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**Pancreatic insulinomas: laparoscopic management**

Antonakis P *et al*. Laparoscopic resection for pancreatic insulinomas

Pantelis Antonakis, Hutan Ashrafian, Alberto Martinez-Isla

**Pantelis Antonakis,** Department of Surgery, Athens Euroclinic, Athens 11521, Greece

**Hutan Ashrafian, Alberto Martinez-Isla,** Northwick Park and St Mark’s Hospital, North West London Hospitals NHS Trust, Watford Road, Harrow, Middlesex, London HA1 3UJ, United Kingdom

**Hutan Ashrafian,** The Department of Surgery and Cancer, Imperial College London, 10th Floor QEQM Building, St Mary’s Hospital, Praed Street, W2 1NY, United Kingdom

**Author contributions:** Martinez-Isla a is lead laparoscopic surgeon, designed the concept and drafted the manuscript; Antonakis p and Ashrafian h researched and drafted the final manuscript.

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**Correspondence to: Alberto Martinez-Isla, FRCS, Consultant Surgeon,** Department of Upper GI Surgery, Northwick Park Hospital, North West London Hospitals NHS Trust, Watford Road, Harrow, Middlesex, London HA1 3UJ, United Kingdom. a.isla@imperial.ac.uk

**Telephone:** +44-208-4532619

**Fax:** +44-208-2425912

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**Abstract**

Insulinomas are rare pancreatic neuroendocrine tumours that are most commonly benign solitary and intra-pancreatic. Uncontrolled insulin overproduction from the tumour produces neurological and adrenergic symptoms of hypoglycaemia. 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 hypoglycaemic agents during a supervised fasting period. This is accompanied by accurate preoperative localization using non-invasive and invasive imaging modalities. Following this, careful preoperative planning is required and where possible the procedure should be carried out laparoscopically. An integral part of the laparoscopic approach is the application of laparoscopic intraoperative ultrasound, which is indispensable for the accurate intraoperative localization of the lesion in the pancreatic region. The extent of laparoscopic resection is dependent on preoperative and intraoperative findings, however most commonly involves tumour 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 to open resection whilst 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

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**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 the body, and distal pancreatectomies for lesions in the body and the tail of the pancreas have shown to be safe and effective in 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 tumours deriving from neoplastic pancreatic islet cells, and occurring almost exclusively in the pancreas[[1](#_ENREF_1),[2](#_ENREF_2)]. They are gastroenteropancreatic neuroendocrine tumours (GEP-NETs) belonging to the subgroup of neuroendocrine tumours (NETs), known as pancreatic endocrine tumours (PETs)[[3](#_ENREF_3)]. In contrast to other PETs, approximately 90% of insulinomas are sporadic, solitary, and benign, measuring less than 2cm in diameter[[1](#_ENREF_1),[2](#_ENREF_2),[4-6](#_ENREF_4)]. These characteristics, along with their highly symptomatic presentation, make complete surgical removal the treatment of choice for affected patients[[2](#_ENREF_2),[7](#_ENREF_7),[8](#_ENREF_8)]. Surgical treatment options include tumour enucleation or regional pancreatic resection[[8](#_ENREF_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](#_ENREF_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](#_ENREF_10),[11](#_ENREF_11)] and case series[[9](#_ENREF_9),[12-31](#_ENREF_12)], including our own[[32-34](#_ENREF_32)], 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](#_ENREF_8),[35-37](#_ENREF_35)]. 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 behaviour 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-years[[38](#_ENREF_38)]. Their rarity combined with the unique challenges presented throughout the course from diagnosis to therapy requires expert referral and management. Centralisation of care is therefore of utmost importance for these patients, and tertiary referral to centres of excellence that follow a multidisciplinary approach is strongly advocated in current treatment guidelines[[8](#_ENREF_8),[35-37](#_ENREF_35)]. The low incidence of insulinomas makes it difficult for any surgeon outside of pancreatic centres of excellence to gain sufficient experience in insulinoma resection[[8](#_ENREF_8),[35-37](#_ENREF_35)]. 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 MEN1**

The vast majority of insulinomas are sporadic, but in 5%-10% of the cases they present in the context of the multiple endocrine syndrome type 1 (MEN1)[[6](#_ENREF_6),[7](#_ENREF_7)]. MEN1 related insulinomas are frequently multifocal and coincide with several other pancreatic lesions (most commonly non-functioning pancreatic endocrine tumours)[[6](#_ENREF_6),[39](#_ENREF_39)]. It therefore becomes very difficult pre-operatively to determine with certainty the lesion(s) to be resected 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](#_ENREF_39),[40](#_ENREF_40)].

