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Laparoscopic approach for solitary insulinoma: a multicentre study

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Abstract *Background:* Surgical resection of insulinomas is the preferred treatment in order to avoid symptoms of hypoglycaemia. During the past years, advances in laparoscopic techniques have allowed surgeons to approach the pancreas and treat these lesions laparoscopically. We analysed the feasibility, safety, and outcome of patients undergoing laparoscopic resection of insulinomas in a large, retrospective, multicentre study. *Methods:* Thirty-six patients with pancreatic insulinomas were enrolled in this study. All patients were suspected of having solitary insulinomas after preoperative localisation tests and underwent a laparoscopic approach. Patients, operating characteristics and outcome were analysed. *Results:* Mean patient age was 48 years (range 20–77 years). Insulinomas were localised in the head (n=7), isthmus (n=2), body (n=14) or tail (n=13) of the pancreas before laparoscopic approach. Mean size of the lesions was 15.5 mm (range 4–25 mm). The surgical procedure was enucleation in 19 cases (52%), spleen-preserving distal pancreatectomy in 12 cases (33%), spleno-pancreatectomy in three cases (8%), one duodenopancreatectomy and one central pancreatectomy. Conversion rate was 30%. The reason for conversion in seven patients (63%) was the inability to localise the tumour during the laparoscopic procedure. In six of these cases laparoscopic ultrasonography was not performed. Mean operating time was 156 min (range 50–420 min). Postoperative course was uneventful in 23 patients (64%). Eleven patients (30%) developed specific complications of pancreatic surgery: intra-abdominal abscess (n=6) or pancreatico-cutaneous fistula (n=5). Mean duration of fistulae was 55 days (range 5–130 days) and all the fistulae were dry at follow-up. After a mean follow-up period of 26 months (range 2–87 months), 33 patients (91%) are free of symptoms, and three patients have been lost to follow-up. *Conclusion:* The laparoscopic approach is safe to treat preoperatively localised insulinoma, with a morbidity rate comparable to that for the open approach. When the tumour is not found during laparoscopy, laparoscopic ultrasonography seems to be the most efficient tool to localise it and probably to prevent conversion.

Keywords Insulinoma · Laparoscopy · Laparoscopic ultrasound

Introduction

The majority of insulinomas are benign, solitary and intrapancreatic, and, because of characteristic neuroglycopenic symptoms, they are usually diagnosed when they are small (less than 15 mm in size) and not metastatic. Surgical resection of insulinomas is the preferred treatment to avoid symptoms of hypoglycaemia due to hyperinsulinism. During the past years, advances in laparoscopic techniques have allowed surgeons to approach the pancreas and to treat these lesions laparoscopically by performing either a resection or an enucleation. Elsewhere, two-thirds of the lesions occur in the body and tail of the pancreas, which are the regions easier to explore by laparoscopy [1]. Additionally, fewer than 5% of the insulinomas are located in regions of difficult access such as the uncinate process. These characteristics render insulinoma generally suitable for a laparoscopic approach. In 1996, Gagner et al. reported the feasibility of laparoscopic resection of islet cell tumours in a retrospective series of 12 patients [2]. Since then, only a few authors have reported laparoscopic resection of pancreatic insulinomas [3–9].

Most insulinomas can be accurately localised in the preoperative setting, but one of the difficulties is still tumour localisation during the laparoscopic approach. Laparoscopic ultrasound seems to allow peroperative localisation of the tumour with high accuracy, but is not yet routinely performed [7]. Laparoscopic pancreatic surgery is considered to be associated with a higher rate of postoperative fistulae when compared with the open approach [10–12]. The well-known advantages of the laparoscopic approach (reduced postoperative pain, hospital stay and recovery time) may consequently be balanced by the potential severity of postoperative fistulae.

The goal of this retrospective multicentre study was to analyse the need for preoperative and peroperative localisation tests, feasibility, safety, and outcome of patients that underwent laparoscopic resection of solitary insulinomas.

Materials and methods

From 1996 to 2003, data of 38 patients with organic hyperinsulinism and symptoms of hypoglycaemia were retrospectively collected for the current study. Participating surgical centres were French (ten centres) and Italian (one centre). All surgeons working in these centres were either members of the Société Française de Chirurgie Laparoscopique (SFCL) or the Association Francophone de Chirurgie Endocrinienne (AFCE). Patients with multiple endocrine neoplasm syndrome type 1 (MENs-1) were excluded from analysis (n=2). Characteristics of the remaining 36 patients (including age, gender, location of the tumour, preoperative diagnosis methods, operating procedure, operating time, specific morbidity, hospital stay, and outcome) were analysed. Specific morbidity was defined as a pancreaticocutaneous fistula with amylase-rich fluid, or intra-abdominal collection (even if the amylase level was not mentioned).

