

# Insulinoma: Diagnostic Strategies and Surgical Treatment. A 22-Year Experience

MCC Machado, JE Monteiro da Cunha, J Jukemura, T Bacchella, S Penteado, EE Abdo  
MAC Machado, P Herman, AL Montagnini, H Pinotti

Department of Gastroenterology, Surgical Division São Paulo, Brazil

Corresponding Author: Marcel CC Machado, Hospital das Clínicas, Av. Dr. Enéas de Carvalho Aguiar  
255-9° andar s/9074, 05403-900 São Paulo, Brasil

Fax: +55 11 883 7720

## KEY WORDS:

Insulinoma;  
Islet cell tumor;  
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## ABBREVIATIONS:

Ultrasonography (US); Computed Tomography (CT); Transhepatic Portal Venous Sampling (THPVS); Nuclear Magnetic Resonance (NMR); Endoscopic Ultrasonography (EUS); Magnetic Resonance Imaging (MRI); Intraoperative Ultrasonography (IOUS)

## ABSTRACT

**Background/Aims:** The efficacy of preoperative localization methods and the results of the surgical treatment of insulinoma were studied.

**Methodology:** Fifty-nine patients referred for surgical treatment were studied and the results of the diagnostic tools for tumor localization were compared with findings at surgical intervention. The influence of the type of surgical procedure in the immediate and late postoperative course was also studied.

**Results:** Ultrasonography had a sensitivity of 30%, computed tomography 25%, angiography 54%, portal vein sampling 94%, endoscopic ultrasonography 27% and magnetic resonance 17%. Intraoperative palpation localized 98.2% of the tumors and by the addition of intraoperative echography, all lesions were identified. In 55 patients with benign lesions, 22 enu-

cleations, 25 distal pancreatectomies, 7 pancreatectomies plus enucleation and one duodenopancreatectomy were performed. Malignant tumors were treated by pancreatic resection, postoperative hepatic artery embolization and systemic chemotherapy.

There was no postoperative mortality. Pancreatic fistula was the most common complication. Three patients who underwent distal pancreatectomy developed late diabetes (9.3%).

**Conclusions:** Extensive preoperative investigation, mainly with invasive methods, is not indicated and by combining intraoperative palpation and echography most of the cases can be adequately dealt with. Preservation of pancreatic tissue with enucleation and preservation of the spleen are the best choice for treatment of benign insulinomas.

## INTRODUCTION

Although insulinoma is the most frequent endocrine tumor of the pancreas, it is a rare disease occurring with a frequency of about four in one million (1), limiting the experience in the treatment of these tumors to a few centers.

Despite the simplicity in making the diagnosis by the demonstration of inappropriately elevated blood insulin levels in the presence of low blood glucose during prolonged fasting (2) several aspects of the management of these tumors are still controversial.

The optimal therapy for pancreatic insulinoma is curative surgical excision, therefore preoperative or intraoperative localization of the lesion, is important for proper surgical treatment. Preoperative localization has included ultrasonography (US), computed tomography (CT) scan, celiac axis and superior mesenteric arteriography, transhepatic portal venous sampling (THPVS) and, more recently, arterial stimulation with venous sampling, nuclear magnetic resonance (NMR), scintigraphy with <sup>111</sup>indium-labeled octreotide and endoscopic ultrasonography (EUS).

Despite the evolution of diagnostic methods during recent years, tumor localization remains a challenge for clinicians and surgeons.

This report evaluates the efficacy, safety and the

real need of the various localization procedures and the results of surgical treatment of 59 patients with insulinoma treated in our institution over the last 22 years.

## METHODOLOGY

Fifty-nine patients with pancreatic insulinoma were treated between 1975 and 1996. They comprised 36 female and 23 male patients (Sex ratio, 1.5:1), mean age of 36.6 years (range, 12-70 years). Most of the patients (94.8%) were younger than 60 years old.

The interval between the onset of clinical manifestations and the diagnosis was less than one year in 27 patients, between one and five years in 21 and more than five years in eleven (range, 45 days to 15 years). The diagnosis was established in every case by demonstrating inappropriately elevated plasma insulin during prolonged fasting (72h) (2). Confirmatory test with determination of C-peptide used in 43 patients was invariably raised.