As such, it is both difficult to determine pre-operatively 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](#_ENREF_39),[41](#_ENREF_41)].

In view of the difficulty in achieving complete clearance, a more radical surgical approach is preferred in MEN1 associated insulinomas[[39](#_ENREF_39),[41](#_ENREF_41),[42](#_ENREF_42)]. Current surgical practice depends on the site of the tumour. For distal lesions, distal pancreatectomy with or without splenic preservation is required. Proximal tumours located in the pancreatic head may be enucleated, but total pancreatectomy may be required in selected cases[[35](#_ENREF_35),[36](#_ENREF_36),[39](#_ENREF_39),[41-44](#_ENREF_41)]. Local resections are not routinely indicated, despite some recently promising results in selected solitary or dominant lesions[[45](#_ENREF_45)]. Moreover, the procedure of choice should be decided after careful preoperative localisation, and taking 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 to mention that in our recent experience enucleation of single lesions in the head in the context of MEN has been successful in rendering the patient asymptomatic, 12 mo after surgery.

**Biological behaviour**

Although the majority of insulinomas are benign and curable by surgical resection, approximately 5%-10% show malignant behaviour[[38](#_ENREF_38)]. However, with an annual incidence of approximately 0.1[[46](#_ENREF_46)] per million persons per year, malignant insulinomas are extremely rare. Similar to all other neuroendocrine pancreatic tumours, the malignant potential of insulinomas is assessed by tumour differentiation (the extent of resemblance to the normal cells), grade (the degree of biologic aggressiveness) and stage (the extent of tumour spread)[[47](#_ENREF_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](#_ENREF_47)].

Local invasion and/or the evidence of liver metastases clearly demonstrates malignancy[[7](#_ENREF_7)]. However, in the absence of these findings malignant behaviour must be determined from the pathologic characteristics of pre-operative tissue biopsies when taken, because in most of this cases at the most EUS-guided FNA is performed. Although the course of malignant insulinomas is more indolent than other malignant neuroendocrine pancreatic tumours, the median survival is only 2 years and 10-year survival only 29%[[5](#_ENREF_5),[6](#_ENREF_6),[48](#_ENREF_48)] Although in some cases malignant insulinomas have been reported with higher survival rates[[49](#_ENREF_49)], this prognosis remains significantly poorer than for benign insulinomas which present a 95%-100% surgical cure rate[[5-7](#_ENREF_5),[48](#_ENREF_48)].

These key facts define the role and the limitations of both laparoscopic and open surgery in patients with malignant insulinoma. It is however possible that extensive surgical resection of the primary tumour, affected lymph nodes and distant metastases may provide alleviation of hypoglycaemia 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 cure and include distal pancreatectomy, pancreaticoduodenectomy with or without metastasectomy, segmentectomy, formal hepatectomy or even liver transplantatation[[6](#_ENREF_6),[30](#_ENREF_30),[36](#_ENREF_36),[37](#_ENREF_37),[49](#_ENREF_49),[50](#_ENREF_50)]. Where disease is unresectable in its entirety, debulking surgery may provide symptomatic relief when combined with medical and ablative therapy. Where malignancy is determined pre-operatively, 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, multidisciplinary assessment is mandatory, most commonly followed by secondary radical open resection in combination with adjunctive therapy.

