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# Surgical Treatment of Pancreatic Insulinomas: A Series of 15 Years

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**ABSTRACT**

Insulinomas, although rare, are the most common pancreatic functioning neuroendocrine tumors. The diagnostic workup is commonly made late in time and surgical treatment is the only curative method. Our aim was to analyze the surgical approach to pancreatic insulinomas, through a 15-year series of patients who underwent surgery for this matter. From January 2006 to December 2020, we performed a retrospective review of the medical records of all the patients who underwent surgical treatment for insulinoma. Fourteen patients with insulinoma performed surgical intervention, 78,6% were of the female gender and the mean age was 48 years (19-86 years). Four (28,6%) of the tumors were located in the head of the pancreas, 5 (35,7%) in the body and 5 (35,7%) in the tail. Complications occurred in 4 patients (28,6%) following surgery. On follow-up, there was one (7,1%) case of local recurrence, thus necessitating a new surgical intervention [1-8].

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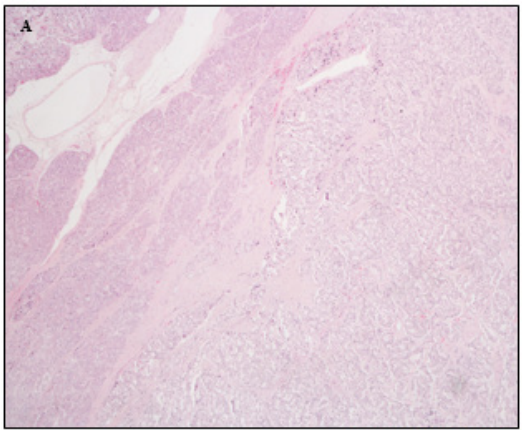
## Introduction

Insulinoma is a functioning neuroendocrine tumor (F-NET) originating from the insulin secreting beta cells of the Langerhans pancreatic islets, with uncontrolled hormone secretion. Although rare, with an estimated incidence of 1-3 cases per million per year, NETs prevalence has been increasing over the past years and insulinoma is the most common pancreatic F-NET, accounting for about 4-20% of resected NETs of the pancreas. It may occur at any age and there is higher incidence in the female gender (60%) [9-11].

Insulinomas are usually benign, solitary and are evenly distributed in the head, body and tail of the pancreas, but in about 10% they are malignant. Extrapancreatic insulinomas are extremely rare but have been described in the duodenal wall, ileum, jejunum and splenic hilum. In 10% they are multiple [12,13]. The hallmark of the diagnosis of insulinoma is "Whipple's triad" or "triad of insulinoma" (symptoms caused by hypoglycemia, low blood glucose level during the episodes and relief of symptom after blood glucose level normalization through glucose administration) and clinical symptoms may be divided into neuroglycopenic (impaired mental status, visual disturbances, stupor, seizures and coma) and autonomic (tremor, diaphoresis, palpitations and anxiety). For insulinoma diagnosis, the best diagnostic test is prolonged fasting (48-72 hours) with measurement of blood glucose, serum insulin, C-peptide and proinsulin, as well as neuroendocrine tumor histology.

Because of this characteristic clinical presentation of hypoglycemia, insulinomas are usually diagnosed earlier in the course, while they are still small in size (<2 cm). However, symptoms may be scarce or uncharacteristic and thus, diagnosis is sometimes made 5 years after the beginning of symptoms. Differential diagnosis includes psychiatric, neurologic and cardiovascular diseases [14-18].

They are usually small, well-demarcated and greyish-white. To our knowledge, there are no true known etiological factors for sporadic solitary insulinomas. However, germline mutations on *MEN1* and *MAFA* are associated with familial insulinomatosis. Moreover, insulinomas share most mutational events with others NETs, such as *MEN1*, *DAXX* and ATRX. Histologically, pancreatic NETs usually have a solid or trabecular growth pattern, sometimes with amyloid deposition (5% of cases). It is not mandatory to evaluate insulin with immunohistochemistry, in the setting of a solitary pancreatic NET, although in cases of insulinomatosis and multiple NETs, insulin stain is required (Figure 1) [7].



