ultrasound, which is indispensable for accurate intraoperative localization of the lesion in the pancreatic region. The extent of laparoscopic resection is dependent on preoperative and intraoperative findings, but most commonly involves tumor enucleation or distal pancreatectomy. When performed in an experienced surgical unit, laparoscopic resection is associated with minimal mortality and excellent long-term cure rates. Furthermore, this approach confers equivalent safety and efficacy rates to open resection, while improving cosmesis and reducing hospital stay. As such, laparoscopic resection should be considered in all cases of benign insulinoma where adequate surgical expertise is available.

Key words: Pancreatic insulinoma; Laparoscopic surgery; Technique; Outcomes; Minimally invasive surgery

Core tip: Insulinomas have always fascinated physicians and surgeons alike, due to the difficulties in: (1) diagnosing them; (2) obtaining accurate preoperative and intraoperative localization; and (3) actually performing

the operation safely and effectively. Laparoscopy stands out in the current literature as the approach of choice, and is employed for virtually all benign insulinomas. Enucleations for insulinomas in the head and body, as well as distal pancreatectomies for lesions in the body and tail of the pancreas, have been shown to be safe and effective in the current series. Laparoscopic intraoperative ultrasound localization has emerged as a standard adjunct to these procedures.

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INTRODUCTION

Insulinomas are insulin-secreting neuroendocrine tumors deriving from neoplastic pancreatic islet cells, and occurring almost exclusively in the pancreas[1,2]. They are gastroenteropancreatic neuroendocrine tumors (GEP-NETs) belonging to the subgroup of neuroendocrine tumors (NETs) known as pancreatic endocrine tumors (PETs)[3]. In contrast to other PETs, approximately 90% of insulinomas are sporadic, solitary, and benign, measuring less than 2 cm in diameter[1,2,4-6]. These characteristics, along with their highly symptomatic presentation, make complete surgical removal the treatment of choice for affected patients[2,7,8]. Surgical treatment options include tumor enucleation and regional pancreatic resection[8]. However, until recently, the only available approach was open surgery.

Laparoscopic enucleation and distal pancreatectomy were first reported in the 1990s by Gagner *et al*[9]. In fact, the small, benign, and solitary nature of insulinomas makes them ideal candidates for a laparoscopic approach, particularly in overweight or obese patients. In the last 20 years, several case reports[10,11] and case series[9,12-31], including our own[32-34], have explored the technical aspects of laparoscopic insulinoma resection. The results presented in these studies demonstrate the feasibility, safety, and reproducibility of laparoscopic insulinoma resection in experienced hands. Consequently, recently published guidelines now consider laparoscopic enucleation an appropriate treatment modality for the majority of insulinomas[8,35-37]. This article reviews the current status of laparoscopic insulinoma management and discusses both the strategic and technical aspects of surgical care in these patients.

BACKGROUND

Insulinomas are rare and exhibit a number of unique characteristics when compared to other PETs. These differences in the epidemiology, clinical features, and biological behavior of insulinomas impact significantly on their management and define the role and limitations of laparoscopic surgical intervention.

EPIDEMIOLOGY: SURGICAL MANAGEMENT OF RARE PATHOLOGY

The estimated annual incidence of insulinomas is 0.7-4 diagnosed cases per million persons[38]. Their rarity, combined with the unique challenges presented throughout the course from diagnosis to therapy, requires expert referral and management. Centralization of care is therefore of utmost importance for these patients, and tertiary referral to centers of excellence that follow a multidisciplinary approach is strongly advocated in current treatment guidelines[8,35-37]. The low incidence of insulinomas makes it difficult for any surgeon outside of pancreatic centers of excellence to gain sufficient experience in insulinoma resection[8,35-37]. Furthermore, although a laparoscopic approach is encouraged, the choice between open and laparoscopic surgery should be left to the discretion of the surgical team. It is therefore paramount that surgeons making such decisions are experienced in both open and minimally invasive procedures, in order to offer their patients the optimal treatment.

INSULINOMAS IN THE CONTEXT OF MULTIPLE ENDOCRINE SYNDROME TYPE 1

The vast majority of insulinomas are sporadic, but in 5%-10% of cases they present in the context of multiple endocrine syndrome type 1 (MEN1)[6,7]. MEN1-related insulinomas are frequently multifocal and coincide with several other pancreatic lesions (most commonly non-functioning pancreatic endocrine tumors)[6,39]. It therefore becomes very difficult preoperatively to determine with certainty the lesions for resection that are responsible for the clinical syndrome. This is further confounded by the fact that not all pancreatic lesions with immunohistochemically proven insulin production capacity produce clinical symptoms[39,40].