**Clinical symptoms and biochemical diagnosis**

Insulinomas most commonly present with hypoglycaemia 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](#_ENREF_4),[6](#_ENREF_6),[7](#_ENREF_7),[43](#_ENREF_43),[51](#_ENREF_51)]. Neurologic symptoms are attributed to the effects of low blood glucose on the nervous system (neuroglycopenia) and include visual disturbances (diplopia, blurred vision), altered mental status, abnormal behaviour, seizures, amnesia and even coma[[4](#_ENREF_4),[6](#_ENREF_6),[7](#_ENREF_7),[43](#_ENREF_43),[51](#_ENREF_51)]. Adrenergic symptoms are attributed to reactive catecholamine overproduction and include nausea, excessive sweating, anxiety, palpitations, weakness, tremors, increased appetite and heat intolerance[[4](#_ENREF_4),[6](#_ENREF_6),[7](#_ENREF_7),[43](#_ENREF_43),[51](#_ENREF_51)]. Each patient usually reports a specific constellation of symptoms[[52](#_ENREF_52),[53](#_ENREF_53)], which are relieved almost immediately after carbohydrate consumption, a feature that is included in Whipple’s diagnostic triad[[54](#_ENREF_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 eventually obesity[[4](#_ENREF_4),[43](#_ENREF_43),[51](#_ENREF_51)].

When there is clinical suspicion of insulinoma, the autonomous overproduction of endogenous insulin must be confirmed biochemically. The basis of this diagnosis is Whipple’s triad[[54](#_ENREF_54)] of biochemically proven hypoglycaemia, hypoglycaemic symptom development and swift reversal after carbohydrate consumption occurring during a supervised fasting period. When symptoms occur concurrently with hypoglycaemia (glucose levels around or below 2.2 mmol/l), increased insulin (≥ 6 μIU/ml with standard non-specific insulin radioimmunoassay or ≥ 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 suggest the presence of an autonomous source of insulin production, insensitive to hypoglycaemia[[1](#_ENREF_1),[8](#_ENREF_8),[43](#_ENREF_43)]. To rule out the presence of exogenous insulin (factitious hypoglycaemia) a negative sulphonylurea/meglitinide screen test is also required, that corroborates with the increased levels of the C peptide[[1](#_ENREF_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 1mg glucagon at the end of the fasting period[[55](#_ENREF_55)] have been used by some authors for decades[[56](#_ENREF_56)] especially in patients who do not drop their blood glucose below 2.5 mmol/l during fasting. Indeed, β-hydroxybutyrate levels have now been included in recent guidelines[[8](#_ENREF_8),[57](#_ENREF_57)], despite recent contradicting reports[[58](#_ENREF_58)].

The actual cut-off points for insulin during fasting vary throughout the literature[[52](#_ENREF_52),[59-61](#_ENREF_59)]. The reasons for this variation are complex and reflect both the altered biochemistry of insulin produced by insulinomas (increased proinsulin and proinsulin-like components, insensitivity versus partial sensitivity of insulinomas to hypoglycaemia) and the inherent limitations of detection assays (minimum detection levels, 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 hypoglycaemia (< 2.5 mmol/l)[[62](#_ENREF_62)]. Subsequent to this study, proinsulin measurement has since been recognised in recent consensus guidelines[[8](#_ENREF_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 in-patient assessment[[52](#_ENREF_52),[53](#_ENREF_53)]. More recently however, modern insulin and pro-insulin specific assays have shown that a fasting period of 48 h is sufficient[[60](#_ENREF_60)]. The lower cost and reduced invasiveness of this 48-hour test have led to its rapid uptake across many institutions, and provided a new standard of care[[1](#_ENREF_1),[43](#_ENREF_43)] that is now reflected in updated diagnostic guidelines[[8](#_ENREF_8),[57](#_ENREF_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 hypoglycaemia[[63](#_ENREF_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.

**Pre- and Intra-operative localisation**

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](#_ENREF_1),[2](#_ENREF_2),[4-6](#_ENREF_4),[48](#_ENREF_48)]. In the past surgeons were reliant on blind distal pancreatectomies for occult impalpable insulinomas due to limited imaging and diagnostic tools[[64-66](#_ENREF_64)]. However, blind distal pancreatectomy was associated with a high failure rate (> 20%), exaggerated by the fact that non-palpable insulinomas often reside in the thicker pancreatic head[[63](#_ENREF_63)]. Over the past 25 years, novel diagnostic modalities have therefore rendered this blind approach obsolete[[67](#_ENREF_67)] in favour of targeted resection.