Statistical analysis Fisher's exact χ^2 test was used to compare qualitative variables, and the Mann–Whitney test was used to compare continuous variables. Results were considered significant if $P<0.05$.

Results

Thirty-six patients underwent a laparoscopic operation for organic hyperinsulinism on the basis of clinical findings, preoperative biochemical results and localisation test that exhibited a solitary tumour. Mean patient age was 48 years (range 20–77 years). There were 12 men and 24 women; the gender ratio was 0.5.

Preoperative localisation tests

Patients underwent a variety of preoperative localisation tests. All but two (95%) underwent computed tomography (CT). Sixteen patients (44%) underwent magnetic resonance imaging (MRI). Twenty-six patients (72%) underwent endoscopic ultrasonography (EUS). Nine patients (25%) underwent octreotide scanning scintigraphy. Two patients underwent selective pancreatic angiography, and one patient underwent calcium stimulating test. All tumours were located preoperatively according to previously mentioned imaging techniques and were considered solitary. Seven lesions (19%) were localized in the head, two (6%) in the isthmus, 14 (39%) in the body and 13 lesions (36%) were in the tail of the pancreas. Mean sizes of the lesions were 16.2, 17.5, 14.7, 15.5 mm (P=NS) in the head, isthmus, body and tail, respectively, of the pancreas.

Laparoscopic ultrasonography

Laparoscopic ultrasonography (LUS) was performed in eight patients (22%). In five of these cases, LUS located insulinomas that had not been found intraoperatively with visual exploration and instrumental palpation, despite preoperative localisation test guidance. In one case, insulinoma was located peroperatively by visual exploration and LUS was performed to check that this tumour was solitary. In two cases, LUS did not allow location of the insulinoma. Among these two patients, the first underwent a conversion to laparotomy to localise the lesion that has been finally treated by enucleation. In the second case, preoperative tests (CT and MRI in the present case) showed a tumour in the tail of the pancreas, and LUS seemed to confirm this point. Laparoscopic spleen-preserving distal pancreatectomy (SPDP) was then performed. Postopera-

tively, the patient was still complaining of hypoglycaemia, and pathological examination showed nesidioblastosis on the specimen, without tumour. This patient underwent further postoperative EUS (while it had not been performed before the primary surgical procedure) that located the insulinoma in the pancreatic head. Finally, the patient was successfully re-operated on 2 months later and underwent an enucleation by laparotomy. The pathological examination confirmed the presence of the insulinoma. In this case, we can consider that it was a false positive result of preoperative CT and MRI and also of LUS.

In the present series, laparoscopic visual exploration and instrumental palpation allowed tumour location in 24 patients (66%). However, when LUS results were taken into account in addition to visual and instrumental palpation, this percentage was shifted from 66% to 81% (29 patients).

Surgical procedures

The position of the patient on the operating table was dictated by the preoperative location of the tumour. When it was localized in the head (n=7), the isthmus (n=2) or the body (n=14) of the pancreas, all patients were positioned in a supine position. In the case of tumours located preoperatively in the tail of the pancreas (n=13), patients were positioned either in a supine position (n=3, 23%) or in the right lateral position (n=10, 77%). Table 1 gives information on the procedures performed with regard to tumour location. Enucleation of the insulinoma was performed in 19 patients (53%). Fifteen patients (42%) underwent a distal pancreatectomy, 12 of which (33%) were SPDPs. One patient (3%) underwent duodeno-pancreatectomy (Whipple procedure), and one patient (3%) underwent central pancreatectomy. In these two cases, the tumours were localized very close to the main pancreatic duct, and the surgeon considered that a safe enucleation was not feasible. In the case of the Whipple procedure, the pancreatic resection was performed laparoscopically, and the performance of the anastomosis required conversion to laparotomy. Mean number of ports used to perform these procedures was 4.22 (range 3–5). Enucleation was performed by electrocautery (n=16, 84%), or harmonic scalpel (n=3, 16%). In cases of distal pancreatectomy, trans-section of the pancreas was performed, with a linear stapler in 11 cases (73%) and an harmonic scalpel (Ultracision) or vessel-sealing device (Ligasure) in four cases (26%). In none of these cases was the main pancreatic duct electively controlled.