As such, it is both difficult to determine preoperatively the lesions responsible for the clinical syndrome and to definitively state whether surgical resection has been curative, even when insulin-producing lesions are documented in the pathology report. Consequently, significantly higher failure and recurrence rates are documented after surgery for MEN1-related insulinomas when compared to sporadic lesions[39,41].

In view of the difficulty in achieving complete clearance, a more radical surgical approach is preferred in MEN1-associated insulinomas[39,41,42]. Current surgical practice depends on the site of the tumor. For distal lesions, distal pancreatectomy with or without splenic preservation is required. Proximal tumors located in the pancreatic head may be enucleated, but total pancreatectomy may be required in selected

cases[35,36,39,41-44]. Local resections are not routinely indicated, despite some recently promising results in selected solitary or dominant lesions[45]. Moreover, the procedure of choice should be decided after careful preoperative localization, and take into account the need for symptom alleviation (*i.e.*, complete resection of all insulinomas), the malignant potential of all existing pancreatic lesions (including, but not limited to, insulinomas), and the expected complications, together with the existence of any previous surgical attempts. It is notable that laparoscopic resection in the context of MEN1 requires advanced minimally-invasive surgical skills due to the inherent difficulties of laparoscopic distal pancreatectomy, particularly where combined enucleations in the head of the pancreas are required. Finally, it should be mentioned that, in our recent experience, enucleation of single lesions in the head of the pancreas in the context of MEN has been successful in rendering the patient asymptomatic 12 mo after surgery.

BIOLOGICAL BEHAVIOR

Although the majority of insulinomas are benign and curable by surgical resection, approximately 5%-10% show malignant behavior[38]. However, with an annual incidence of approximately 0.1 per million persons per year[46], malignant insulinomas are extremely rare. Similar to all other neuroendocrine pancreatic tumors, the malignant potential of insulinomas is assessed by tumor differentiation (extent of resemblance to normal cells), grade (degree of biologic aggressiveness), and stage (extent of tumor spread)[47]. Of note, although a number of different pathological grading and clinicopathologic staging classifications have been suggested, no single system has been universally adopted[47].

Local invasion and/or evidence of liver metastases clearly demonstrate malignancy[7]. However, in the absence of these findings, malignant behavior must be determined from the pathologic characteristics of preoperative tissue biopsies when they were taken, because in most cases, EUS-guided Fine Needle Aspiration is performed at most. Although the course of malignant insulinomas is more indolent than other malignant neuroendocrine pancreatic tumors, the median survival is only 2 years, while the 10-year survival rate is only 29%[5,6,48]. Although, in some cases, malignant insulinomas have been reported with higher survival rates[49], this prognosis remains significantly poorer than for benign insulinomas, which present a 95%-100% surgical cure rate[5-7,48].

These key facts define the role and the limitations of both laparoscopic and open surgery in patients with malignant insulinoma. However, it is possible that extensive surgical resection of the primary tumor, affected lymph nodes, and distant metastases may provide alleviation for hypoglycemia and long-term survival when combined with adjunctive therapy such as medical treatment, radiofrequency ablation, transarterial chemoembolization, somatostatin analogues, chemotherapy, or biological agents. In resectable malignant disease, surgical options may provide a cure, and include distal pancreatectomy, pancreaticoduodenectomy with or without metastasectomy, segmentectomy, formal hepatectomy, or even liver transplantation[6,30,36,37,49,50]. Where the disease is unresectable in its entirety, debulking surgery may provide symptomatic relief when combined with medical and ablative therapy. Whenever malignancy is determined preoperatively, these operations are performed exclusively *via* laparotomy. Laparoscopic resection is not routinely practiced and no guidelines currently exist as to the role of laparoscopic intervention in these cases. Conversely however, in some cases the malignant potential of an insulinoma may only be acknowledged after laparoscopic resection as a result of specimen histology, symptom recurrence, and/or metastasis development during follow-up. In these cases, a multidisciplinary assessment is mandatory, and is most commonly followed by secondary radical open resection in combination with adjunctive therapy.

CLINICAL SYMPTOMS AND BIOCHEMICAL DIAGNOSIS

Insulinomas most commonly present with hypoglycemia caused by inappropriate excessive endogenous insulin production. Physical exercise and fasting usually provoke the symptoms, which fall in two major categories: Neurologic and adrenergic[4,6,7,43,51]. Neurologic symptoms are attributed to the effects of low blood glucose on the nervous system (neuroglycopenia) and include visual disturbances (diplopia and blurred vision), altered mental status, abnormal behavior, seizures, amnesia, and even coma[4,6,7,43,51]. Adrenergic symptoms are attributed to reactive catecholamine overproduction and include nausea, excessive sweating, anxiety, palpitations, weakness, tremors, increased appetite, and heat intolerance[4,6,7,43,51]. Each patient usually reports a specific collection of symptoms[52,53], which are relieved almost immediately after carbohydrate consumption, a feature that is included in Whipple's diagnostic triad[54]. Furthermore, the combination of weakness and increased appetite, alongside the ability of carbohydrate consumption to act as a relieving factor, frequently leads to excessive calorie consumption, weight gain, and eventual obesity[4,43,51].

