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Surgical management of insulinoma over three decades

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Parenchyma-sparing pancreatectomy; Enucleation; Neuroendocrine tumours; Postoperative complications.

Abstract

Introduction: This paper reports our experience of the perioperative management of patients with sporadic, non-malignant, pancreatic insulinoma.

Methods: A retrospective monocentric cohort study was performed from January 1989 to July 2019 using a prospectively maintained database, including all the patients who had been operated on for pancreatic insulinoma as of the time of the study. The preoperative work-up, surgical management, and postoperative outcome were analyzed.

Results: Eighty patients underwent surgery for sporadic pancreatic insulinoma, 50 of which were female (62%), with a median age of 50 (36–70) years. Preoperatively, the tumors were localized in 76 patients (95%). Computed tomography (CT) and magnetic resonance imaging allowed exact preoperative tumor localization in 76% of the patients (64–85 and 58–88 patients, respectively), increasing to 96% when endoscopic ultrasonography was performed in addition to CT. Forty-one **parenchyma-sparing pancreatectomies** (including enucleation, **caudal** pancreatectomy, and uncinata process resection) and 39 pancreatic resections were performed, 32% via laparoscopy. The mortality rate was 6% (n = 5, 4 after pancreaticoduodenectomy), with a morbidity rate of 72%, including 24 severe complications (30%) and 35 pancreatic fistulas (44%). No differences were found between **formal pancreatectomy** and **parenchyma-sparing pancreatectomy** in terms of postoperative outcome procedures. The surgery was curative in all the patients, with long-term postoperative normalization of the glycemia and insulin blood levels.

Conclusion: CT used in combination with endoscopic ultrasonography allows accurate localization of insulinomas in almost all patients. When possible, a **parenchyma-sparing pancreatectomy** should be proposed as the first-line surgical strategy.

Introduction

Insulinoma is the most common functional pancreatic neuroendocrine tumor. In most patients, it is a small, sporadic, solitary, and intrapancreatic benign tumor,¹⁻³ but its diagnosis can be difficult and is often delayed because of the highly variable and non-specific symptoms of hypoglycemia. When a diagnosis of organic hypoglycemia **with inappropriately elevated endogenously produced insulin** after a 48–72 h fasting test⁴ is confirmed, the next issue is to accurately localize the insulinoma to anticipate the surgical approach, which has long been exclusively based on intraoperative ultrasonography and thorough pancreatic palpation. This is often challenging because the tumors distributed throughout the pancreatic gland are usually small. The combination of cross-sectional imaging techniques, nuclear medicine, and endoscopic ultrasonography, however, has dramatically changed the preoperative assessment of insulinomas.⁵⁻⁷ Thus, blind pancreatectomy is no longer recommended.⁸ Surgery remains the cornerstone of insulinoma treatment.⁹ As it is benign in most patients, it should ideally be done through **parenchyma-sparing pancreatectomy**¹⁰ ideally enucleation^{11,12} to preserve both the exocrine and endocrine functions.¹ Nevertheless, these procedures often expose patients to substantial postoperative morbidity.¹³

Reported herein are **the evolution** in the pre- and perioperative management of patients with sporadic non-malignant insulinoma and our experience in relation to such, with specific attention given to preoperative localization and postoperative outcome following pancreatectomy **and the development of the laparoscopic approach.**

Methods

Patients and methods

Data collection

All the patients who underwent pancreatectomy for sporadic non-malignant insulinoma within the period from 1989 to 2019 at Cochin Hospital, Paris, France, a tertiary referral center for endocrine diseases, were included in this study. Demographic, clinical, radiological, pathologic, and follow-up data were obtained from a prospectively maintained database, with additional retrospective review. For each patient, the diagnosis was confirmed by an experienced pathologist. Malignant (i.e., metastatic insulinoma) and multiple endocrine neoplasia type 1 (MEN1) insulinoma were excluded from the analysis. Postoperative mortality included all the deaths that occurred within 90 days from the surgery. Morbidity included all the complications that occurred within 90 days from the surgery and was graded according to the Clavien-Dindo classification¹³. Postoperative pancreatic fistula, hemorrhage, and delayed gastric emptying were defined according to the International Study Group of Pancreatic Surgery¹⁴⁻¹⁷. The follow-up was based on clinical, radiological, and laboratory assessments and was updated on the basis of outpatient reviews and correspondence. All the patients were followed up at least 1 year after surgery. The year 2000 was considered a time landmark because it marked the beginning of the evolution of imaging, endoscopic, and laparoscopic techniques. The study protocol was approved by the hospital's medical ethics committee.