Conversion rate was 30% (11 of 36). Reasons for conversion and the procedures performed by open approach are listed in Table 2. Lesion size and location were statistically not different in the laparoscopic group when compared with the converted group (P=0.59, P=0.31 respectively). Reason for conversion in seven patients (63%) was the inability to locate the tumour during the laparoscopic procedure, but in six out of these seven cases, LUS was not performed because it was not available.

Mean operating time was 156 min (range 50–420 min) for all patients. Mean operating time was statistically longer in cases of conversion [218 min (range 90–420 min) vs 136 min (range 50–240 min), P=0.01]. Furthermore, we can see that mean operating time was shorter for laparoscopic enucleation than for laparoscopic distal pancreatectomy with or without spleen preservation [115 min (range 50–190 min) vs 175 min (range 120–240 min), P=0.01].

To decrease the risk of postoperative pancreatic fistula we gave nine patients (25%) octreotide injection during the perioperative period (seven enucleations, one splenopancreatectomy and one SPDP); eight patients (22%) underwent octreotide injection and fibrin glue application into the operating field (three enucleations and five SPDPs); two patient (6%) underwent fibrin glue application alone (one central pancreatectomy and one SPDP).

Morbidity

Postoperative course was uneventful in 23 patients (64%). Two patients (6%) were re-operated on at postoperative day 1: one evisceration in a patient who underwent a

Table 1 Surgical procedures with regard to the location and size of the tumour

Parameter	Enucleation (n=19)	Distal pancreatectomy		Whipple (n=1)	Central pancreatectomy (n=1)
		Without splenectomy (n=12)	With splenectomy (n=3)		
Localization					
Head	6	–	–	1	–
Isthmus	1	–	–	–	1
Body	9	3	2	–	–
Tail	3	9	1	–	–
Mean size, mm (range)	15 (10–25)	16 (4–20)	16 (11–25)	18	20

Table 2 Conversions: location and size of the tumours, LUS, reasons for conversion and procedures performed in patients converted to laparotomy (*IOUS* intraoperative ultrasonography, *DPS* distal pancreatectomy with splenectomy)

Number	Preoperative localization	Size (mm)	IOUS	Reasons for conversion	Performed procedure
1	Head	18	+	Technique	Whipple
2	Head	25	+	Technique	Enucleation
3	Head	15	+	Localization	Enucleation
4	Tail	20	−	Localization	SPDP
5	Body	11	−	Localization	DPS
6	Body	24	−	Localization	SPDP
7	Tail	12	−	Localization	SPDP
8	Tail	12	−	Localization	SPDP
9	Body	15	−	Localization	SPDP
10	Tail	18	−	Splenic vein bleeding	SPDP
11	Body	12	+	Splenic vein bleeding	DPS

SPDP after conversion to laparotomy, and one peritonitis related to gastric injury that had not been seen during the laparoscopic approach. Eleven patients (30%) developed specific complications of pancreatic surgery: intra-abdominal collection (n=6) or pancreatico-cutaneous fistula (n=5). Nine of these patients (81%) had been treated perioperatively by octreotide and/or by fibrin glue application (five perioperative octreotide injection alone, one fibrin glue application alone, and three perioperative octreotide injection associated with fibrin glue application). Specific morbidity occurred in eight patients who underwent enucleation (8/19, 42%) and in only three patients who underwent pancreatic resection (3/17, 17%). This difference was not statistically significant (P=0.16).

Management of "specific morbidity"

None of the five patients with pancreatico-cutaneous fistula was re-operated on. Four of them (80%) were treated by octreotide perfusion after the diagnosis of fistula had been made. Mean duration of fistula was 55 days (range 5–130 days) and all fistulae were dry at the end of follow-up. Three patients with intra-abdominal abscess were successfully treated by drainage: radiological drainage in two cases and surgical drainage (laparoscopic approach) in one case.

Hospital stay

Mean postoperative hospital stay was 11.0 days (range 5–32 days) for patients whose lesions were resected laparoscopically and 13.8 days (range 7–39 days) for patients whose surgical procedures were converted to laparotomy, but this difference was not significant (P=0.09). Excluding patients with postoperative "specific morbidity", mean postoperative hospital stay was shorter after laparoscopic resection than after open resection [8.2 days (range 5–11 days) vs 11.3 days (range 7–15 days), P=0.01].