When there is clinical suspicion of insulinoma, the autonomous overproduction of endogenous insulin must be confirmed biochemically. The basis of this diagnosis is the Whipple's triad[54] of biochemically-proven hypoglycemia, hypoglycemic symptom development, and swift reversal after carbohydrate consumption that occurs during a supervised fasting period. When symptoms occur concurrently with hypoglycemia (glucose levels around or below 2.2 mmol/L), increased insulin ($\geqslant$ 6 μIU/mL with standard non-specific insulin radioimmunoassay or $\geqslant$ 3 μIU/mL

with immunoradiometric or immunochemiluminescent insulin specific assays which are devoid of cross-reactivity for proinsulin and proinsulin-like components), proinsulin (≥ 5 pmol/L), and C-peptide (≥ 200 mmol/L) levels, this suggests the presence of an autonomous source of insulin production which is insensitive to hypoglycemia[1,8,43]. In order to rule out the presence of exogenous insulin (factitious hypoglycemia), a negative sulfonylurea/meglitinide screen test is also required that corroborates with the increased levels of C-peptide[1]. Surrogate markers of insulin presence, including low β-hydroxybutyrate levels (no more than 2.7 mmol/L) and a generous rise of glucose levels (more than 1.4 mmol/L) after the administration of 1 mg glucagon at the end of the fasting period[55], have been used by some authors for decades[56], especially for patients in which their blood glucose does not fall below 2.5 mmol/L during fasting. Indeed, β-hydroxybutyrate levels have now been included in recent guidelines[8,57], despite recent contradicting reports[58].

The actual cut-off points for insulin during fasting vary throughout the literature[52,59-61]. The reasons for this variation are complex and reflect both the altered biochemistry of insulin produced by insulinomas (increased proinsulin and proinsulin-like components, as well as insensitivity *vs* partial sensitivity of insulinomas to hypoglycemia) and the inherent limitations of detection assays (minimum detection levels and non-specificity to insulin in older radioimmunoassays). As such, despite a general agreement in the published cut-off values for insulinoma diagnosis, it is likely that this will remain a matter of contention. In fact, results from a recent comparative study have demonstrated proinsulin levels exceeding 5 pmol/L to be a more reliable diagnostic test for endogenous hyperinsulinism than absolute insulin levels at the time of hypoglycemia (< 2.5 mmol/L)[62]. Subsequent to this study, proinsulin measurement has since been recognized in recent consensus guidelines[8].

Practically, it is important to also consider the duration of these fasting tests when providing a biochemical diagnosis of endogenous hyperinsulinism. Traditionally, the gold standard has been a 72-h supervised inpatient assessment[52,53]. More recently however, modern insulin and pro-insulin specific assays have shown that a fasting period of 48 h is sufficient[60]. The lower cost and reduced invasiveness of this 48-h test have led to its rapid uptake across many institutions, thereby providing a new standard of care[1,43] that is reflected in updated diagnostic guidelines[8,57].

Surgeons currently have a limited role in the diagnosis of insulinoma, as this is usually confirmed prior to surgical referral. However, this by no means obviates the need for careful clinical assessment and thorough review of the patient's records and biochemistry prior to intervention. In a recent study, out of 17 patients referred to the United States National Institute of Health after a failed blind distal pancreatectomy, 5 were eventually diagnosed as having factitious hypoglycemia[63]. These patients underwent completely unnecessary major surgery. It is therefore the surgeon's professional and ethical responsibility to comprehend and fully agree with the diagnosis of insulinoma prior to undertaking any surgical intervention.

PREOPERATIVE AND INTRAOPERATIVE LOCALIZATION

Once biochemical diagnosis of insulinoma has been confirmed, the next important and demanding task is to accurately determine the location of the lesion within the pancreas[1,2,4-6,48]. In the past, surgeons were reliant on blind distal pancreatectomies for occult impalpable insulinomas due to limited imaging and diagnostic tools[64-66]. However, blind distal pancreatectomy was associated with a high failure rate (> 20%) that was exaggerated by the fact that non-palpable insulinomas often reside in the thicker pancreatic head[63]. Over the past 25 years, novel diagnostic modalities have rendered this blind approach obsolete[67] in favor of targeted resection.