Preoperative work-up and surgical indications

The preoperative work-up (all performed in Cochin Hospital) included a clinical evaluation with patient questioning and a complete hormonal and radiological evaluation with triphasic computed tomography (CT) examination (unenhanced, arterial, and portal phases)

and endoscopic ultrasound (EUS) since it became available. Additional investigations with magnetic resonance imaging (MRI) including standard sequences and cholangiopancreatography images and somatostatin receptor scintigraphy or positron emission tomography (PET)/CT either with ^{111}In -DTPA-octreotide or more recently ^{68}Ga -DOTATOC or EUS with fine needle aspiration (FNA) were left to the surgeon's discretion. The policy regarding the use of nuclear medicine imaging has evolved over time. ^{111}In -DTPA-octreotide, despite its low sensibility, was initially used but was later replaced by ^{68}Ga -DOTATOC when it became more easily available. All surgical indications were discussed in a multidisciplinary tumor board that included surgeons, radiologists, nuclear physicians, endocrinologists, pathologists, and gastroenterologists.

Surgical techniques

The type of surgical resection that was performed was based on the tumor location and the distance to the main pancreatic duct. Distal pancreatectomy was defined as a pancreatectomy with pancreatic resection at the level of the isthmus. Caudal pancreatectomy, on the other hand, which is considered parenchyma-sparing pancreatectomy, was defined as a pancreatectomy with pancreatic resection on the left side of the isthmus. Enucleation and parenchyma-sparing pancreatectomy (central pancreatectomy, resection of the uncinate process, and caudal pancreatectomy) was preferred whenever possible. During surgery, pancreatic exploration after mobilization of the transverse colon root was first performed through visual inspection and surgical ultrasonography to confirm the tumor location.

Statistical analysis

The variables were expressed as medians, interquartiles, or numbers and percentages of patients, as appropriate. The continuous variables were evaluated for normal distribution

using the Komogorov-Smirnov test. Chi square or Fisher's exact test was used to evaluate the categorical variables. The continuous variables were analyzed using Student's t-test or Mann-Whitney test, as appropriate. The capability of each imaging test to determine the exact tumor location was calculated in terms of the true location rate, using the surgical and histopathological findings as the standards of reference. The McNemar test was used to compare the diagnostic tests. All the tests were two-tailed, and significance was set at $p < 0.05$. The analysis was conducted with the R software.¹⁴

Results

Characteristics of the population and preoperative imaging

The final study population included 80 patients who underwent surgery for pancreatic insulinoma, 50 (62%) of which were women and 30 (38%) men, with a median age of 50 (36–70) years (**Table 1**). Most of the patients were ASA 1 or 2 (n = 76; 95%) and presented neuroglycopenic symptoms (n = 74; 92%), including fainting (40%; n = 32). The median time interval between the first symptoms and the surgery was 13 months (4–26 months).

The proportions of tumors that were correctly localized using the different preoperative imaging tests are shown in **Table 2**. The exact preoperative location was obtained in 76/80 patients (95%), and the preoperative tumor location was accurate in all the patients who underwent CT, MRI, EUS, and somatostatin receptor imaging (19/19; 100%; 95% confidence interval [CI]: 79–100). When CT was used in combination with EUS, an accurate preoperative tumor location was obtained in 65/68 patients (96%; 95% CI: 87–99). The results of the other combinations are given in **Table 2**. CT, MRI, and EUS showed more accurate preoperative tumor locations (p = 0.009, 0.01, and 0.02, respectively) than octreoscan, with only four DOTAPETs realised after the year 2000 and only one positive for a 7 mm lesion. There were no differences in size between the negative and positive octreoscans and before and after the year 2000. No significant differences were found between CT, MRI, and EUS. Four patients were operated on without a preoperative location, all before 1995. For the lesion in the tail of the pancreas detected via intraoperative ultrasonography or palpation, none of the patients had preoperative MRI or EUS.