Follow-up

Thirty-two patients (89%) were free of symptoms postoperatively. One patient was still complaining of hypoglycaemia. This was the patient in whom insulinoma was not found during laparoscopic procedure, who underwent an SPDP according to preoperative localisation tests and LUS. The pathological findings showed nesidioblastosis without any tumour, and postoperative endoscopic ultrasonography finally found an insulinoma in the head of the pancreas. The patient was finally operated on by laparotomy 2 months later and underwent an enucleation. He was free of symptoms at the end of follow-up.

Finally, after a mean follow-up time of 26 months (range 2–87 months), 33 patients (91%) were free of symptoms, and three patients (8%) had been lost to follow-up.

Discussion

The combination of EUS or intraoperative ultrasonography (IOUS) and operative manual palpation allows one to localise nearly 100% of the tumours at primary operation in experienced institutions [13]. According to these points, we can consider that preoperative localisation tests are not helpful if the operation has to be performed by an open approach and that the best localisation tests is probably an experienced endocrine surgeon. However, in case of laparoscopic surgery, manual palpation is lacking, and LUS is not always available. For these reasons, most endoscopic and endocrine surgeons use preoperative localisation tests to facilitate the laparoscopic approach. In the present series, all patients underwent preoperative localisation tests that exhibited a solitary tumour. Despite this preoperative localisation, the majority of conversions were done because the tumour, finally, was not localised during the laparoscopic procedure, suggesting that preoperative localisation tests are probably the key point to treat these patients laparoscopically. Because of the retrospective and multicentre aspect of this study the preoperative localisation tests

were various. Even though it is known that CT and MRI have low sensitivity and specificity, almost all patients underwent CT and half of them MRI preoperatively in this series [14]. One of the reasons is probably that new modalities of imaging techniques, such as dual-phase spiral CT with 1-mm shifts, have much improved sensitivity for the detection of small insulinomas [15]. Furthermore, these imaging techniques are non-invasive when compared to EUS, angiography or intra-arterial calcium-stimulating tests. CT is also probably indicated to exclude liver metastases or the presence of a large malignant primary tumour. In a recent review, EUS was found to have an overall sensitivity and accuracy of 93% for pancreatic neuroendocrine tumour, but the sensitivity of EUS depends on the location of the tumour (83% sensitivity for pancreatic head insulinoma vs 37% for distal pancreatic insulinomas) [16, 17]. Won et al. [18] proposed invasive exploration, such as pancreatic angiography or intra-arterial calcium stimulation with hepatic venous sampling, to localise insulinomas with 88% accuracy. Those authors argued that this test appears to be the most sensitive preoperative localisation method, when compared with CT or MRI. In the present retrospective and multicentre series, pancreatic angiography or calcium-stimulating tests were performed in three cases, but it is interesting to note that in these three cases the CT was not performed with a new generation dual-phase spiral CT.

The most effective method for localising an insulinoma at surgery is known to be IOUS, which identifies tumours based on a difference in echogenicity between the lesion and the surrounding pancreas [19]. Intraoperative ultrasound can also screen the anatomic relationship of the tumour with adjacent structures, such as the pancreatic duct and splenic and mesenteric vessels. Confirming these anatomical relationships seems to be essential for the surgeon to decide whether to perform an enucleation or a pancreatic resection. Even though laparoscopy and LUS provide similar information to that obtained by open IOUS, preoperative localisation seems essential for guidance of the laparoscopic approach, as it can influence the patient's position. This seems to be especially true when LUS is not available. In this series, when the tumour was localised in the head, isthmus or body of the pancreas, all patients were put into the supine position, while they were put in the right lateral position in 77% of the cases when the tumour was localised in the tail of the pancreas. In our series, LUS was only performed during eight laparoscopic explorations among 36. In two of those cases (25%), LUS failed to localise the insulinoma. On the other hand, in the group of seven patients for whom the tumour was not localised and who were converted to laparotomy, LUS was performed only in one case, while it was not performed in six patients (85%). We are not able to affirm that these conversions would have been avoided if LUS had been performed, but, with regard to the high accuracy of LUS (90%), we can speculate that some of these patients would have been totally treated by laparoscopy [5]. Unfortunately, our data cannot prove this hypothesis in this current series.

In the literature, conversion rates vary from 20% to 33%, and the reasons for conversion are either the inability to localise the lesion, even with LUS, or technical difficulties with the performance of the planned pancreatic resection [3–5, 7–9]. In our experience, the inability to localise the tumour (with or without LUS) is the main reason for conversion (n=7, 63%). The other reasons are technical difficulties (n=2, 18%), or peroperative bleeding (n=2, 18%). The overall conversion rate of 30% is comparable to the data in the literature [3, 5, 8, 9].