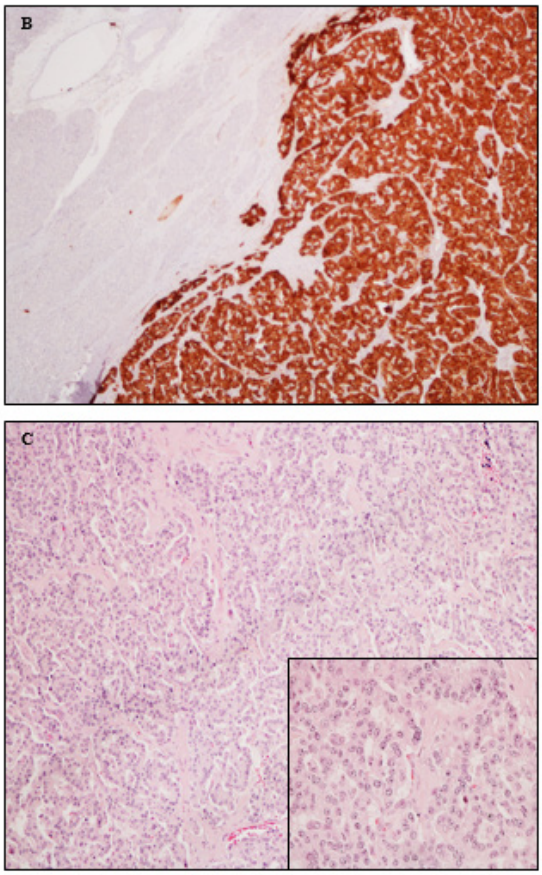



**Figure 1:** Interface between normal pancreas parenchyma and insulinoma (A – H&E, 40X; B – Insulin, 40X). This tumor is composed of cords, trabeculae and solid areas of cells with abundant eosinophilic cytoplam (C – H&E, 100X), and round to oval nuclei with "salt and pepper" cromatin (Insert – H&E, 400X).

Diagnosis is confirmed with clinical, laboratory and radiological results. Computerized Tomography (CT) is the most commonly used imaging tool, with a sensitivity reaching up to 94% [19]. Tumor location prior to surgery is of major importance, especially when laparoscopic surgery is being considered. When performed by experienced surgeons, the combination of tumor palpation and intraoperative ultrasound (US) has a very high diagnostic acuity. Surgical resection is the only curative method and surgical options are enucleation, distal pancreatectomy with or without splenectomy, pancreatoduodenectomy, central pancreatectomy and total pancreatectomy, depending on tumor location, size and malignancy risk. Laparoscopy has been increasingly used and has shown to be safe and feasible in experienced centers. The expected 5-year survival rate following resection is up to 95-100% and recurrence may be seen in about 5%.

## Patients and Methods

Between January 2006 and December 2020, we made a retrospective analysis of 14 patients with the diagnosis of insulinoma and who were submitted to surgery at the Department of Surgery of Centro Hospitalar Universitário Lisboa Norte, Portugal. All patients had hypoglycemia and hypoglycemic symptoms that developed after fasting or exertion and improved after glucose intake. Diagnosis was made using European Neuroendocrine Tumor Society criteria [20-22]. The most commonly performed imaging method was abdominal CT (71%). The surgical choice was made based on tumor size, location and risk of malignancy. Intraoperative US was performed routinely. All cases were reviewed and classified according to the 5th edition of WHO Classification of Digestive System Tumours [7]. Follow-up was based on clinical, laboratory and radiological evaluation of the patients.

## Results

Fourteen patients were studied with a mean age of 48 years (range, 19-86 years) and 78,6% were of the female gender. Diagnosis was made preoperatively in all patients based on symptoms, laboratory results and imaging findings on CT or Magnetic resonance imaging (MRI), and confirmed postoperatively with histopathological examination. The average time from initial symptoms to diagnosis was of 3 years.

Tables 1 and 2 summarize and compare the surgical characteristics of these patients.

Four (28,6%) of the tumors were located in the head of the pancreas, 5 (35,7%) in the body and 5 (35,7%) in the tail. Average size was 1,5cm (range, 0,4-2,6 cm). Enucleation was performed in 7 patients (50%), central pancreatectomy in 2 (14,3%) and distal pancreatectomy in 5 (35,7%). 4 of the distal pancreatectomies were spleen preserving. In all procedures intraoperative ultrasound was performed. 3 procedures were undertaken laparoscopically: 1 enucleation and 2 distal pancreatectomies but conversion to open surgery was undertaken in 1 case of distal pancreatectomy due to technical difficulties. Median length of postoperative stay was 15 days (range, 2-54 days).

**Table 1: Surgical characteristics of 14 patients with pancreatic insulinomas**

| | Patients, No. (%) | | | |
|---|---|---|---|---|
| | **Overall (n=14)** | **Enucleation (n=7)** | **Central Pancreatectomy (n=2)** | **Distal Pancreatectomy (n=5)** |
| Tumor site | | | | |
| • Head | 4 (28,6) | 4 (57) | 0 (0) | 0 (0) |
| • Body | 5 (35,7) | 1 (14) | 2 (100) | 2 (40) |
| • Tail | 5 (35,7) | 2 (29) | 0 (0) | 3 (60) |
| Length of postoperative stay | | | | |
| • Average (range, days) | 15 (2-54) | 18 (5-54) | 18 (17-19) | 9 (2-18) |
| • Median (days) | 9 | 6 | 18 | 7 |
| Mortality | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Morbidity | 4 (29) | 2 (29) | 1 (50) | 1 (20) |
| Intra-abdominal collections | 2 (14) | 1 (14) | 1 (50) | 0 (0) |
| Grade B pancreatic fistulas | 2 (14) | 2 (29) | 0 (0) | 0 (0) |
| Pancreatic insufficiency | 1 (7) | 0 (0) | 0 (0) | 1 (20) |
| Local recurrence | 1 (7) | 1 (14) | 0 (0) | 0 (0) |

