Surgical Strategy in the Treatment of Pancreatic Neuroendocrine Tumors

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Summary

Endocrine pancreatic tumors are rare and their surgical treatment is often debated. This review analyzes the management and the different indications in functioning and non-functioning neoplasms. The choice among different procedures is described as well as the role of intraoperative ultrasound. Moreover, the different patterns of tumor spread are considered (local, loco-regional and metastatic) along with the indications according to the main controversies relating to cytoreductive surgery, transplantation and multiple endocrine neoplasia type 1 patients.

Introduction

In recent years, new diagnostic and therapeutic procedures have increased the attention given to pancreatic endocrine tumors, but they still remain a rare disease (incidence 4/1,000,000 inhabitants/year) [1]. They are usually characterized by a good prognosis (5-year overall survival of 80%) and by a slow progression, giving a wide range of options for surgical treatment [2]. Moreover, surgery is justified not only for curative purposes but also for palliative purposes.

Even if they belong to the same family, they can be very different as for functional status, tumor size, multiplicity, potential or manifest malignancy and stage of the disease at the time of diagnosis. In 2000, WHO published a new clinicopathological classification which can be useful in better correlating these parameters with the prognosis [3]. However, their heterogeneity makes it hard to define accepted surgical protocol. The matter is further complicated by the length of the natural history. But in the case of radical resection, it is difficult to establish what the true impact of surgical therapy on prognosis actually is.

In the present paper, we will try to point out the more important issues on the surgical strategy in non-functioning and functioning pancreatic endocrine neoplasms.

Surgical Indications in the Case of Unidentified Lesions

The presence of a hormonal syndrome may give rise to a singular problem for surgical strategy, namely, making an early clinical diagnosis, without the presence of an evident lesion at imaging techniques. This is especially true for the two most common functioning pancreatic tumors, such as insulinoma and gastrinoma. Notwithstanding achievements accomplished in the field of imaging techniques, they are not able to evidence the tumor in 10-20% of cases, due to their small size and, in the case of
gastrinomas, due to their possible extraduodenal pancreatic origin. In this situation, when a team of experts reaches a diagnosis, the surgeon can perform a laparotomy with a good certainty of identifying the tumor. The surgical procedures have to be quite rigorous [4, 5, 6]. After a careful abdominal exploration, the pancreatic gland should be widely exposed using the Kocher maneuver, and dissection of both the superior and the inferior margins of the gland and of the splenic ligament. In this way, the pancreas will become accessible for a bi-digital manual examination and the entire parenchyma can be studied using intra-operative ultrasound with a 10 or a 7.5 MHz probe. Insulinomas appear visually as gray-reddish masses, with a higher consistency in comparison to the surrounding parenchyma. Ultrasound reveals a hypoechogenic aspect. The use of intra-operative ultrasound allows the identification of 88% of insulinomas, 91% of pancreatic gastrinomas and approximately 30% of duodenal gastrinomas [7, 8].

Since gastrinomas may have an extraduodenal pancreatic localization, the procedure should be completed with a careful exploration of the stomach, the mesenterium, and the entire abdominal and pelvic cavities. In Zollinger-Ellison syndrome, the surgeon should also perform a duodenal transillumination followed by a 3 cm longitudinal duodenal incision. This maneuver allows a complete examination of the entire mucosal surface, including the medial wall. The sensitivity of duodenotomy is indeed higher (100%) in comparison to palpation (61%), and intra-operative ultrasound imaging (26%) associated with trans-illumination (64%) [9]. If properly executed, this protocol is associated with an extremely low percentage of failure (less than 7%) in identifying the tumor [4]. According to Norton et al. [10], in the case of gastrinomas, the use of this protocol has increased the frequency of detection from 64 to 92% largely due to the increased attention to duodenal localizations. When, despite such a procedure, the tumor cannot be localized, the literature clearly states the uselessness of a so-called “blind resection” [11, 12]. In consideration of the fact that insulinomas do not have a particular prevalence for any specific localization within the pancreas and their low grade of malignancy (only 10% of cases) [13], a surgeon who fails to identify the lesion during laparotomy, should refrain from pancreatic resection. A postoperative Dopmann test must be carried out in order to localize the disease [14, 15]. When even this latter fails to localize the tumor, close follow-up of the patient is recommended until the lesion is identified. Although data regarding this issue are incomplete, it would seem that a blind resection of the pancreas should be considered only in those cases in which venous sampling allows the localization of the tumor and when medical therapy does not result in satisfactory control of the clinical symptoms [16]. As regards gastrinomas, although these tumors are characterized by a high grade of malignancy (60-90% of cases) [12], a blind resection would appear in any case disproportionate due to both the high variability of localization and, thanks to medical therapy, the current control of disease progression. Proton pump inhibitors have restricted the indication for surgical procedures, such as antrectomy and total gastrectomy, with the aim of controlling clinical symptoms through the removal of the target organ [11, 17].