With regard to the technical aspects of treating insulinoma, the most logical approach seems to be enucleation, because most insulinomas are benign with no need for wide resection, and because it preserves the surrounding pancreatic parenchyma. However, enucleation is not always applicable especially because of the localisation of the tumour. Tumours in the head of the pancreas and/or close to the pancreatic duct or vessels are particularly difficult to treat by laparoscopy. In our series, most of the enucleated tumours were localised in the body or in the tail of the pancreas (13 of 19, 68%). Among the seven patients with a tumour in the head, four patients underwent laparoscopic enucleation and three were converted to laparotomy (two enucleation and one Whipple procedure). In the case of inability to enucleate tumours localised in the body or tail of the pancreas, the most common procedure is distal pancreatectomy (DP) with or without spleen preservation. In our experience, DP was performed in 15 cases (41%), but in eight of these cases it was performed after conversion to laparotomy. The spleen was preserved in 12 of these cases (80%). Furthermore, in one of them, the splenic vessels were divided without splenectomy. In a recent study, Gagner et al. [12] reported a series of 22 laparoscopic pancreatic resections with a higher rate of distal pancreatectomy with splenectomy (59%). However, in this last series the indication for operation were various (neuroendocrine tumours, cystic pancreatic tumours, chronic pancreatitis). We believe that in case of benign tumour of the pancreas, the spleen has to be preserved if possible, even if the splenic vessels have to be resected.

Postoperative morbidity occurred in 36% of the patients; 30% was considered to be specific morbidity of pancreatic surgery. This morbidity rate is comparable to the complication rate reported after insulinoma resection either by laparotomy or by laparoscopy. In an international review of benign insulinoma treated by open surgery, Rothmund et al. [20] reported a complication rate of 32%, and, in a very recent series, Jaroszewski et al. [21] reported a postoperative morbidity rate of 33% in a series of nine patients who underwent laparoscopic resection of insulinoma. Lillemoe et al. [10] reported low postoperative morbidity rates after distal pancreatectomy performed by laparotomy in 235 patients (pancreatic fistulae in 5% and intra-abdominal abscesses in 4%). On the other hand, laparoscopic enu-

cleations, as well as open enucleations, were considered to carry the risk of postoperative pancreatic fistula (25% after laparoscopic approach for Mabrut et al. [11] and 29% after an open approach for Sauvanet et al. [22]). In our series, even if the specific morbidity rate seemed to be more important in the enucleation group, the difference was not statistically significant when compared with pancreatic resection (42% vs 17%, P=0.16). This probably has to be evaluated in larger studies.

Some authors consider that the use of an endoscopic stapler on the pancreas is probably a cause of pancreatic fistula, arguing that the pancreatic duct is not always individualised. They also propose elective ligature of the pancreatic duct, which is not always easy because of localisation failure [23]. In recent years new devices, such as Ligasure or Ultracision, have been used to divide the pancreatic parenchyma. Promoters of these techniques argue that the pancreatic duct is more accurately closed with these devices. In our patients these devices were used in four cases of distal pancreatectomy, but we are unable to affirm that it decreased the fistula rate. It probably should also be studied in a larger series.

Some authors proposed fibrin glue application or perioperative octreotide administration in order to decrease postoperative morbidity [24, 25]. In our experience, 81% of patients that developed specific morbidity had undergone fibrin glue application and/or octreotide administration. The retrospective and multicentre aspect of this study is probably the reason for this finding. It is likely that surgeons used these tricks in patients with high risk of fistula.

Finally, laparoscopic resection of insulinomas is feasible, safe and does not increase postoperative morbidity, in comparison with the open approach. In this retrospective series, the potential advantages of laparoscopic approach over open surgery, including cost of the procedure (occupation of the operating room, cost of ports, stapler...), postoperative pain and recovery time, were not studied. Further prospective study could probably demonstrate these potential advantages. The key point allowing the laparoscopic approach seems to be the localisation of the tumour preoperatively and peroperatively. Preoperative localisation is essential for patient positioning. Peroperative localisation with LUS is certainly useful to confirm the preoperative findings, mostly when the tumour is not superficial and cannot be visualised during laparoscopic approach, or to determine the precise relationship of the tumour with the pancreatic duct and vessels. This perioperative information could probably avoid conversion to laparotomy in some cases, but this would have to be proven with larger series.

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