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Neuroendocrine pancreatic tumors: the laparoscopic approach

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Die laparoskopische Chirurgie neuroendokriner Pankreastumore

Zusammenfassung. *Grundlagen:* Laparoskopische Eingriffe am Pankreas bei Patienten mit neuroendokrinen Tumoren befinden sich in Bezug auf ihre Indikationen und ihre Technik noch in der Evaluationsphase. Das Ziel dieser Arbeit ist einerseits die klinischen und die histologischen Aspekte unterschiedlicher neuroendokriner Tumore des Pankreas zu diskutieren und andererseits ihre chirurgischen Therapiemöglichkeiten in Bezug auf die laparoskopische Chirurgie zu evaluieren.

Methodik: Wir stellen einen Überblick über die unterschiedlichen Formen der minimal invasiven Techniken für die Therapie neuroendokriner Pankreastumore dar. Welcher Patient von welchem laparoskopischen Eingriff profitieren wird, kann nur durch ausreichende Information über die Erkrankung erarbeitet werden.

Ergebnisse: In Abhängigkeit von der Lokalisation, Größe und der Nähe des Tumors zum Pankreasgang hängt die Notwendigkeit der laparoskopischen Enukleation oder einer distalen Pankreasresektion ab. Die Milzerhaltung während einer laparoskopischen distalen Pankreasresektion ist möglich.

Schlussfolgerungen: Die laparoskopische Enukleation oder laparoskopische Pankreasresektion bringen bei Patienten mit einem neuroendokrinen Pankreastumor einen klaren Vorteil in Bezug auf Kürzung des Spitalsaufenthaltes, rasche Erholung, früherem Erlangen der körperlichen Aktivitäten und einem exzellenten kosmetischen Ergebnis. Die genaue Auswahl der Patienten ist eine unerlässliche Bedingung für ein erfolgreiches Ergebnis.

Schlüsselwörter: Laparoskopische Pankreasresektion, laparoskopische Enukleation, neuroendokrine Pankreastumore.

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Summary. *Background:* Laparoscopic pancreatic procedures in patients with neuroendocrine pancreatic tumors are still at an evaluation stage with regard to their indications and techniques. The aim of this paper is to discuss the clinical and pathological features of a variety of neuroendocrine pancreatic tumors and the surgical approach by means of minimally access surgery.

Methods: We provide an overview of the different minimally access techniques for the treatment of neuroendocrine pancreatic tumors. This knowledge will provide the information needed to ascertain the suitability of the laparoscopic approach for any particular patient.

Results: Laparoscopic treatment consists of enucleation or distal pancreatectomy; the choice is based on the size, location and proximity of the lesion to the pancreatic duct. Splenic preservation is feasible when performing laparoscopic distal pancreatectomy.

Conclusions: Laparoscopic pancreatic enucleation or laparoscopic pancreatic resection offers a clear benefit for patients with neuroendocrine pancreatic tumors in terms of reduction of hospital stay, a rapid recovery to initiate previous activities and excellent cosmesis. Careful selection of patients is essential to successful outcomes.

Key words: Laparoscopic pancreatic resections, laparoscopic pancreatic enucleation, neuroendocrine pancreatic tumors.

Introduction

Neuroendocrine tumors of the pancreas (NPTs) are slowly growing neoplasms and are of relatively benign nature in 70–80% of individuals. With the exception of gastrinomas and somatostatinomas which are found in the pancreatic head in the 60–70% of cases other NPTs are located predominantly in the body and tail of the pancreas. This localization makes NPTs suitable for the laparoscopic approach. However NPTs are rare neoplasms and the evaluation of the indications and limits of laparoscopic surgery is difficult to establish for an individual surgeon.