Radical Resections

After identification, there is no doubt about the surgical indication in all localized tumors. The choice of procedure will depend on the risk of malignancy based on parameters such as type, size and features of the mass. Atypical resection (enucleation or middle pancreatectomy) has the advantage of preserving the pancreatic parenchyma as much as possible, thereby reducing the risk of late exocrine/endocrine insufficiency. However, since in these procedures, a lymphadenectomy is not usually performed, they are not “foolproof” in oncological terms.
Enucleation can usually be performed in those cases where the lesion is single, capsulated, of limited dimensions (less than 4 cm in diameter) and does not involve, or is “sufficiently far” from the main pancreatic duct [18]. When the lesion is in the body and/or nearby the Wirsung duct, a middle pancreatectomy should be the procedure of choice. In these instances, enucleation would be at very high risk for a postoperative fistula. Insulinomas and small non-functioning tumors are the most indicated cases. It has been debated whether or not enucleation is the correct treatment also for gastrinomas which are usually small in size but with a high rate of malignancy. Authors advocating atypical resection report a 10-year survival rate of 94% but with a low disease-free postoperative rate (51%) [4]. This percentage is reported to be close to 90% by authors who routinely perform typical resections [19]. In all other situations, a typical resection (pancreaticoduodenectomy or distal pancreatectomy), in accordance with the site, appears to be the standard procedure [20, 21, 22]. In fact, in the case of malignancy, these resections allow a consensual node dissection as standardized for exocrine tumors.

Extended Resections

When radicality is doubtful or only achievable by the demolition of nearby organs (stomach, colon, kidney, adrenal gland) or by further vascular resection, an intra-operative histological diagnosis is indicated [12, 23, 24, 25, 26]. If the endocrine nature of the tumor is confirmed, an aggressive treatment is justified even if other organs and/or portal-mesenteric vein confluence resection are necessary. The involvement of the superior mesenteric artery and/or the celiac trunk is less frequent [23, 25]. In our experience, the median survival of this group of patients is 65 months, but 66% of them eventually present liver metastases at follow-up.

Radical Resections in Case of Liver Involvement

At diagnosis, about 60% of non-functioning endocrine pancreatic tumors and 50% of gastrinomas are metastatic. Whenever a resection leaves no residual disease, an aggressive approach is proposed in the presence of synchronous or metachronous hepatic metastases [27, 28, 29, 30]. In fact, simultaneous resection of both the primary tumor and all the hepatic metastases (or their subsequent removal) does not seem to be an unfavorable prognostic factor [31, 32]. Unfortunately, at diagnosis, this is feasible in only less than 20% of patients, due to the high percentage of multifocal and bilateral metastases. When this approach is applicable, the 5-year actuarial survival rate is 73%, but recurrence is almost always the rule, with the time to progression proportional to the intrahepatic diffusion [31, 32].

Not Radical Surgical Resections (Debulking)

The appropriate management of patients whose resection would leave macroscopic residual disease (R2) is still being debated. This situation is usually due to the presence of “notable and massive” local infiltration (vessels, organs, retroperitoneum) and/or not completely resectable liver metastases. Many surgeons have suggested cytoreductive surgery or debulking. What cytoreductive surgery means is an even more controversial matter. It should be remembered that, from an oncological point of view, the debulking must reduce the mass by at least 90%, which is seldom possible. This rationale is based on: 1) the possibility of treating the residual mass with loco-regional therapies; 2) allowing better control of the symptoms due to hypersecretion, whenever present; 3) prolonging survival. Duodenal pancreatic mass debulking has also been suggested as a preventive method against complications.
related to local growth of the tumor, such as recurrent pancreatitis, biliary or intestinal occlusion and gastrointestinal bleeding. In truth, surgical resection does not appear justifiable in all cases of locally incomplete resectable disease. In fact, existing data do not justify a local partial resection of the mass, which would lead to the fragmentation of the tumor in the peritoneal cavity. Moreover, the hypervascularization of these neoplasms implies a high risk of bleeding. Since local relapse is the rule, the eventual palliation of symptoms due to the mass is only temporary. Furthermore, the survival rate of unresected patients with locally advanced disease remains 44% at 5 years [33].