Surgical procedure

In most cases, the actual surgery follows the preoperative planning. In 2 cases in this study, however, the planned enucleation of a large cephalic lesion was not possible because of

the intraoperative lateral wound in the main pancreatic duct; as such, pancreaticoduodenectomy was performed instead. Overall, 25/50 patients (31%) underwent surgery via the laparoscopic approach, and 5 (20%) required conversion to accurately locate and resect the tumor. Twelve (48%) patients underwent pancreatic enucleation; 6 (40%), distal pancreatectomy; 3 (12%), distal pancreatectomy with splenectomy; and 4 (16%), caudal pancreatectomy. In addition, an open approach was adopted in 55/80 patients (69%); among them, 24/55 (44%) had pancreatic enucleation; 9/55 (16%), pancreaticoduodenectomy; 15/55 (27%), distal pancreatectomy; 6/55 (11%), distal pancreatectomy with splenectomy; and 1/55 (2%), resection of the uncinate process. Regarding the surgical approach, 34/80 patients (43%) had a tumor located in the head of the pancreas, 32/34 (94%) of whom were operated on using the open approach whereas 22/46 patients (48%) with tumors in other locations underwent laparoscopy ($p < 0.001$). In summary, 41 parenchyma-sparing pancreatectomies, including enucleation, caudal pancreatectomy, and uncinate process resection, were realised, with a 41% laparoscopic rate. The rate of laparoscopy was 28% before the year 2000 and increased to 55% after 2000 ($p = 0.09$) for the patients who underwent parenchyma-sparing pancreatectomy. In all the cases, the pancreas was considered soft.

Postoperative outcomes

The postoperative course is summarised in **Table 3**. The mortality rate was 6% (5/80), including 1 death from septic shock from the venous central catheter, 2 from grade C pancreatic fistula (bleeding and septic shock), 1 from liver abscesses due to hepatic artery thrombosis, and 1 from fungal septicemia. Four of these deaths occurred after pancreaticoduodenectomy. The morbidity rate was 72% ($n = 58$), including 24 severe (grade III/IV or V) complications (30%), and a pancreatic fistula occurred in 35 patients (44%), with 19 (24%) grade B or C. No significant differences were found between the patients who

underwent **parenchyma-sparing pancreatectomy** and those who underwent **formal pancreatectomy**. The surgery was successful in all the patients, with long-term postoperative normalization of the glycemia and insulin blood levels. One patient presented a distant liver recurrence 6 years after the initial pancreatic resection of a 2 cm insulinoma.

Evolution over time

The use of MRI increased after 2000 (< 2000: 24% vs. > 2000: 71%; $p < 0.001$) along with the rate of detected lesions (< 2000: 93% vs. > 2000: 97%; $p = 0.6$). The rate of laparoscopy also increased after 2000 (< 2000: 22% vs. > 2000: 41%; $p = 0.1$). The severe complications (death, severe complication, or severe leakage) did not significantly differ between the two study periods.

Discussion

Reported herein is the pre- and perioperative management of patients with sporadic non-malignant insulinoma over three decades, and several questions were raised. Once the hormonal diagnosis of organic hypoglycemia has been confirmed by a 72 h fasting test, the main challenge for the surgeon is *to accurately determine the tumor location*. The second challenge is *to define the best surgical strategy* with regard to the type of resection (**formal pancreatectomy** vs. **parenchyma-sparing pancreatectomy**) and the surgical approach (laparotomy vs. laparoscopy). The final objective is *to decrease the perioperative morbidity and minimize the late functional consequences of surgery*.