Table 1. Functioning neuroendocrine pancreatic tumors

Tumor	Cell type	Predominant hormone	Major clinical symptoms	Tumor location	Percent malignant
Gastrinomas	G	Gastrin	Recurrent peptic ulcer	Pancreas 50% Duodenum 50%	90
Insulinoma	B	Insulin	Hypoglycemia (fasting or nocturnal)	Pancreas	10
VIPoma	?	Vasoactive intestinal polypeptide (VIP)	Watery diarrea, hypokalemia, achlorhydria	Pancreas 90%	60
Glucagonoma	A	Glucagon	Diabetes mellitus, necrolytic migratory erythema	Pancreas	90
Somatostatinoma	D	Somatostatin	Diabetes mellitus	Pancreas 55% Duodenum 45%	80
GRFoma	?	Growth-hormone releasing-hormone	Acromegaly	Pancreas 30% Lung 50% Jejunum 15%	60
ACTHoma	?	ACTH	Cushing's syndrome	Pancreas 90%	95
Ppoma	PP/F	Pancreatic polypeptide (PP)	Hepatomegaly Abdominal pain	Pancreas100%	80

The aim of this paper is to discuss the clinical and pathological features of a variety of NPTs. This knowledge will provide the information needed to ascertain the suitability of the laparoscopic approach for any particular patient.

Indications and limits of the laparoscopic approach

NPTs may be functioning or nonfunctioning. Functioning tumors are those associated with a clinical syndrome that is caused by hormone release, and are named according to the hormone that they secrete (Table 1) [1]. The most established tumors are the following:

Gastrinomas have an annual incidence of 0.5–1.5 per 10^6 persons [1], the majority of the tumors are located either in the pancreas or duodenum. Less frequent sites are the small intestine and the stomach. Approximately 20% of patients have a family history of neuroendocrine tumors, and 20–25% of patients (particularly those with duodenal tumors) have the MEN1 syndrome. MEN1 patients –associated gastrinomas usually present at an earlier age, and most MEN-1 patients have coexisting hyperparathyroidism or pituitary disease at the time of presentation.

Gastrinomas manifest with the characteristic Zollinger-Ellison syndrome (ZES), which is caused by hypergastrinemia associated with hypersecretion of gastric acid. The most common symptom is abdominal pain caused by *peptic ulceration.* Ulcers are often recurrent and/or resistant to medical or surgical treatment. The other characteristic component of the syndrome is diarrhea, which occurs in the majority of patients. An estimated 60% of gastrinomas run a malignant course. Approximately 50% of patients with pancreatic or duodenal gastrinomas have lymph node and/or liver metastases at presentation. The laparoscopic approach should be attempted only in patients with well localized tumors in the pancreas [2].

Insulinomas have an annual incidence of 1–2/10^6 persons /year, and usually occur in patients between 30 and 60 years of age. Insulinomas are small (81% measure 20 mm or less), usually solitary, and are almost always confined to the pancreas. Approximately 10% of the tumors are malignant tumors. Multiple tumors occur in up to 10% of patients and should raise the possibility of MEN-1 syndrome. The tumor is characterized by hypersecretion of insulin and hypoglycemia. Most patients present with neurological symptoms of hypoglycemia, such as visual disturbances, altered mood/confusion, weakness, transient motor defects, fatigue, dizziness, and even coma. Small insulinomas can be treated effectively by either laparoscopic enucleation or laparoscopic pancreatic resection [2–15].

Vasoactive intestinal polypeptide (VIP)-secreting tumors (VIPomas) account for less than 10% of NPTs. They are much more common in women (with a female:male ratio of 3:1), and most frequently occur at around the fourth decade of life. Up to 90% of VIPomas originate from the pancreas, and are usually solitary tumors. Approximately 5% of VIPomas are MEN-1 associated. Over 60% of pancreatic VIPomas are malignant, and by the time of diagnosis up to 60% have metastasized to lymph nodes, liver, kidneys, or bone. The hypersecretion of VIP produces a syndrome characterized by severe secretory diarrhea, associated with hypokalemia and dehydration, and is commonly called the *Verner-Morrison Syndrome*. The diarrhea is intermittent in 53% of patients, and continuous in 47%. A less frequent symptom is cutaneous flushing, which is characteristically erythematous, and occurs in 20% of patients. Analysis of the Mayo Clinic data reported by Smith et al. [16] showed that only 44% of patients were the VIPomas resectable, and those tumors only 28% were resectable for cure. Of the patients with resectable disease, the laparoscopic approach may be indicated when the tumor is localized in the body-tail of the pancreas and has no metastatic spread.