Although in the past open surgeons had often bypassed preoperative localization in favor of intra-operative palpation and ultrasound (IOUS)[64-66], this approach was never widely adopted[1,53,67,68] and is certainly unacceptable for laparoscopy. Reliance on laparoscopic intraoperative ultrasound (LIOUS) alone led to open conversion in one of every three cases[16]. As a result, more recent series[17-19,31], including our own, reflect the current guidelines advocating accurate localization prior to laparoscopic surgical intervention[8]. We strongly advise against laparoscopic intervention without accurate preoperative localization[32] for a number of reasons: Firstly, the lack of intraoperative tactile feedback removes the ability to assess the tumor by palpation; secondly, patient positioning and trocar placement is determined by the location of the tumor; and finally, whilst LIOUS is a mandatory intraoperative adjunct for accurate localization and delineating regional anatomy, it is certainly not a diagnostic tool. Furthermore, the prolonged time required and inability to apply the probe to the whole pancreas without additional port placement limits its diagnostic role. Appropriate use of LIOUS requires knowledge of the regional location of the tumor (head, uncinate process, body, or tail) from preoperative investigations. In this way, the surgeon may utilize this tool to exactly locate and delineate the anatomic relationships of non-palpable lesions. It is the failure of accurate preoperative imaging that makes some authors use LIOUS to detect undiagnosed lesions or those found not to be located in the area indicated by preoperative assessment[9,16,69]. However, it is our opinion that this use limits the diagnostic yield of LIOUS, making it much lower than when used in conjunction with accurate preoperative localization. As such, we believe that accurate preoperative localization is a requirement of the laparoscopic approach. Failure to adequately assess tumor location should initially lead to repeat imaging and reassessment in an attempt

to improve localization accuracy. However, where this fails, surgeons should reconsider the appropriateness of laparoscopic intervention.

STRATEGY FOR PREOPERATIVE LOCALIZATION

There is no consensus on either the optimal type of preoperative localization modalities or on the exact order in which they should be performed. Recent guidelines suggest that non-invasive imaging should be performed first[8,35-37,57], and should include one or two from the following: transabdominal ultrasound (US), computerized tomography (CT), and magnetic resonance imaging (MRI). These modalities are usually readily available and, with the recent addition of contrast enhancement (CE), have been reported to have a high sensitivity in insulinoma detection (about 90% for CE US[70] and about 100% for CE CT and MRI[71]). However, due to variation in technology and radiological expertise, not all institutions may be able to achieve such excellent detection rates. In our experience, transabdominal unenhanced ultrasound has been associated with a sub-optimal diagnostic yield and, as such, we do not routinely employ this modality in our preoperative assessments. Although this approach is in line with recent guidelines[35-37,57], it is contrary to the reports of some authors who have had excellent results from the use of US[7].

Failure to obtain diagnosis through CT or MRI should lead to further assessment using endoscopic ultrasound (EUS)[8,35-37,57]. Although this modality is invasive, operator dependent, and of limited availability, it may yield an accuracy exceeding 90%[72,73], and is thus now advocated in all established guidelines[8,35-37,57]. As EUS performs better in the head, but less well in the body and worse in the tail of the pancreas[74,75], it may be considered a complementary modality to CT[73], which may miss lesions in the pancreatic head[76]. Notably, in our experience, lesions of greater tumor density are best detected on the arterial phase of the CT.

Following these investigations, the next test we routinely employ is selective pancreatic angiography with venous sampling after intra-arterial calcium stimulation (ASVS)[67,77]. Although highly invasive, ASVS is associated with a sensitivity of approximately 95% and is indispensable when previous tests are equivocal. ASVS allows hypervascular insulinomas to be detected by arteriography, with added regional localization in difficult cases through stimulated venous sampling. Using this technique, localization can be determined according to the arterial branch injected. The presence of insulinoma in a particular territory is indicated by a greater than two-fold elevation in insulin levels (sampled at 30 and/or 60 s from the hepatic vein) on calcium gluconate stimulation[78]. The use of ASVS is now widespread[7,79] and is included in most[8,36,37,57], but not all[35], recent guidelines.

Whilst other authors advocate the use of PET/CT[80] and SPECT/CT[81], this is not routine practice in our experience, as both techniques remain investigational[8]. However, promising results have recently been reported with glucagon-like peptide-1 (GLP-1) analogue SPECT/CT[82] imaging. Insulinomas are known to overexpress GLP-1 receptors in high density[83], thus overcoming the limitations of somatostatin-like tracers. The high selectivity of GLP-1 receptor agonists and their high affinity for insulinoma cells provides a promising future for preoperative insulinoma localization, and is likely to have increasing clinical importance with the development of novel tracers and improved imaging diagnostics[84].