Although in the past open surgeons had often bypassed preoperative localization in favour of intra-operative palpation and ultrasound (IOUS)[[64-66](#_ENREF_64)], this approach was never widely adopted[[1](#_ENREF_1),[53](#_ENREF_53),[67](#_ENREF_67),[68](#_ENREF_68)] and is certainly unacceptable for laparoscopy. Reliance on laparoscopic intra-operative ultrasound (LIOUS) alone led to open conversion of one every three cases[[16](#_ENREF_16)]. As a result, more recent series[[17-19](#_ENREF_17),[31](#_ENREF_31)], including our own, reflect current guidelines advocating accurate localisation prior to laparoscopic surgical intervention[[8](#_ENREF_8)]. We strongly advise against laparoscopic intervention without accurate preoperative localization[[32](#_ENREF_32)] for a number of reasons: Firstly, the lack of intraoperative tactile feedback removes the ability to assess the tumour by palpation; secondly, patient positioning and trocar placement is determined by the location of the tumour; and finally whilst LIOUS is a mandatory intra-operative 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 tumour (head, uncinate process, body or tail) from preoperative investigations. In this way the surgeon may utilise 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 pre-operative assessment[[9](#_ENREF_9),[16](#_ENREF_16),[69](#_ENREF_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 tumour location should initially lead to repeat imaging and re-assessment in an attempt to improve localisation accuracy. However, where this fails, surgeons should re-consider 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](#_ENREF_8),[35-37](#_ENREF_35),[57](#_ENREF_57)], and should include one or two from the following: transabdominal ultrasound (US), computerised tomography (CT) and magnetic resonance imaging (MRI). These modalities are usually readily available, and recently with the addition of contrast enhancement (CE), have been reported to have a high sensitivity in insulinoma detection (about 90% for CE US[[70](#_ENREF_70)] and about 100% for CE CT and MRI[[71](#_ENREF_71)]). However, due to variation in technology and radiological expertise, not all institutions may 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. This approach is in line with recent guidelines[[35-37](#_ENREF_35),[57](#_ENREF_57)] and contrary to some authors who have excellent results from the use of US[[7](#_ENREF_7)].

Failure to obtain diagnosis through CT or MRI should lead to further assessment using endoscopic ultrasound (EUS)[[8](#_ENREF_8),[35-37](#_ENREF_35),[57](#_ENREF_57)]. This modality is invasive, operator dependent and of limited availability, however may yield an accuracy exceeding 90%[[72](#_ENREF_72),[73](#_ENREF_73)] and is now advocated in all established guidelines[[8](#_ENREF_8),[35-37](#_ENREF_35),[57](#_ENREF_57)]. As EUS performs better in the head, but less well in the body and worse in the tail of the pancreas[[74](#_ENREF_74),[75](#_ENREF_75)], it may be considered a complementary modality to the CT[[73](#_ENREF_73)], which may miss lesions in the pancreatic head[[76](#_ENREF_76)]. Notably, in our experience, lesions of greater tumour 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](#_ENREF_67),[77](#_ENREF_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 localisation in difficult cases through stimulated venous sampling. Using this technique, localisation can be determined according to the arterial branch injected. The presence of insulinoma in a particular territory is indicated by greater than two-fold elevation in insulin levels (sampled at 30 and/or 60 s from the hepatic vein) on calcium gluconate stimulation[[78](#_ENREF_78)]. The use of ASVS is now widespread[[7](#_ENREF_7),[79](#_ENREF_79)] and is included in most[[8](#_ENREF_8),[36](#_ENREF_36),[37](#_ENREF_37),[57](#_ENREF_57)] but not all[[35](#_ENREF_35)] recent guidelines.

Whilst other authors advocate the use of PET/CT[[80](#_ENREF_80)] and SPECT/CT[[81](#_ENREF_81)], this is not routine practice in our experience, as both techniques remain investigational[[8](#_ENREF_8)]. However, promising results have recently been reported with glucagon-like peptide -1 (GLP-1) analogue SPECT/CT[[82](#_ENREF_82)] imaging. Insulinomas are known to overexpress GLP-1 receptors in high density[[83](#_ENREF_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 pre-operative insulinoma localisation, and is likely to become of increasing clinical importance with the development of novel tracers and improved imaging diagnostics[[84](#_ENREF_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 localisation of the insulinoma(s). 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 2mm (and preferably 3mm) 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](#_ENREF_7),[8](#_ENREF_8),[35](#_ENREF_35),[49](#_ENREF_49),[50](#_ENREF_50)]. In these cases resection of liver metastases ideally precedes excision of the pancreatic lesion[[35](#_ENREF_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](#_ENREF_85)], however we do acknowledge the work of other surgeons who advocate laparoscopic resection of malignant lesions[[26](#_ENREF_26)].