Glucagonomas are less than half as common as VIPomas, with an annual incidence of 0.01–0.1 new cases per million. They are slightly more common in women (55%), and usually occur after 45 years of age. Most glucagonomas are large solitary tumors, which are almost exclusively found in the pancreas. They generally exhibit highly malignant behaviour: approximately 90% of patients already have lymph node and/or liver metastases at presentation. Glucagonoma is rarely associated with MEN-1. Glucagonomas secrete excessive amounts of glucagon and cause a distinct syndrome that is characterized by a specific dermatitis (necrolytic migratory erythema), weight loss, diabetes mellitus, and anemia. The cutaneous lesions are one of the most common manifestations of the disease, being present in about 90% of patients. Glucose intolerance, with or without frank diabetes mellitus, develops in 85%, principally due to the hyperglycemia that results from glucagons-stimulated hepatic glycogenolysis and gluconeogenesis. Weight loss is almost universal, and probably reflects the known catabolic actions of glucagon. Most glucagonomas are found in the pancreatic head and are usually large tumors. The laparoscopic approach is rarely used in the surgical management of these tumors [2].

Somatostatinoma are usually solitary tumors, which originate in the pancreas or small intestine. They are tumors, and account for less than 5% of NPTs. Somatostatinomas release large amounts of somatostatin and cause a distinct clinical syndrome characterized by diabetes mellitus, gallbladder disease, and diarrhea with steatorrhoea. Approximately 40% of patients with somatostatinomas remain asymptomatic, and the tumor is discovered incidentally. The laparoscopic approach may be indicated in well localized tumors suitable for curative pancreatic resection [2].

ACTHomas tumors are very rare, and are usually located in the pancreas (90% of cases). They produce ACTH and ectopic Cushing's syndrome. The tumors often co-secrete, and so the syndrome is often associated with another syndrome. Approximately 95% have metastasized at the time of diagnosis.

Nonfunctioning tumors are those that have all the histological characteristics of a NPTs, but have no associated clinical syndrome related to hormone hypersecretion. The incidence of non-functioning pancreatic endocrine tumors is $1–2/10^6$ persons/year, and these tumors represent about 60% of the total number of NPTs. These tumors are often producing hormones, but remain clinically "silent" for a number of reasons. The peptides or hormones produced may not produce a known specific clinical syndrome, for example, pancreatic polypeptide (PPomas), calcitonin, and chromogranin A. In other cases, the tumor may produce a peptide which is well known to produce a clinical syndrome, but fails to release it, or produces it at only very low plasma concentrations. The tumors are usually unifocal, between 20 and 40% of non-functioning NPTs are MEN-1 associated, and in this situation may be multifocal. Patients present with symptoms related to expanding tumor mass, most commonly jaundice and epigastric pain, but also with weight loss, steatorrhoea, upper gastrointestinal bleeding, recurrent pancreatitis, fatigue and malaise. An increasing number are being detected incidentally. Reported malignancy rates at presentation are 60–90%. Patients with left-sided pancreatic lesions are appropriate candidates for laparoscopic pancreatic resections [4].

Preoperative evaluation: localization and extent of NPTs

The most important step in the management of NPTs is the determination of the primary tumor location, and the tumor extent (location and extent metastasis). Somatostatin receptor scintigraphy (SRS) is the initial imaging modality of choice in patients with any type of NPT, except insulinoma, for its great sensitivity in detecting both the primary tumor, and hepatic metastasis and bone metastasis. SRS should be used in combination with CT and MRI to assess the localization and extent of the tumor, in order to plan the surgical treatment, to monitor the effects of treatment, and to monitor the progression of the disease.