Until 1981 the preoperative identification of the tumor site was based essentially on the results of biselective celiac and mesenteric artery angiography. Since that time, besides selective angiography, performed in 24 patients, localization has included ultrasonography in 30 cases, CT scan in 28 and transhep-

atic portal vein sampling in 19. Magnetic resonance imaging (MRI) and EUS were performed in 6 and in 11 cases, respectively.

All patients underwent surgical treatment. At laparotomy, systematic search for possible metastasis was performed.

The pancreas was widely exposed to facilitate a thorough palpation of the gland in order to localize the tumor. Intraoperative ultrasonography (IOUS) was performed in the last 10 cases. The choice of the surgical procedure depended upon the tumor site within the pancreas and its relationship with the pancreatic vessels and ducts.

Enucleation was the preferred technique for tumors located in the head of the pancreas. Until 1990 tumors located in the body and tail of the gland were managed with partial pancreatic resection. Since that time the addition of IOUS limited the indications of pancreatic resection to those cases in which enucleation might jeopardize the main pancreatic duct integrity.

In patients with MEN Type I syndrome, extensive distal pancreatectomy associated with enucleation of head lesions were performed. Patients with multiple tumors were also treated by enucleation of head lesions associated with distal pancreatic resection.

Patients with malignant tumors were submitted to pancreatic resection and adjuvant chemotherapy, and when indicated, to hepatic artery embolization.

Frozen sections to confirm the diagnosis of neuroendocrine tumors were performed in all patients. Intra- and postoperative monitoring of blood glucose was performed in a routinely basis.

Eventual abdominal drain effluent was tested at postoperative day 7 for amylase content. A pancreatic fistula was diagnosed whenever any amount of effluent with amylase levels over two times the serum levels came out through the drain site

All patients were followed up for a period of 2 to 22 years.

## RESULTS

The results of preoperative methods used to localize the insulinoma are summarized in **Table 1**. The location of benign tumors within the pancreas is shown in **Table 2**. Multiple tumors, including those associated with MEN type I, were located mainly in body and tail of the pancreas (87.8%).

To evaluate the importance of preoperative procedures for tumor location, 59 patients were divided into three groups according to the period of the study.

In the first period (1979-1981), angiography was considered the procedure of choice. In one of the three patients treated in this period, angiography was not able to localize the lesion. All tumors were identified during the surgical exploration and successfully removed.

In the second period (1981-1990), when THPVS became available in our institution, the strategy used for localization of these lesions was changed. Arteriography was indicated when noninvasive methods (US and CT) were inconclusive. Nineteen patients in

**TABLE 1 Sensitivity of Preoperative Tumor Localization Methods**

Method	Patients N	True	False	False	Sensitivity %
		positive	positive	negative	
Ultrasonography	30	9	0	21	30
Angiography	24	13	1	11	54
Computed tomography	28	7	0	21	25
Portal vein sampling	18	17	1	1	94
Endoscopic					
ultrasonography	11	3	0	8	27
Magnetic resonance	6	1	0	5	17

**TABLE 2 Location of Benign Tumors (55 Patients)**

SITE	No. of patients	%
Head	16	29.1
Uncinate	7	12.7
Body	16	29.1
Tail	7	12.7
Multiple	9	16.4

which all these methods were negative, were submitted to THPVS, which was technically successful in 18 cases. Two patients (11%) experienced complications (bleeding and bile leak) after transhepatic portal venous sampling that required emergency operations.

During the second period, 38 patients were surgically treated and in 37 the lesions were correctly identified and removed. In only one patient, who had a blind distal pancreatectomy performed elsewhere, despite positive tumor localization in the head of the pancreas by the portal venous sampling, the lesion could not be identified during surgery due to intense scar tissue. At reoperation, after 12 months, the tumor was correctly localized by intraoperative ultrasonography and removed.

In the third period (1991-1996) invasive methods were abandoned as routine procedures because of their high morbidity. Within this period 18 patients were surgically treated.