**Table 2: Open vs. Laparoscopic surgery**

| | Patients, No. (%) | | |
|---|---|---|---|
| | **Overall (n=14)** | **Open surgery (n=12)** | **Laparoscopic surgery (n=2)** |
| Tumor site | | | |
| • Head | 4 (28,6) | 3 (25) | 1 (50) |
| • Body | 5 (35,7) | 5 (42) | 0 (0) |
| • Tail | 5 (35,7) | 4 (33) | 1 (50) |
| Length of postoperative stay | | | |
| • Average (range, days) | 15 (2-54) | 14 (4-54) | 21 (2-40) |
| • Median (days) | 9 | 9 | 21 |
| Mortality | 0 (0) | 0 (0) | 0 (0) |
| Morbidity | 4 (29) | 3 (25) | 1 (50) |
| Intra-abdominal collections | 2 (14) | 1 (8) | 1 (50) |
| Grade B pancreatic fistulas | 2 (14) | 1 (8) | 1 (50) |
| Pancreatic insufficiency | 1 (7) | 1 (8) | 0 (0) |
| Local recurrence | 1 (7) | 1 (8) | 0 (0) |

There were no mortality cases and morbidity was observed in 4 patients (28,6%) following surgery. One patient had an intra-abdominal collection, another had a grade B pancreatic fistula, and one had both complications. Pancreatic insufficiency was seen in one patient. Intra-abdominal collections were treated with percutaneous drainage. One grade B pancreatic fistula was treated conservatively and the other with endoscopic retrograde cholangiopancreatography (ERCP) and placement of a pancreatic prothesis in the Wirsung's canal. On follow-up, there was one (7,1%) case of local recurrence, in an insulinoma of the tail submitted to enucleation. 2 years following surgery the patient began with hypoglycemic symptoms, and CT confirmed local recurrence. The patient underwent distal pancreatectomy with splenectomy and is currently free of recurrence. Mean follow-up time was of 26 months. Histopathologic confirmation of insulinoma was made in all surgical specimens. All but one of the tumors were G1 well-differentiated NETs (Ki67 < 3%, mitotic count <2 per 10 high-power field (HPF)), with the remaining tumor being G2 well-differentiated NET (Ki67 4%, mitotic count <2 per 10 HPF).

## Discussion

Pancreatic insulinomas were more prevalent in the fifth decade and in the female gender. Tumor location was similarly distributed throughout the pancreas. These findings match the results seen in literature [9-11]. All insulinomas located in the head of the pancreas were submitted to enucleation, but those located in the body or tail had different surgical approaches depending on tumor location, size and malignancy potential.

Enucleation was the most performed procedure (50%), mainly in tumors located in the head of the pancreas. Although it was verified that the average length of postoperative stay following enucleation was long, it may be explained by the two patients who had postoperative complications, as the median length of postoperative stay was lower comparing to the other procedures. Distal pancreatectomy was associated with low average and median length of postoperative stay.

Albeit the small number of laparoscopic surgeries in this study, its usage in our center has been increasing and has been shown to be safe. There's been no mortality cases, but 4 patients presented morbidity: 2 of the patients were submitted to enucleation (1 laparoscopic surgery and 1 open surgery), 1 to central pancreatectomy and 1 to distal pancreatectomy. Both enucleations were in women aged 59 and 70 with insulinomas located in the head and body respectively. The tumor sizes were 1,7 and 1,1cm respectively. The first patient underwent laparoscopic surgery and developed abdominal collection treated with percutaneous drainage, and a grade B pancreatic fistula treated conservatively. The second patient also presented with a grade B pancreatic fistula treated with a pancreatic duct prothesis via ERCP [23].

Although enucleation is a less invasive surgical technique, it's association with postoperative pancreatic fistula is relatively high, thus it's important to emphasize that pre and intra-operative tumor location and its distance to the main pancreatic duct is of major importance [24-36]. There was also one case of intra-abdominal collection in a 30-year-old man submitted to central pancreatectomy. This complication was treated with percutaneous drainage. The fourth patient was a 53-year-old woman with an insulinoma of the body submitted to distal pancreatectomy. The surgery began via laparoscopy but was converted to open surgery due to technical difficulties in approaching the tumor with safety. The patient developed pancreatic insufficiency post-operatively.

Even though central pancreatectomy entails a more technically challenging surgery, it has the advantage of preserving more pancreatic parenchyma, thus reducing the risk of pancreatic insufficiency. Recurrence following resection is low, and it's more likely in neuroendocrine tumors grade G2. In our study, we had one case of local recurrence, in a 48-year-old man with an insulinoma of the body submitted to enucleation. The pathologic evaluation reported a G1 T1N0 NET with Ki-67 of 1% and a mitotic count 0 per 10 HPF. Tumor margin was not assessable. Following diagnosis of recurrence, the patient underwent distal pancreatectomy with splenectomy and is currently free of recurrence.

## Conclusion

Pancreatic insulinomas are the most common functioning neuroendocrine tumors of the pancreas. Diagnosis is often made late in time and surgery is the only curative treatment. The most important prognostic markers are stage and grade. The role of minimally invasive interventions has been increasingly used, not only as a surgical approach, but also in the treatment of post-operative complications.

## Conflict of Interest and Funding

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