Accurate preoperative localization of insulinoma is one of the main issues in the management of this tumor. Indeed, insulinomas are small lesions (with 84% typically < 2 cm) randomly distributed in a fragile retroperitoneal organ⁶. Our study reported high accuracy in the detection and localization of insulinoma. We previously reported that dual-phase thin-section multidetector CT showed 93% localization sensitivity⁵. The performances of MRI reported in our study are also in line with those reported in previous studies^{15,16} and had been increased by the addition of diffusion-weighted MRI sequences^{15,17}. EUS has also been a major improvement in insulinoma location, with very high sensibility and specificity^{15,18}. **Nevertheless, as the results of the other investigation methods are usually available when EUS is done, the investigator is often helped by such results.**

EUS also allows contrast-enhanced ultrasonography, which began to be used in our department only after 2010, improving the localization of the pancreatic mass to approximately 8–10%^{19,20} and providing additional information about the vascularization of the tumor, FNA or biopsy (uncommonly needed for insulinoma), or EUS fiducial placement for an accurate intraoperative location of smaller lesions^{15,18,21}. Nuclear medicine has also improved the location and characterization of insulinoma since the disappointing sensitivity of

¹¹¹In-pentetreotide somatostatin receptor scintigraphy. Other somatostatin receptor imaging methods, such as ⁶⁸Ga-DOTATATE PET/CT, have shown sufficiently high sensitivity for identifying most insulinomas, and are considered by some adjunct imaging studies when the previous imaging findings were negative⁷. ¹⁸F-FDOPA PET/CT with carbidopa premedication has also shown interesting results, accurately **locating more than 80% of lesions when combined with carbidopa premedication and early pancreatic acquisitions**^{22,23}. **The policy regarding the use of nuclear-medicine imaging has evolved over time**, and more recently, ⁶⁸Ga-NOTA-exendin-4 PET/CT scan has shown high sensitivity and specificity for the detection and localization of insulinoma^{7,24}. With modern imaging tools combining CT, MRI, EUS, and nuclear medicine, insulinoma detection and localization can be adequately achieved preoperatively in nearly 100% of patients. In this setting, blind pancreatectomy or exploratory laparotomy is no longer advised⁸.

When the lesion has been identified, the next step for the surgical management of insulinoma is to define the best surgical procedure (**parenchyma-sparing pancreatectomy vs. formal pancreatectomy**) and surgical approach (laparoscopy vs. laparotomy). It is important to emphasize that the open approach to pancreatectomy remains the standard of care, and that there is no clear consensus regarding the indications for a minimally invasive approach in pancreatic surgery. Regarding pancreaticoduodenectomy, the laparoscopic approach did not show any clear advantage over open pancreaticoduodenectomy²⁵. Additionally, a Dutch multicentric randomized controlled study comparing laparoscopic and open pancreaticoduodenectomy was prematurely stopped because of increased mortality in the laparoscopic arm²⁶. In contrast, pancreatectomy without reconstruction (i.e., distal **or caudal** pancreatectomy and enucleation) remains the best procedure for insulinoma when feasible. Several studies and meta-analyses have reported that laparoscopic distal pancreatectomy is a safe and effective procedure associated with a lower rate of complications and a shorter length

of hospital stay compared to open surgery^{25,26}, but very few of these studies specifically focused on pancreas neuroendocrine tumors (PNETs). Similarly, laparoscopic enucleation is safe and effective for the treatment of benign and borderline pancreatic neoplasms²⁷, as confirmed by a meta-analysis of more than 400 patients, which showed that a minimally invasive approach does not induce a higher risk of pancreatic fistula and offers numerous advantages over the conventional surgery for pancreatic enucleation²⁸. This, along with the increasing relevant technical skills and experience, explains the more frequent use of the laparoscopic approach for **parenchyma-sparing pancreatectomy**. The choice of surgical technique between **parenchyma-sparing pancreatectomy** and **formal pancreatectomy** for the treatment of insulinoma is a crucial issue. The decision should be made according to anatomical considerations (size and location) and should take into account the distance between the lesion and the main pancreatic duct, which should be greater than 2–3 mm⁸. Nevertheless, **parenchyma-sparing pancreatectomy** has a similar postoperative mortality rate as and a higher risk of developing pancreatic fistula than **formal pancreatectomy**, especially when performed on a soft pancreas²⁹. Moreover, it is associated with excellent long-term functional results²⁹. In the present study, its overall morbidity rate was high, with 30% severe complications, 24% grade B or C pancreatic fistulas, and a 6% postoperative death rate, mainly observed after pancreaticoduodenectomy, with **an unusually high mortality rate. This underlines the risk posed by pancreatic surgery on a soft pancreas without main-pancreatic-duct dilatation even if performed in young and fit patients.** The **high** morbidity in recent years might have also been the consequence of the greater use of laparoscopic **parenchyma-sparing pancreatectomy**.