Only US and CT were used in the preoperative period after the diagnosis of organic hyperinsulinism had been made. In this period, EUS and IOUS also became available and were used in 11 and 10 patients, respectively. In one patient, only IOUS was able to localize the tumor.

Another emphasis in this third period was the usage of conservative surgical procedures. In two patients, IOUS now routinely used in our service, avoided extensive pancreatic resection as it correctly delineated the pancreatic anatomy. In this same period five spleen-preserving distal pancreatectomies were performed.

Surgical procedures and the outcome of the 55 patients with benign tumors are depicted in **Table 3**. Only one patient with a persistent pancreatic fistula was reoperated for the implantation of the fistula in a Roux-en-Y jejunal loop 4 months after a tumor enucleation. The other patients with pancreatic leaks presented spontaneous healing. The patient with a com-

**TABLE 3 Surgical Procedure and Postoperative Complications in 55 Benign Tumors**

Surgical procedure	No.	Pancreatic fistula <sup>xx</sup>		Common bile duct injury		Biliary fistula	
		no.	(%)	no.	(%)	no.	(%)
Enucleation	22	9	40.9	1	4.5	1	4.5
Distal pancreatectomy	25	15	60	-	-	-	-
Distal pancreatectomy plus enucleation	7	5	71	-	-	-	-
Pancreatico-duodenectomy	1	-	-	-	-	-	-
Total	55	29	52.7	1	1.8	1	1.8

<sup>xx</sup>: Any volume of drainage with an amylase level above 2x the serum value.

**TABLE 4 Operations Performed in Four Patients with Malignant Tumors**

Surgical procedures	No. of patients	Survival years
Distal pancreatectomy	2	1 and 14*
Pancreatoduodenectomy	1	2
Enucleation plus oophorectomy	1	3

\* Still alive.

mon bile duct injury caused by the enucleation of a 3-cm deep-seated cephalic tumor was successfully submitted to a choledocojejunostomy in the early postoperative period.

The operations performed on patients with malignant tumors are shown in **Table 4**. Two patients with multiple hepatic metastasis were submitted to pancreatic resection followed by systemic chemotherapy and hepatic artery embolization. Both died at one and two years after the procedure with uncontrollable hypoglycemia.

The patient submitted to tumor enucleation and oophorectomy had a small pancreatic tumor, peritoneal spread and ovaries implantations. After resection of all visible lesions, the patient was treated with systemic chemotherapy and died 3 years later.

The only patient with malignant tumor that survived more than 5 years has a MEN type I syndrome. This patient treated by subtotal pancreatectomy and a metastatic peripancreatic lymph-node removal is still alive 14 years after the procedure.

Three patients (9.3%) developed insulin dependent diabetes two years after distal pancreatectomy for treatment of benign tumor. One patient had an episode of hypoglycemia 3 years after tumor enucleation. He is now on diet control without hypoglycemia. All other patients remain asymptomatic.

## DISCUSSION

Insulinoma is the most common endocrine tumor of the pancreas accounting for 17% of all islet tumors of the digestive tract (3). However, it is a rare tumor that affects 4/1.000.000 people but this rate is probably underestimated (1).

The disease presents a higher incidence between 30 and 60 years (4). In this report 94.8% of the patients were younger than 60 years.

The time delay before diagnosis is often long due to the nonspecific nature of symptoms. In this series,

46.4% of the patients were diagnosed before one year of symptoms but, in 17.8%, the delay was longer than 5 years as has been reported by others (1,5). This delay may be the reason for neurological and psychiatric impairment seen in some patients (6).

Since surgical excision is the treatment of choice for these tumors associated to the fact that, in 10-20% of the cases the lesions cannot be identified during surgical exploration (7,8), many surgeons emphasize the importance of preoperative localization of insulinomas (9-11). However, the most effective technique to localize small and benign insulinomas, is still under discussion. Different techniques for localization of the tumor have been studied showing a great disparity in the success rates.

The inexpensive and noninvasive US predicted preoperatively the exact tumor site in 28.1% of the cases in this series (**Table 1**). In other reports, the sensitivity of US was slightly higher but there is high operator dependence (12,13).