SURGICAL DECISION-MAKING

Multidisciplinary assessment should form the cornerstone of insulinoma management. However, prior to intervention, the surgeon must be certain of both the biochemical diagnosis and localization of the insulinomas. Where results remain equivocal, we strongly advocate further testing or repeat imaging until adequate information is provided.

A summary of our surgical decision-making is shown in Figure 1. Of note, although we do not recommend enucleation of lesions less than 2 mm (preferably 3 mm) from the main pancreatic duct (MPD) or portal vein (due the risk of pancreatic fistula), solitary lesions in the head close to the MPD should be considered an exception, as the only alternative is a duodenopancreatectomy.

Malignant insulinomas are generally not amendable to laparoscopic surgery[7,8,35,49,50]. In these cases, resection of liver metastases ideally precedes excision of the pancreatic lesion[35], and the resultant extensive adhesions preclude a laparoscopic approach. When suspicion of malignancy is raised during planned laparoscopic surgery (Table 1), we prefer to convert to open resection[85-87], however we do acknowledge the work of other surgeons who advocate laparoscopic resection of malignant lesions[26].

In the context of MEN1, we follow a conservative but widely-accepted approach[8,37], due to the increased failure and reoperation rate inherent in the resection of MEN1-related insulinomas[43]. However, laparoscopic management of insulinomas in the context of MEN1[20,88,89] is possible in appropriate cases, particularly where only a single lesion is identified preoperatively. Where multiple lesions are present, distal pancreatectomy combined with multiple enucleations of pancreatic head lesions may also be considered. However, the laparoscopic approach to MEN1-related insulinomas is not currently widely accepted, and it should also be noted that MEN1 is considered a contraindication to laparoscopy in several large comparative series[30,31]. As mentioned previously, in our recent experience, enucleation of a single lesion in the pancreatic head has been successful in a single case.

Table 1 Features suggestive of malignant insulinoma[43]

Features suggestive of malignant insulinoma
Hard lesions
Infiltration of the surrounding pancreatic parenchyma
Evidence of tissue scarring
Major pancreatic duct dilatation

Contrary to several other published studies[16-18,21,29], we routinely perform laparoscopic enucleation of solitary pancreatic head insulinomas, not only for protruding lesions, but also for those embedded in the parenchyma, provided there is sufficient distance from the main pancreatic duct and the portal vein (Figure 1). We appreciate that some authors have expressed concern over the high complication rates in these cases[90], however we do believe that enucleation has a valuable role to play in the treatment of solitary lesions of the pancreatic head and uncinate process. Exposure is of paramount importance when dealing with pancreatic head and uncinate process insulinomas, however there are a number of techniques that can be employed to provide direct access to the posterior aspect of both[33,91]. Such approaches minimize unnecessary damage to the pancreatic parenchyma and the subsequent risk of complications.

Non-visible lesions embedded in the pancreatic head present a particular challenge, and classically have been treated with multiple extensive pancreatotomies. However, we have recently described a technique similar to wire-guided breast biopsy, which may enable the surgeon to accurately localize and laparoscopically resect these difficult insulinomas[34], thus minimizing the number and size of pancreatotomies. Assisted by LIOUS, an 18 G fine-needle may be inserted directly into the lesion to act as a probe, accurately defining the position of the insulinoma. The parenchyma of the pancreas can subsequently be divided following the needle, until the dome of the insulinoma is identified and a localized resection is performed[34].

The decision to plan a distal pancreatectomy over enucleation based on preoperative data is a rather difficult one. For lesions > 3 mm away from the pancreatic duct, enucleation is always the procedure of choice; however, we have a low threshold for distal pancreatectomy, and the more distal the position of the insulinoma, the greater the likelihood that this will be required. This is evident in several series[19,29-31] and is a natural consequence of the fact that the metabolic effects of added resection become less as the pancreatic parenchyma becomes thinner towards the tail.

TECHNICAL CONSIDERATIONS

Patient positioning can either greatly assist or hinder laparoscopic resection, and is thus crucially important to surgical set-up. For lesions in the anterior aspect of the head, isthmus, and body/proximal tail of the pancreas, the patient may be placed in a supine position with an anti-Trendelenburg tilt. A right tilt (left side up) is applied for lesions in the body/proximal tail of the pancreas. For lesions of the posterior aspect of the pancreatic head, both supine[12] and left semi-lateral positions have been reported in the literature[88]. In our experience, a full left lateral position is preferable, especially when combined with a retroduodenal and retropancreatic approach to the lesion following full kocherization[33]. We prefer this to the gastrocolic ligament approach proposed by other authors[88]. For lesions in the distal pancreatic tail, positioning may be either supine with a right tilt, right semi-lateral, or right full lateral. The choice of position for these lesions is therefore a matter of personal preference, similar to that with laparoscopic splenectomy[91]. Our practice is the right full lateral position because: (1) the chances of a distal pancreatectomy for lesions located in this area are higher and a right table tilt always facilitates this procedure; and (2) this position can easily be changed to semi-lateral with a generous left table tilt, giving the surgeon the liberty to choose between an anterior approach of the tail without spleen mobilization and a posterior one with full medial mobilization of the spleen.