The major challenge for pancreatic surgeons is the significant rate of postoperative complications. In large surgical series for insulinoma, the reported mortality rate is 0–6%, with a 33–56% morbidity rate, whereas the mortality rate of pancreatic surgery ranges from

1% to 3% in high-volume centers^{38,39}, increasing to 6–10% when nationwide centers are considered^{40–42}. Considering these heterogeneous results, being treated in expert-organized high-volume centers presents a clear benefit for patients^{40–42}. Considering that the mortality rate of pancreatectomy is mainly related to pancreaticoduodenectomy, other therapeutic options have emerged in the last few years. From a technical view point, the prophylactic endoscopic placement of a pancreatic stent for “deep” pancreatic enucleations⁴³ may help extend the surgical indications for pancreatic enucleation, but this advantage may be overshadowed by the risk of developing post-endoscopic retrograde cholangiopancreatography pancreatitis. Controlled studies, although desirable, are unlikely to be feasible due to the low incidence of such lesions. If surgical resection has been advocated for years as the only curative option for insulinoma, local destruction of tumors through radiofrequency ablation (RFA) may be proposed as an alternative despite the fact that very few such procedures have been performed to date. In the literature, only about 60 patients with PNETs have been treated with RFA^{44–53}, but it has a clinical success rate of 83.3–100%^{44–53}. Nevertheless, the morbidity rate, technical constraints, and long-term results of this emerging treatment should be investigated in depth. Considering the experience with RFA so far, we believe that local ablation of tumors through it may be considered a suitable alternative for insulinomas located in the head of the pancreas.

The main limitation of this study is its retrospective design spanning over three decades due to the low incidence of insulinoma. This long inclusion period saw improvements in imaging techniques and perioperative management with the development of the laparoscopic approach. Even though this study’s sample consisting of 80 patients operated on for insulinoma may be viewed as restricted, this study was one of the largest monocentric studies that have been conducted to date, providing an interesting overview of the management of the rare disease of insulinoma^{8,16,18,30–34}.

In conclusion, the management of insulinoma has evolved dramatically over the recent decades with the emergence of modern imaging techniques, including cross-sectional imaging, EUS, and nuclear medicine. As such, accurate preoperative detection and localization is obtained in most patients. A major challenge remains, however: the significant postoperative morbidity rate, which is high after parenchyma-sparing pancreatectomy, counterbalancing the long-term benefits on both the exocrine and endocrine functions.

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Table and figures

Table 1: Characteristics of the study population (n = 80)

Characteristics		Median [IQR]; (range) or n (%)
Comorbidity	Age (years)	50 [36, 70]
	Gender (female)	50 (62%)
	BMI (kg/m ²)	26 [23, 28]
	ASA score	
	<i>I/II</i>	76 (95%)
	<i>III/IV</i>	4 (5%)
Diagnostic	Duration of symptoms before surgery (months)	13 [4–26]
	Glycopenic symptoms	74 (92%)
	<i>Coma</i>	10 (12%)
	<i>Faint</i>	32 (40%)
	<i>Epilepsy</i>	8 (10%)
	Adrenergic symptoms	46 (58%)
	Weight gain	40 (50%)
Surgery	Surgery after 2000	39 (49%)
	Laparoscopic approach	25 (31%)
	Parenchyma-sparing pancreatectomy	41 (51%)
	Type of surgery	
	<i>Enucleation</i>	37 (46%)
	<i>Pancreaticoduodenectomy</i>	9 (11%)
	<i>Distal pancreatectomy</i>	21 (26%)
	<i>Distal pancreatectomy with splenectomy</i>	9 (11%)
	<i>Caudal pancreatectomy</i>	4 (5%)
	<i>Uncinate process resection</i>	1 (1%)
	Duration of surgery (min)	210 [162, 240]
Accurate location before surgery	76 (95%)	