In the context of MEN1 we follow a conservative but widely accepted approach[[8](#_ENREF_8),[37](#_ENREF_37)] due to the increased failure and reoperation rate inherent in the resection of MEN1 related insulinomas[[43](#_ENREF_43)]. Laparoscopic management of insulinomas in the context of MEN1[[20](#_ENREF_20),[88](#_ENREF_88),[89](#_ENREF_89)] is however possible in appropriate cases particularly where only a single lesion is identified pre-operatively. 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 be noted that MEN1 is considered a contraindication to laparoscopy in several large comparative series[[30](#_ENREF_30),[31](#_ENREF_31)]. As mentioned before in our recent experience enucleation of a single lesion in the pancreatic head has been successful in a single case.

Contrary to several other published studies[[16-18](#_ENREF_16),[21](#_ENREF_21),[29](#_ENREF_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 express concerns over high complication rates in these cases[[90](#_ENREF_90)], however, we do believe that enucleation has a valuable role to play in the treatment of solitary lesions of the head and uncinate process. Exposure is of paramount importance when dealing with pancreatic head/uncinate process insulinomas, however there are a number of techniques that can be employed to provide direct access to both the posterior aspect of the pancreatic head and uncinate process[[33](#_ENREF_33),[91](#_ENREF_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 multiples and extensive pancreatotomies. Recently, we have however described a technique similar to wire guided breast biopsy which may enable the surgeon to accurately localise and laparoscopically resect these difficult insulinomas[[34](#_ENREF_92)] thus minimizing the number and size of the pancreatotomies. Here, assisted by laparoscopic intraoperative ultrasound (LIOUS) an 18G 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 localised resection performed[[34](#_ENREF_92)].

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](#_ENREF_19),[29-31](#_ENREF_29)] 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 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 the body/proximal tail of the pancreas, the patient may be positioned supine 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](#_ENREF_12)] and left semilateral positions have been reported in the literature[[88](#_ENREF_88)]. In our experience, a full left lateral position is preferable, especially when combined with a retroduodenal and retropancreatic approach to the lesion following a full Kocherization[[33](#_ENREF_33)]. We prefer this to the gastrocolic ligament approach proposed by other authors[[88](#_ENREF_88)]. For lesions in the distal pancreatic tail, positioning may be either supine with a right tilt, right semilateral, 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](#_ENREF_91)]. Our practice is the right full lateral position because (a) the chances of a distal pancreatectomy for lesions located in this area are higher and a right table tilt always facilitates this procedure, and (b) this position can easily be changed to lest semilateral with a generous left table tilt, giving the surgeon 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 placement is at the discretion of the operating surgeon and varies throughout published reports[[12](#_ENREF_12),[17](#_ENREF_17),[24](#_ENREF_24),[26](#_ENREF_26),[91](#_ENREF_91)]. Generally, we use a standard array of five ports, the first for the laparoscope at the centre 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 Nathason’s 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](#_ENREF_33)].

Gaining wide access to the pancreatic region of interest is of utmost importance in order to provide adequate space for surgical manoeuvres and instruments such as the LIOUS probe and the endoscopic stapler. For insulinomas of the posterior aspect of the pancreatic head, full mobilization of the hepatic flexure and the placement of two Nathason’s liver retractors, one for the liver and may be one for the right kidney greatly facilitates surgical access[[33](#_ENREF_33)]. On the other hand for insulinomas of the anterior aspect of the pancreatic head, the body and the tail of the pancreas, mobilization of the splenic flexure and the retraction of the stomach to access the lesser cavity serve 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 localisation of the lesion but also outlines the surrounding anatomy in terms of tumour size, local invasion, and distance from pancreatic duct and/or portal vein. If the combination of careful inspection and thorough LIOUS evaluation fails to adequately localise or characterise the insulinoma, we advocate that further surgical intervention be postponed in favour of repeat imaging and biochemical testing[[92](#_ENREF_93)].