Similarly, the number and position of trocar placements is at the discretion of the operating surgeon and varies throughout published reports[12,17,24,26,91]. Generally, we use a standard array of five ports: the first for the laparoscope at the center of the operating field, then two working ports for the surgeon on each side of the first, one laterally to the surgeon's right hand for the assistant, and one 5 mm in the epigastric area for a Nathanson liver retractor. For lesions in the posterior aspect of the pancreatic head where retraction of the kidney is sometimes required, a sixth trocar may be introduced to accommodate a second liver retractor for this purpose[33].

Gaining wide access to the pancreatic region of interest is of utmost importance in order to provide adequate space for surgical maneuvers and instruments such as the LIOUS probe and endoscopic stapler. For insulinomas of the posterior aspect of the pancreatic head, full mobilization of the hepatic flexure and the placement of two Nathanson liver retractors (one for the liver and possibly one for the right kidney) greatly facilitates surgical access[33]. On the other hand, for insulinomas of the anterior aspect of the pancreatic head, body, and tail, mobilization of the splenic flexure and retraction of the stomach to access the lesser cavity serves the same purpose.

After adequate mobilization of the pancreatic region of interest, the next step is LIOUS performed by a dedicated radiologist. This forms an integral part of laparoscopic insulinoma resection, as it not only allows for accurate localization of the lesion, but also outlines the surrounding anatomy in terms of tumor size, local invasion, and distance from the pancreatic duct and/or portal vein. If the combination of careful inspection and thorough LIOUS evaluation fails to adequately localize or characterize the insulinoma, we advocate that further