Notwithstanding recent refinements in imaging techniques for patients with insulinoma, preoperative diagnostic studies still have the same limitations when assessing the number and exact locations of the tumors. Endoscopic ultrasonography (EUS) is the most sensitive modality for detecting insulinomas, with preoperative detection rates of 86–93%. In recent years, spiral CT scanning has become more successful in localizing insulinoma and may also provide additional information regarding suspected malignancy. The accuracy rate of ^{111}-pentatreotide scintigraphy is 20–70%. Most believe that preoperative imaging is of limited benefit when an operative procedure is combined with intraoperative ultrasonography. The laparoscopic approach and laparoscopic ultrasonography (LapUS) provide information similar to that obtained by means of open intraoperative ultrasonography and can identify lesions that are undetectable by preoperative imaging techniques. Preoperative imaging might be unnecessary in patients using open surgery; however, when using the laparoscopic approach, despite the advantages of LapUS, it is still worthwhile to attempt preoperative imaging, as it provides useful information for patients positioning and port placement.

Surgical treatment: the laparoscopic approach

Surgery remains the only curative modality currently available for resectable NPTs. Complete surgical resection may be possible in those tumors that are localized at presentation (60% of gastrinomas, 90% of insulinomas, 10–30% of nonfunctioning tumors, and 10–40% of vipomas and glucagonomas). Surgical management varies with tumor type, location, and size. Small NPTs may be treated with enucleation. NPTs exceeding 3 cm in diameter should be managed with either a Whipple resection and periduodenal node resection or distal pancreatectomy with resection of the peripancreatic lymph nodes, depending on the localization of the tumor. But the question remains open on laparoscopic approach. With the latter, the advantages should be those of all laparoscopic procedures, which obviously reduce the parietal damage in the abdomen. This may be associated with reductions in postoperative pain, hospital stay, reduced

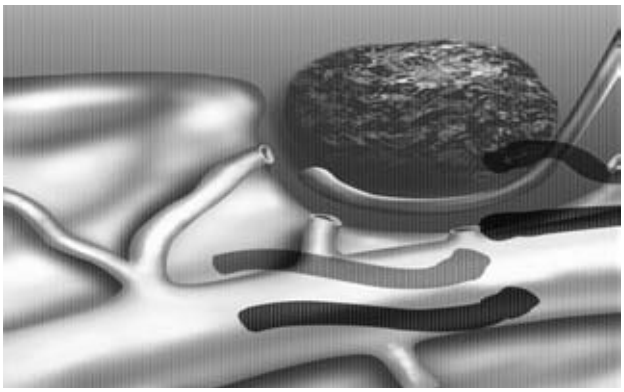

Fig. 1. Insulinoma in the body of the pancreas. An incision with the cautery is made around the area (defined by LapUS) of the adenoma. The lesion is usually shelled out with a blunt dissection placing clips on the pancreas slide and cauterizing toward the insulinoma side. The bed of the tumor should be examined to be certain there is no evidence of a major pancreatic duct injury that occurred during dissection.

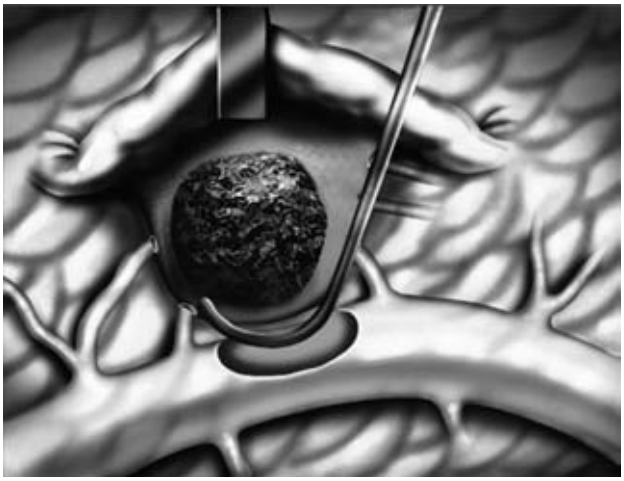

Fig. 2. Great care should be taken during tumor enucleation by blunt dissection. A danger is the injury of the Wirsung duct when using the blunt end of the hook coagulator.

