Surgical Therapy

10

Rossella Bettini, Stefano Partelli, Stefano Crippa,
Letizia Boninsegna and Massimo Falconi

10.1 Introduction

The surgical management of pancreatic neuroendocrine neoplasm (PanNEN) is often challenging due to the heterogeneous presentation and the different biological behavior of these neoplasms. Recent research advances have led to more accurate recommendations for the management of these tumors [1-3]. This chapter summarizes the state of the art concerning the indications for surgery and the optimal surgical approach of sporadic tumors as well as PanNENs associated with multiple endocrine neoplasm type 1 (MEN1) syndrome.

10.2 Sporadic Disease

Surgery of sporadic PanNENs should be tailored according to the stage of the disease and the biological behavior of the tumor(s).

10.2.1 Functioning PanNENs of Unknown Primary

When primary tumor cannot be assessed but the presence of a hormonal syndrome related to endocrine pancreatic tumor hypersecretion has been ascertained, the main aim is to identify the lesion. Despite the widespread use of high-quality imaging techniques, insulinomas and gastrinomas remain undetected in 10-20% of cases [4, 5]. However, the absence of a preoperative local-

M. Falconi (✉)
Department of Surgery and Oncology, "G.B. Rossi" University Hospital, Verona, Italy
and General Surgery Unit, "Sacro Cuore – Don Calabria" Hospital,
Negrar (VR), Italy
e-mail: massimo.falconi@univr.it

P. Pederzoli and C. Bassi (eds.), *Uncommon Pancreatic Neoplasms*,
Updates in Surgery
DOI: 10.1007/978-88-470-2673-5_10, © Springer-Verlag Italia 2013

ization should not be considered a contraindication for surgery in patients with proven functional disease.

In these cases, an exploratory laparotomy should include a careful abdominal inspection of the liver, stomach, and mesentery. The pancreatic gland should be well exposed according to the Kocher maneuver and its superior and inferior margins accurately dissected. The entire pancreatic gland is then accessible for a bi-digital manual examination and the parenchyma can be thoroughly explored by intraoperative ultrasound (IOUS) with a 7.5- or 10-MHz probe. Macroscopically, insulinomas appear as gray-reddish masses, with a harder consistency than the surrounding parenchyma; the ultrasound examination reveals a hypoechogeneic aspect. An intraoperative localization, as determined by IOUS, can be achieved in 92–98% of the cases [4-6]. IOUS can also assess the relationship of the tumor with the main pancreatic duct, guiding the surgeon in an enucleation or a standard pancreatic resection.

Whereas IOUS is able to identify nearly 91% of pancreatic gastrinomas, the detection rate decreases to approximately 30% for duodenal gastrinomas. In this setting, pancreatic exploration must be followed by a trans-illumination of the duodenum and a 3-cm incision of the descending duodenum, in order to assess the medial wall, where the majority of gastrinomas are found. The accuracy of duodenotomy is indeed higher than either palpation alone or IOUS imaging associated with trans-illumination [4, 5]. The surgical procedure should also include a resection of the peri-pancreatic lymph nodes as well as a lymphadenectomy of the celiac trunk and hepatic ligament, based on the risk of a primary lymph node gastrinoma.

In all cases, a careful intraoperative examination of the specimen by the pathologist is mandatory in order to confirm the presence of the lesion.

If this protocol fails, "blind" resections are discouraged and patients should undergo strict follow-up while the hypersecretion symptom is controlled by medical therapy [7].

10.2.2 Localized PanNENs

When a PanNEN is localized, surgery is the treatment of choice. Nevertheless with the advent of high-resolution imaging techniques, small non-functioning PanNENs are increasingly discovered, and it is now debated whether all small and asymptomatic lesions should be routinely resected [8]. In this subgroup of patients, non-operative management has been recently advocated for incidentally discovered PanNENs < 2 cm [9]. Although data on the non-operative management of these forms are still lacking, a strict yearly follow-up seems to be a reasonable recommendation. Any significant increasing in the size of these tumors should be promptly recognized and patients should be addressed to surgery.