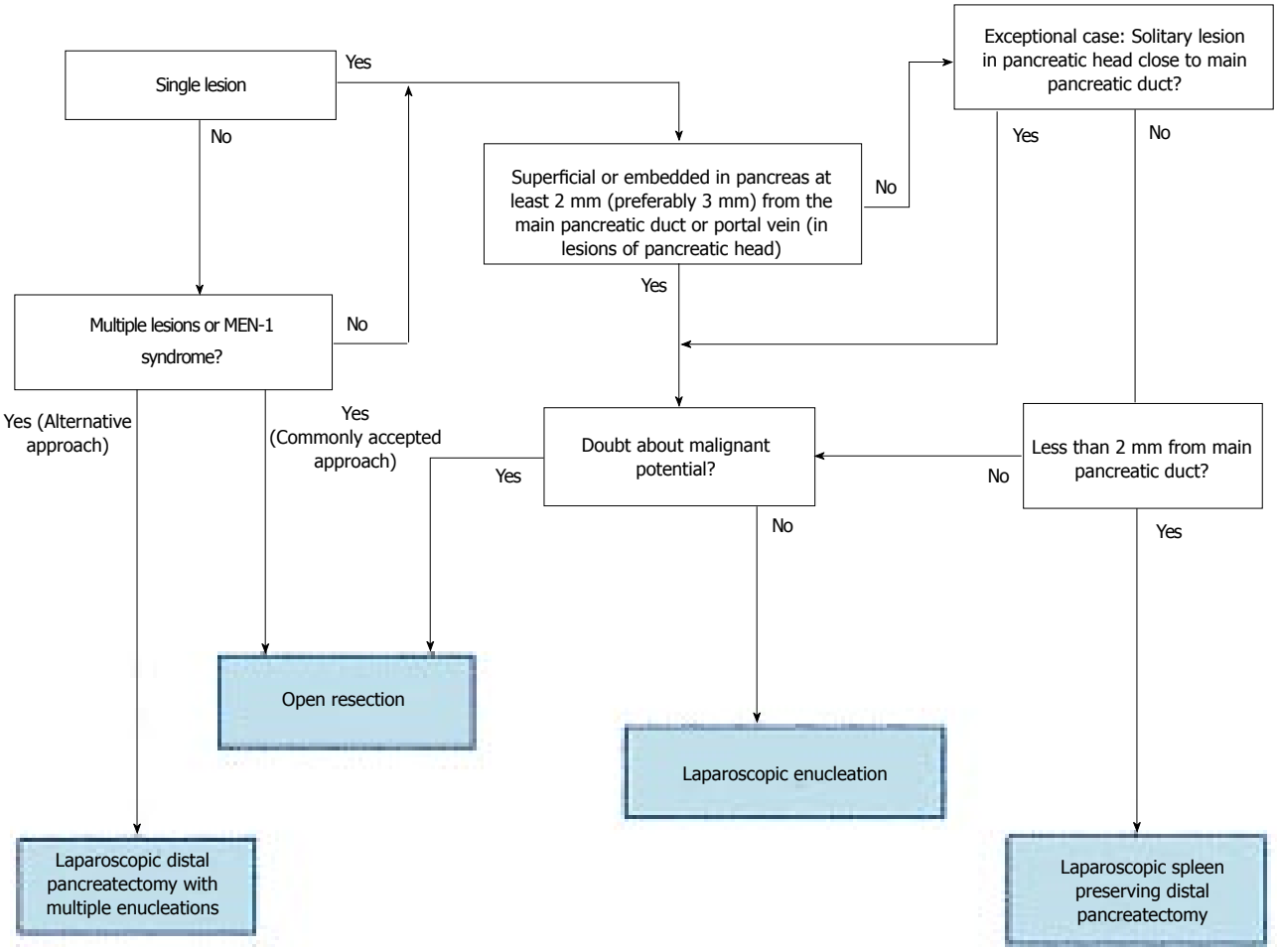

Figure 1 Flow chart demonstrating our surgical decision-making in pancreatic insulinomas. MEN-1: Multiple endocrine syndrome type 1.

surgical intervention be postponed in favor of repeat imaging and biochemical testing[92].

Once accurate intraoperative localization has been determined, surgical dissection is straightforward and performed with hook electrocautery and/or ultrasonic dissection. Generally, this is greatly helped by the placement of a traction suture through the insulinoma, which then can be exteriorized using an Endo Close. For lesions embedded in the pancreatic parenchyma but amenable to enucleation (Figure 1), the shortest route is chosen for dissection in order to minimize surgical trauma to the normal pancreatic parenchyma. As previously described, the LIOUS-guided placement of a fine needle in the center of the insulinoma greatly facilitates this dissection, which may be further aided by the placement of additional traction sutures to progressively open the pancreatotomy. Again, when the dome of the insulinoma becomes apparent, a further traction suture may be placed to improve the ease of enucleation.

For lesions in the body/tail of the pancreas that are not amendable to enucleation, the procedure of choice is spleen-preserving distal pancreatectomy. Careful dissection is necessary to avoid bleeding, particularly in the groove of the pancreas in which the pancreatic vein lies. In the event of inadvertent injury to the splenic vessels, if the left gastroepiploic and short gastric vessels remain intact, splenectomy can be avoided in favor of spleen-preserving distal pancreatectomy without splenic vessel preservation. However, where the left gastroepiploic and the short gastric vessels are not preserved, splenectomy is mandated. Division of the pancreas is usually carried out with an endoscopic linear stapler, combined with either oversewing the entire staple line or selectively oversewing the main pancreatic duct.

LAPAROSCOPIC SURGICAL OUTCOMES IN INSULINOMA MANAGEMENT

Due to the rarity of insulinomas and the retrospective nature of published series, it is difficult to extract robust data on the outcomes of laparoscopic insulinoma resection. Furthermore, these results have often been grouped with other pancreatic NETs and/or pancreatic tumors (*e.g.*, cystadenoma) making it impossible to separate insulinoma specific outcome data[9,17,85,89,93]. This is likely to be as a result of the small number of cases reported in early series and from the collective approach to tumor categorization later employed by major governing bodies and reflected in

published guidelines[8,35-37]. Whilst this classification is taxonomically accurate, it produces difficulties when studying insulinoma-specific outcomes, as insulinomas exhibit very distinct characteristics to other PETs and non-endocrine pancreatic tumors. Fortunately, however, the intriguing nature of these tumors has resulted in a number of laparoscopic case series specific to insulinomas[7,12-16,19-23,28,32], as well as those in the context of other PETs[26] and those comparing open and laparoscopic cases[18,24,25,27,29-31]. Furthermore, a recent meta-analysis comparing safety outcomes between laparoscopic and open approaches has been published[94].

The majority of published series[14,15,18-22,24-32] report established preoperative localization in > 90% of patients, with very few exceptions[12,16]. This highlights that preoperative localization has now become common practice, rather than the sole reliance on intraoperative LIOUS. Furthermore, this practice has increased the intraoperative accuracy of LIOUS to almost 100%, as well as almost eliminating inadequate localization as a cause for open conversion in the majority of cases[14,15,20-22,26,28,32]. Conversely, it is also notable that series reporting low preoperative localization rates[12,16] or limited use of LIOUS[19] also often describe inadequate localization as a common reason for conversion.