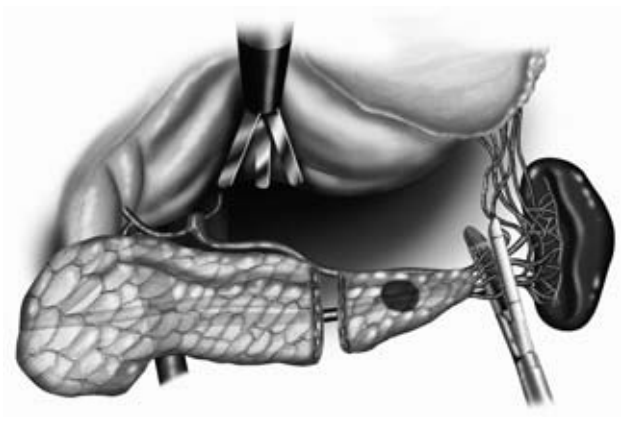

Fig. 3. Spleen-preserving distal pancreatectomy with splenic vessels preservation. When the insulinoma is localized in the tail of the pancreas enucleation is usually not possible because of the proximity of the tumor to the Wirsung duct.

peritoneal adhesions, and an earlier return to previous activity. A cosmetic advantage is also clear because of the absence of long abdominal incisions, and this should be taken into account, especially in young women with NPTs. At present, laparoscopic tumor enucleation and laparoscopic left pancreatic resection are feasible and safe procedures. Although the feasibility of laparoscopic Whipple resection has been clearly demonstrated, its safety and efficacy have not.

Sporadic insulinoma, which are characterized as solitary, small, resectable, and not metastasic, are suitable for the laparoscopic approach. Approximately 81–90% of insulinomas are less than 2 cm in size, and the lesions are distributed equally throughout the head, body, and tail of the pancreas. The surgical strategy in patients with solitary insulinoma should be restricted to remove the solitary tumor in about 90% of the cases. Enucleation or resection will depend upon the localization of the tumor in the pancreas and the findings from LapUS (Figs. 1, 2, 3). Clear indications for enucleation are tumors located at the periphery of the gland and tumors on the surface of the parenchyma totally or partially covered by a thin layer of pancreatic tissue. However, when a tumor is located in the distal part of the tail of the pancreas, it may be more convenient to remove that part of the gland containing the adenoma. Also, when the tumor is in close proximity to the Wirsung duct, resection should be indicated to avoid pancreatic fistula or profuse bleeding. The reported success rate for laparoscopic resection of insulinoma varies from 60 to 100% [4, 6, 11–13]. In most reports the reasons for conversions were failure of LapUS to localize the tumor intraoperatively or location of tumor in difficult access sites.

Whenever insulinoma are multiple, multiple endocrine neoplasia type I (MEN-I) should be suspected. Demeure et al. [17] suggested that patients with insulinomas associated to MEN-I required a different surgical approach than the usual method used for patients with sporadic insulinomas. Enucleation alone of an insulinoma in patients with MEN-1 would likely lead to missed tumors and failed operation. More than 75% of patients with insulinoma and MEN-1 had multiple pancreatic tumors. It seems that subtotal distal pancreatectomy, preserving the spleen, combined with enucleation of any tumors identified in the pancreatic head should be the standard operation. In these patients, we encourage the use of the laparoscopic approach (Figs. 4, 5).

It is mandatory to LapUS to recognize other tumors not seen in preoperative localization studies, in order to identify the demarcation between normal pancreas and macroscopic disease pancreas, and to determine the optimal site of transection.

For other NPTs, laparoscopic surgery should be also indicated. Without evidence of distant metastasis or local invasion, the malignancy of NPTs is difficult to demonstrate before and even during surgery. Tumor size is usually considered an indicator of malignancy, but remains relatively insensitive and nonspecific. We have demonstrated in 10 patients with non-functioning tumors (mean size 6 cm) that the laparoscopic approach is technically feasible and safe for large, benign-appearing pancreatic tumors localized in the body–tail of the pancreas, up to