BMI = Body Mass Index; ASA = American Society of Anesthesiologists

Table 2: Capabilities of imaging tests for preoperative tumour detection

Imaging tests	Number of patients (%)	Number of patients with a correctly localised lesion	True localisation rate (%)	95% Confidence interval
CT	76 (96%)	58	76%	64–85
MRI	37 (47%)	28	76%	58–88
EUS	71 (89%)	64	90%	80–96
Somatostatin receptor imaging	26 (34%)	10	38%	21–59
CT and MRI	35 (44%)	32	91%	76–98
CT and EUS	68 (85%)	65	96%	87–99
CT and IRM and EUS and somatostatin receptor imaging	19 (34%)	19	100%	79–100

CT = computed tomography; MRI = magnetic resonance imaging; EUS = Endoscopic ultrasonography

Table 3: Outcome after pancreatic surgery for insulinoma in 80 patients

Outcomes	Total (n = 80)	Parenchyma- sparing pancreatectomy (n = 41)	Formal resection (n = 39)	p
90-day mortality	5 (6%)	1 (2.5%)	4 (10%)	0.95
90-day morbidity	58 (72%)	32 (78%)	26 (67%)	0.37
<i>Grade III, IV, V complications</i>	24 (30%)	13 (32%)	11 (28%)	0.92
Pancreatic fistula	35 (44%)	20 (49%)	15 (38%)	0.48
Grade B/C	19(24%)	13 (32%)	6 (15%)	0.15

Table 4: Outcome after pancreatic surgery for insulinoma in 80 patients

	Variables	Total (n=80)	Before 2000 (n=41)	After 2000 (n=39)	p	
Preoperative	Age	50 [36, 70]	50 [33, 62]	59 [36, 72]	0.28	
	Male	30 (38%)	16 (39%)	14 (36%)	0.95	
	ASA score	<i>I and II</i>	76 (95%)	40 (98%)	36 (92%)	
		<i>III and IV</i>	4 (5%)	1 (2%)	3 (8%)	0.57
	Neuroglycopenic symptoms	46 (58%)	17 (41%)	29 (74%)	0.006	
	CT	76 (96%)	38 (95%)	38 (97%)	1	
	MRI	37 (47%)	10 (24%)	27 (71%)	<0.001	
	Somatostatin receptor imaging	26 (32%)	9 (22%)	17 (44%)	0.07	
	EUS	71 (89%)	36 (88%)	35 (90%)	1	
	Non-located tumour	4 (5%)	3 (7%)	1 (3%)	0.64	
Intraoperative	Parenchyma-sparing pancreatectomy	41 (51%)	21 (51%)	20 (51%)	1.00	
	Laparoscopy	25 (31%)	9 (22%)	16 (41%)	0.11	
	Type of surgery	<i>Enucleation</i>	36 (45%)	21 (51%)	15 (38%)	0.14
		<i>Pancreaticoduodenectomy</i>	9 (11%)	3 (7%)	6 (15%)	
		<i>Distal pancreatectomy</i>	21 (26%)	14 (34%)	7 (18%)	
		<i>Distal pancreatectomy with splenectomy</i>	9 (11%)	2 (5%)	7 (18%)	
		<i>Caudal pancreatectomy</i>	4 (5%)	1 (2%)	3 (8%)	
		<i>Uncinate process resection</i>	1 (1%)	.	1 (3%)	
Drainage	74 (92%)	41 (100%)	33 (85%)	0.03		
Postoperative	Postoperative death	5 (6%)	4 (10%)	1 (3%)	0.39	
	Overall morbidity	58 (72%)	24 (59%)	34 (87%)	0.009	
	Severe complications	24 (30%)	12 (29%)	12 (31%)	1	
	Pancreatic fistula	35 (44%)	11 (27%)	24 (62%)	0.004	
	Severe fistula	19 (24%)	7 (17%)	12 (31%)	0.24	

CT = computed tomography; ASA = American Society of Anesthesiologists; MRI = Magnetic resonance imaging; EUS = Endoscopic Ultrasound