In the present report, CT was successful in 25% of the cases (**Table 1**). Low sensitivity of CT was also observed in other series (6,12). Spiral CT may have a higher accuracy than ordinary CT but there is still a lack of experience with this method. Biselective celiac axis and superior mesenteric arteriography enabled definite localization of the tumor in 54,1% of the cases in this series. Though similar results were obtained by others (4,12-14), they are substantially lower than those reported from the Hammersmith Hospital and the Mayo Clinic (6,15). The low sensitivity of EUS in this study may be due to the fact that, most of the tumors were localized in the body and tail of the pancreas, where a low sensitivity of EUS has been reported (16). However, higher diagnostic EUS rates, have been achieved in other series (17,18).

MRI was used in a few patients in this series with high cost-effective rates. However, a recent study with ten patients showed excellent results with 100% of the lesions detected by this method (19).

THPVS was a reliable method for localizing insulin secretion sites in this report (94.4%). This is an invasive technique and not free from morbidity (11.1% in this series) (12). A possible useful method for the detection of insulinoma is the calcium stimulation by arterial injection followed by venous sampling. This technique was found to be promising in the first nine cases reported by Doppman *et al.* (20). Although these methods can identify the pancreatic region where the tumor is most likely located, the surgeon still needs to palpate or visualize the tumor by the use of IOUS before embarking on a resection. It seems not reasonable to carry on a pancreatic resection based only on the findings of one of the former methods as it has been previously proposed (21).

Scintigraphy with <sup>111</sup>indium-labeled octreotide has also been reported as a useful method for localization of insulinomas but its sensitivity is lower than arteriolar stimulation and venous sampling (22).

In this series, intraoperative palpation enabled precise tumor localization in 54 out of 55 benign cases. This finding is in agreement with many other authors

(10,12,13,18,23). However, there are some reports showing 80-95% of positive localization rates with the use of intraoperative palpation (4,24) what led many authors to stress the value of IOUS in the precise localization of insulinoma (7,13,25-27).

Besides tumor localization, IOUS may also serve as a guide to the decision between enucleation and resection, since it delineates the relationship between the tumor and the main pancreatic duct.

In this series, the combination of palpation and IOUS enabled tumor localization in 100% of the cases as reported by others (18,25). On the basis of the excellent results obtained in the third period of this study, without the use of angiography, portal venous sampling or arterial simulations, we believe that invasive techniques should be performed only after unsuccessful surgical exploration and when all other methods were negative (9,24,28).

The high incidence of late diabetes (9.3%) observed after distal pancreatectomy, makes enucleation the treatment of choice for pancreatic insulinomas. However, deeply seated tumors or those closely related to the main pancreatic duct, are best treated by pancreatic resection. In these situations, segmental resection could be the alternative to reduce the impairment of pancreatic function (29). In the last 5 years, spleen-preserving technique has been our choice when distal pancreatectomy is indicated for body and tail tumors (30).

In patients with multiple endocrine neoplasia type I tumors were always multiple and, in 87.8% of the cases, located in the body and tail of the pancreas. These patients were managed by extensive left pancreatectomy plus enucleation of the head tumors as has been previously proposed with excellent results. (31-33).

Only one patient with malignant tumor is still alive 14 years after pancreatic resection and removal of a metastatic lymph node. This patient had a MEN type I syndrome that is probably the reason for his long survival since malignant insulinoma not associated with MEN type I syndrome is a severe disease with high recurrence rates.

There was no postoperative mortality and despite the high incidence of pancreatic fistulas, as has been previously observed (34), only one patient required reoperation. The high incidence of pancreatic fistula in this report may be due to the criteria used for the definition of this complication.

Our present policy is to limit preoperative investigation in patients with proved hyperinsulinism to conventional US and proceed to surgical exploration and careful pancreatic palpation combined with IOUS. Other diagnostic methods for tumor delineation are indicated only in patients submitted to previous surgical exploration, bearing scar tissue that makes impossible the distinction between tumor and normal pancreatic tissue.

Late diabetes and postoperative septic complications may be avoided by preservation of pancreatic tissue and spleen.

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