Once accurate intraoperative localization has been determined, surgical dissection is straightforward and performed with hook electrocautery and/or ultrasonic dissection. This in general is greatly helped by the placement of a traction suture through the insulinoma, which then can be exteriorized using an Endoclose. For lesions embedded in the pancreatic parenchyma but amenable to enucleation (see Figure 1), the shortest route is chosen for dissection, in order to minimise surgical trauma to the normal pancreatic parenchyma. As previously described, the LIOUS guided placement of a fine needle in the centre 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 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 favour 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 NET’s and/or pancreatic tumours (*e.g.*, cystadenoma) making it impossible to separate insulinoma specific outcome data[[9](#_ENREF_9),[17](#_ENREF_17),[85](#_ENREF_85),[89](#_ENREF_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 tumour categorisation later employed by major governing bodies and reflected in published guidelines[[8](#_ENREF_8),[35-37](#_ENREF_35)]. Whilst this classification is taxonomically accurate, it produces difficulty when studying insulinoma specific outcomes, as insulinomas exhibit very distinct characteristics to other PETs and non-endocrine pancreatic tumours. Fortunately however, the intriguing nature of these tumours has resulted in a number of laparoscopic case series specific to insulinomas[[7](#_ENREF_7),[12-16](#_ENREF_12),[19-23](#_ENREF_19),[28](#_ENREF_28),[32](#_ENREF_32)] as well as those in the context of other PETs[[26](#_ENREF_26)], and those comparing open and laparoscopic cases[[18](#_ENREF_18),[24](#_ENREF_24),[25](#_ENREF_25),[27](#_ENREF_27),[29-31](#_ENREF_29)]. Furthermore, a recent meta-analysis comparing safety outcomes between laparoscopic and open approaches has been published[[94](#_ENREF_95)].

The majority of published series[[14](#_ENREF_14),[15](#_ENREF_15),[18-22](#_ENREF_18),[24-32](#_ENREF_24)] report established pre-operative localisation in > 90% of patients with very few exceptions[[12](#_ENREF_12),[16](#_ENREF_16)]. This highlights that pre-operative localisation has now become common practice rather than reliance solely on intra-operative LIOUS. Furthermore, this practice has increased the intraoperative accuracy of LIOUS to almost 100% and almost eliminated inadequate localisation as a cause for open conversion in the majority of cases[[14](#_ENREF_14),[15](#_ENREF_15),[20-22](#_ENREF_20),[26](#_ENREF_26),[28](#_ENREF_28),[32](#_ENREF_32)]. Conversely, it is also notable that series reporting low preoperative localization rates[[12](#_ENREF_12),[16](#_ENREF_16)] or limited use of LIOUS[[19](#_ENREF_19)] also often describe inadequate localisation as a common reason for conversion.

The median operative time is between 2 and 3.5 h and varies significantly in published series[[12](#_ENREF_12),[14-16](#_ENREF_14),[19-22](#_ENREF_19),[26](#_ENREF_26),[28](#_ENREF_28),[32](#_ENREF_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](#_ENREF_32)]. Furthermore, although comparative studies demonstrate, as expected, that laparoscopic procedures remain longer than their open counterparts[[18](#_ENREF_18),[24](#_ENREF_24),[31](#_ENREF_31)] and that enucleation may be performed in a shorter time than distal pancreatectomy[[16](#_ENREF_16),[19](#_ENREF_19),[20](#_ENREF_20),[28](#_ENREF_28)], this was not evident when pooled operative time was examined in the aforementioned meta-analysis[[95](#_ENREF_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](#_ENREF_12),[15](#_ENREF_15),[28](#_ENREF_28),[32](#_ENREF_32)], and laparoscopic procedures resulted in significantly reduced blood loss when compared to open procedures[[18](#_ENREF_18),[25](#_ENREF_25),[29](#_ENREF_29),[30](#_ENREF_30),[95](#_ENREF_95)]. Again however, it is important to consider these results in the context of small sample numbers.