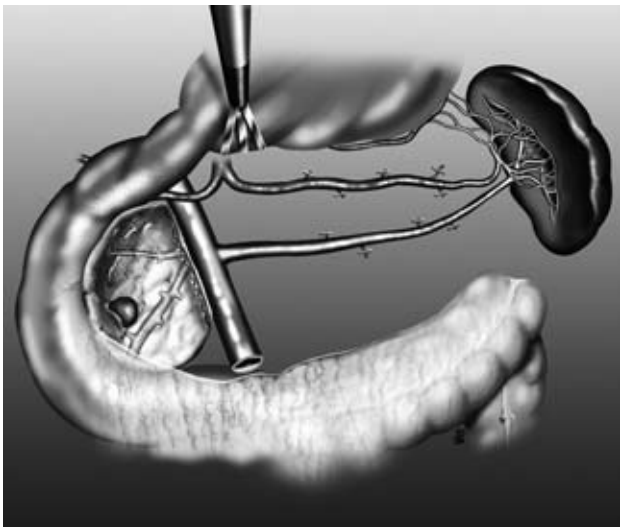

Fig. 4. Spleen-preserving 70–80% distal pancreatectomy with splenic vessels preservation for patients with insulinomas in the setting of MEN-1. Laparoscopic enucleation when a tumor is found in the head of the pancreas.

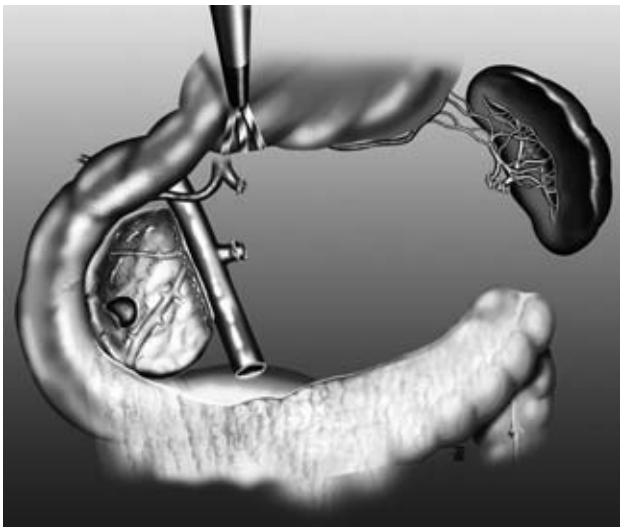

Fig. 5. Spleen-preserving 70–80% distal pancreatectomy without splenic vessels preservation. It is mandatory to preserve the short gastric vessels and if possible the left gastroepiploic vessels. Laparoscopic ultrasonography is also mandatory to rule out a macroscopic tumor in the head of the pancreas. In case of localized tumor in the pancreatic head, tumor enucleation should be attempted.

11 cm. For the surgeon, the main risk during laparoscopic dissection of a large pancreatic tumor is tumor spillage. Currently, we believe that this approach is contraindicated in patients with locally advanced tumors that may require en bloc resection of adjacent organs. However, in experienced hands, laparoscopic surgery can be performed for large, potentially malignant NPTs.

We attempted laparoscopic pancreatic resection in one patient with VIPoma, but the case was converted to open surgery after documenting lymph node metastasic spread. Also, the laparoscopic approach was successfully used in two patients with glucagonoma. Laparoscopy has been used in the treatment of hepatic neuroendocrine metastasis. Berber et al. [19] have recently reported, that laparoscopic radiofrequency ablation in patients with liver metastasis from neuroendocrine tumors, provides excellent local tumor control with overnight hospitalization and low morbidity.

Conclusion

Using the criteria of Cushieri and Jakimowicz [18], the probable benefit of minimally invasive surgery over conventional open surgery depends on the ratio of access trauma to procedural trauma. Surgical enucleation for solitary, small, benign insulinomas is better achieved using the laparoscopic approach (rather than laparotomy) in terms of parietal damage of the abdomen. LapUS facilitates operative decision-making. Laparoscopic pancreatic resection is feasible and safe in patients with left-sided NPTs, thereby avoiding long abdominal incisions. LapUS identifies the demarcation between normal pancreas and the tumor and is useful for determining the optimal site of transection. Spleen salvage should be attempted with and without splenic vessels preservation.

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