For those patients who complain of biliary and/or gastrointestinal tract occlusion, palliative surgical procedures are indicated. The long-term life expectancy of these patients, whenever endoscopic palliative treatment was preferred, would mean endoprosthesis substitution several times during the course of their lives [12, 34]. For this reason, surgical bypasses would be preferred. In the case of jaundice, even without alimentary disturbances, it might be useful to add a prophylactic gastrointestinal-anastomosis to biliary decompression [35, 36, 37].

The cytoreductive surgery of the hepatic metastases after radical resection of the primary tumor seems to play a limited role in non-functioning or low symptomatic tumors since it does not lead to a significant increase in survival [31, 38]. In non-functioning lesions, when less than 90% of the tumor is resectable and there are no symptoms of loco-regional compression, chemoembolization seems to be the best treatment [31]. Whenever feasible, debulking seems to better control the symptoms in functioning tumors such as malignant insulinomas. In this latter situation, medical treatment leads only to limited relief. On the contrary, for gastrinomas, the availability of an effective medical therapy contraindicates liver cytoreduction. However, even in the presence of unresectable liver metastases, total resection of the primary tumor seems to play a role [34]. In fact, resection of the primary tumor might avoid compressive symptoms, optimizing palliation. Moreover, the disease can be “compartmentalized” exclusively to the liver, thus facilitating subsequent appropriate therapies.

As an alternative to surgery, embolization and chemoembolization may be proposed for treatment of residual hepatic disease [38, 39, 40, 41, 42, 43, 44]. To tie off the hepatic artery alone is not enough since collateral circulation quickly appears [45]. At present, the first results with dia-termo-ablation are beginning to emerge [46]. Limited experience still makes this technique experimental.

Liver transplantation should be also considered as experimental. Authors agree in selecting patients under 60 years of age, with non-resectable hepatic metastases, no extra-hepatic abdominal diffusion and when the most standard therapeutic options have failed [47, 48, 49]. Patients selected following the above indications show a global survival rate of 36% at 5 years with 17% of survivors completely disease-free [49]. Indications based on rapid tumor growth seem to be more disputable [47, 48].

Cholecystectomy

Somatostatin analogue therapy is usually the treatment of choice for those patients suffering from non-resectable disease. This treatment is associated with a risk of developing gallstones and gallstone sludge in up to 50% of cases. Moreover, liver chemoembolization presents a high risk of cholecystitis. For all these reasons, cholecystectomy should be performed whenever a surgical procedure is required [50].

Surgical Indications in multiple endocrine neoplasia type 1 (MEN-1)

Surgeons should bear in mind that the association of endocrine pancreatic tumors
with hereditary diseases, such as MEN-1, may change surgical strategy. Up to 75% of patients affected by MEN-1 develop synchronous or metachronous islet cell pancreatic or duodenal tumors: gastrinomas (60%), insulinomas and non-functional tumors (20% each) [51]. The operative management must be individualized taking into account their tendency towards multicentricity and the high recurrence rates. The timing of surgery is still under debate. Some authors suggest surgery only for masses larger than 2-3 cm in size due to their high metastatic potential [52, 53]. Others feel that aggressive surgery is indicated in the presence of any biochemical positive marker [54]. The aim of surgery is to achieve complete tumor resection preserving the pancreatic function and minimizing the morbidity. Due to the high rate of multicentricity, intraoperative ultrasound is mandatory. The frequent multiplicity of the lesions often results in a subtotal distal pancreatectomy with enucleation of those tumors located in the head or in the duodenum [55]. Total pancreatectomy, though effective as “organ disease eradication” and as prevention of relapses, is not generally recommended. It should be taken into consideration only in those cases in which lesions are multicentric and the familial history evidences high mortality rates for the disease.

**Keywords**
Neuroendocrine Tumors; Pancreatic Neoplasms; Surgical Procedures, Operative

**Abbreviations**
MEN-1: multiple endocrine neoplasia type 1

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