Laparoscopic treatment of insulinomas is safe, and is accompanied by minimal mortality in almost all published series[[12](#_ENREF_12),[14-16](#_ENREF_14),[19-22](#_ENREF_19),[26](#_ENREF_26),[28](#_ENREF_28),[32](#_ENREF_32)]. Morbidity on the other hand, may be high and is reported to vary between 15% and 77%[[12](#_ENREF_12),[14-16](#_ENREF_14),[18-22](#_ENREF_18),[24-32](#_ENREF_24)]. The most common complication is pancreatic fistula[[95](#_ENREF_96)], 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 than with open surgery[[94](#_ENREF_95)]. 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 case 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 a laparoscopic insulinoma resection is difficult to determine, due to the inherent differences in institutional protocols and also because patients can come from far away as being referred to a tertiary centre. Indeed, uncomplicated laparoscopic resection required a hospital stay of one to two days in some studies[[16](#_ENREF_16),[22](#_ENREF_22),[32](#_ENREF_32)], while in others patients remained hospitalized for 5-7 d[[18](#_ENREF_18),[21](#_ENREF_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-analysed[[94](#_ENREF_95)].

Importantly, laparoscopic insulinoma resection is associated with good long-term outcomes. In fact, whilst some series report long-term normoglycaemia to be maintained in at least 95% of cases[[24](#_ENREF_24),[25](#_ENREF_25),[30](#_ENREF_30),[31](#_ENREF_31)], others demonstrate a long-term cure rate of 100%[[12](#_ENREF_12),[14](#_ENREF_14),[19-22](#_ENREF_19),[26](#_ENREF_26),[28](#_ENREF_28),[32](#_ENREF_32)].

**Conclusion**

Insulinomas are rare pancreatic neuroendocrine tumours that may be definitively cured with surgical resection. Dedicated multidisciplinary assessment is however paramount prior to surgical intervention and should include thorough clinically and biochemical diagnosis. Localisation of the tumour should be achieved through an array of non-invasive (US, CT, MRI) and inevitably some invasive (EUS, 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 irrespectively 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 laparoscopic intra-operative ultrasound (LIOUS), which forms an indispensable part of any laparoscopic resection. In this way, localisation of the lesion can be confirmed intra-operatively, and the tumour 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 normal parenchyma, the 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 now 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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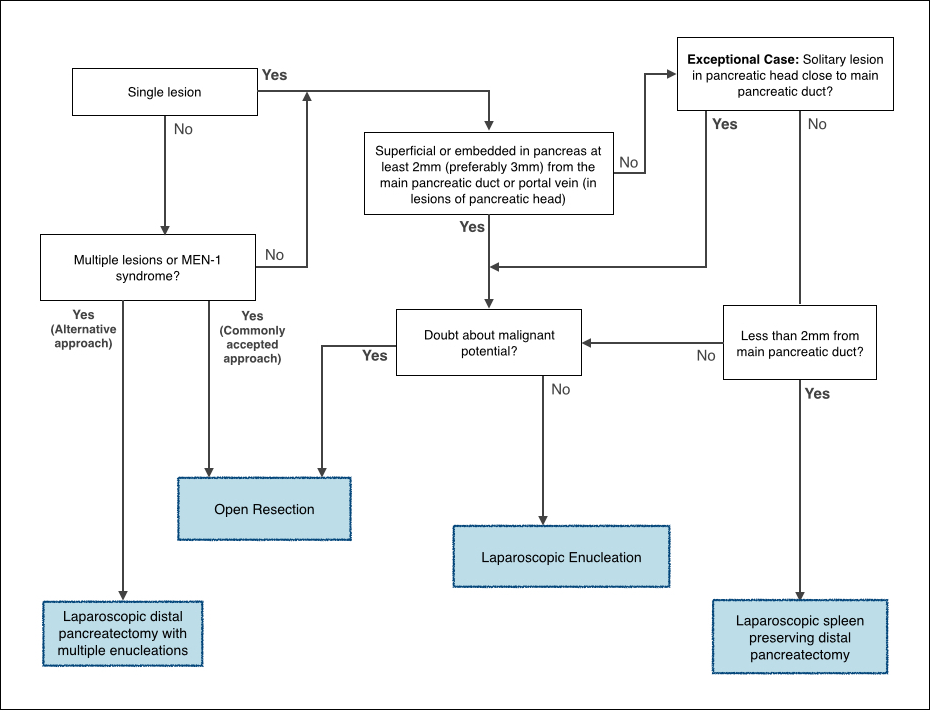
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**Table 1 Features suggestive of malignant insulinoma[**[**43**](#_ENREF_43)**]**

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



**Figure 1 Flow chart demonstrating our surgical decision-making in pancreatic insulinomas.**