Median operative time is between 2 and 3.5 h, and varies significantly in published series[12,14-16,19-22,26,28,32]. However, these figures may be somewhat misleading due to small patient numbers and significant outliers. For example, in our own experience, operating time demonstrates a broad range from 25 to 420 min, with a median of 120 min[32]. Furthermore, although comparative studies demonstrate, as expected, that laparoscopic procedures take longer than their open counterparts[18,24,31] and that enucleation may be performed in a shorter time than distal pancreatectomy[16,19,20,28], this was not evident when pooled operative time was examined in the aforementioned meta-analysis[95].

Estimated median blood loss during laparoscopic insulinoma resection is limited and varies between 50 and 300 mL. Notably, however, there was no reported requirement for blood transfusion[12,15,28,32], and laparoscopic procedures resulted in significantly reduced blood loss when compared to open procedures[18,25,29,30,95]. Again, however, it is important to consider these results in the context of small sample numbers.

Laparoscopic treatment of insulinomas is safe and accompanied by minimal mortality in almost all published series[12,14-16,19-22,26,28,32]. Morbidity, on the other hand, may be high, and is reported to vary between 15% and 77%[12,14-16,18-22,24-32]. The most common complication is pancreatic fistula[95], however these are usually simple to manage and commonly resolve spontaneously within 2-3 wk. Nonetheless, in rare cases, specific treatment, drainage, or reoperation may be required. Importantly, the aforementioned recent meta-analysis has highlighted that laparoscopic insulinoma resection is not associated with a higher rate of fistula formation compared to open surgery[94]. Surgical precautions to avoid fistula formation first and foremost require respect for the minimum distance between the insulinoma and main pancreatic duct. Secondly, it is paramount to limit tissue damage by avoiding unnecessary dissection and keeping electrocautery heat production to a minimum. Oversewing the transection line after distal pancreatectomy and suture closure, or fibrin glue application to the site of enucleation, may also reduce fistulation, however in no cases do these measures counterbalance lacerations in the pancreatic duct, extensive destruction of the parenchyma, or inappropriately applied staples.

The length of in-hospital stay after laparoscopic insulinoma resection is difficult to determine, due to the inherent differences in institutional protocols and because patients from far away can be referred to a tertiary center. Indeed, uncomplicated laparoscopic resection required a hospital stay of one to two days in some studies[16,22,32], while patients remained hospitalized for 5-7 d in others[18,21]. However, it is notable that laparoscopic procedures are associated with a significantly shorter overall hospital stay than open procedures (without significant heterogeneity) when pooled data from directly comparative studies are meta-analyzed[94].

Importantly, laparoscopic insulinoma resection is associated with good long-term outcomes. In fact, whilst some series report long-term normoglycemia to be maintained in at least 95% of cases[24,25,30,31], others demonstrate a long-term cure rate of 100%[12,14,19-22,26,28,32].

CONCLUSION

Insulinomas are rare pancreatic neuroendocrine tumors that may be definitively cured with surgical resection. A dedicated multidisciplinary assessment is paramount prior to surgical intervention and should include thorough clinical and biochemical diagnosis. Localization of the tumor should be achieved through an array of non-invasive (US, CT, and MRI) and inevitably some invasive (EUS and AVSV) investigations, and the subsequent decision to undertake laparoscopic resection should only be made by an experienced laparoscopic pancreatic surgeon. For solitary benign insulinomas, laparoscopic enucleation suffices irrespective of location, provided the lesion lies a safe distance from the pancreatic duct and associated large vessels. Where these conditions are not met, laparoscopic distal pancreatectomy is advisable for lesions of the body/tail of the pancreas. This decision should be aided by LIOUS, which forms an indispensable part of any laparoscopic resection. In this way, localization of the lesion can be confirmed intraoperatively, and the tumor can be clearly delineated from adjacent structures. From a technical perspective, it is paramount to ensure ample access to the operating field in order to minimize damage to the

normal parenchyma, pancreatic duct, and associated vessels. Although no prospective randomized trials exist comparing laparoscopic and open approaches to insulinoma resection, case series, comparative series, and a recent meta-analysis supports the notion that laparoscopic resection is equally as safe and effective as an open approach. Moreover, laparoscopic intervention may not only improve cosmesis, but also reduce post-operative stay. Further large series and comparative studies are required in order to establish the true potential for laparoscopic resection and to continue to advance both diagnostic and technical aspects of surgical insulinoma management.

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