The optimal surgical resection for localized PanNEN is still debated. Two main surgical approaches are currently available: typical (i.e., pancreatico-

duodenectomy or left pancreatectomy with or without spleen preservation) and atypical (i.e., enucleation or middle pancreatectomy) resections. The surgical choice is based on technical considerations (site, proximity to Wirsung duct, etc.) and on the aggressiveness of the disease, which is mainly correlated with the size of the lesion [8, 9] and with the invasion of nearby organs. A typical pancreatic resection is always recommended in the presence of large PanNENs (main diameter > 2 cm), organ invasion and/or clinical symptoms. Typical pancreatic resections are associated with a high incidence of peri-operative complications as well as exocrine and endocrine insufficiency. These complications along with the increasingly incidental recognition of small and asymptomatic lesions have led to the increased use of parenchyma-sparing techniques or atypical resections, such as enucleation and middle pancreatectomy. Atypical resections have been proposed in the management of PanNENs, especially when they are well-demarcated and small in size [10]. In the absence of others signs of malignancies, tumor size represents the main criteria in the choice of the most appropriate surgical approach. Currently, a diameter of 2 cm seems to be reasonably safe for a limited resection [10]. A middle pancreatectomy can be appropriate for small tumors of the pancreatic body whereas an enucleation should be considered only if the main pancreatic duct can be safely preserved. Atypical resections reduce the risk of long-term endocrine/exocrine impairment as pancreatic parenchyma is spared by these techniques [11, 12]. However, atypical resections are associated with a high rate of pancreatic fistulas although the latter are mostly transient and with a low clinical impact [11]. Second-look surgery for those tumors with high-grade malignancy is mandatory after an atypical resection. Furthermore, the most recent guidelines suggest that nodal sampling with intraoperative pathological examination should be always performed [13].

10.2.3 Locally Advanced PanNENs

When a PanNEN is locally advanced and a potentially curative resection is feasible (R0–R1), a more aggressive surgical approach is justified. Several authors have demonstrated the benefit in terms of survival after pancreatic resection of locally advanced PanNENs when no residual macroscopic disease is present along the surgical margins [14].

Surgery always includes a typical pancreatic resection with standard lymphadenectomy, associated, if necessary, with nearby organ resection or vascular resection. Splenectomy is routinely performed in distal pancreatectomy. During this procedure, the adrenal gland, retroperitoneal tissue, and left kidney can be easily removed, if infiltrated. Tumors of the pancreatic head that involve the stomach can be removed by a Whipple procedure, while those infiltrating the colon require standard or segmental colon resection. When the entire pancreatic gland is involved, total pancreatectomy should be considered. A portal or superior mesenteric vein infiltration can occasionally occur;

in these cases, the surgeon can achieve negative resection margins by performing segmental resection of the superior mesenteric vein or splenomesenteric portal vein confluence. By contrast, an arterial resection is rarely performed when the mesenteric-celiac arterial axis is completely involved. The presence of celiac trunk invasion is not an absolute limitation for distal pancreatectomy, as prior reports have described efficacious dissection of the central-axis arteries or graft substitution; however, these procedures can be associated with severe diarrhea due to denervation of the intestinal plexa. The role of lymphadenectomy in these tumors is still a matter of debate, but a regional lymph node dissection along the hepatoduodenal ligament, celiac trunk, and superior mesenteric artery should be a standardized technique for invasive PanNENs.

When locally advanced pancreatic carcinomas present with massive local infiltration and resection would be incomplete, leaving macroscopic residual disease, there is no support for cytoreductive surgery (R2). A partial resection would, in fact, expose the patient to a high risk of bleeding and to the possible spread of tumor cells in the peritoneum. Recurrence, moreover, is the rule, with no guarantee of there being any advantage in terms of survival.

10.2.4 Metastatic PanNENs

Surgery also plays an important role in metastatic disease, although the presence of extra-abdominal disease should always be ruled out preoperatively. Hepatic surgery might require a wide range of different types of resections according to the number of liver metastases, their locations, and the hepatic reserve [15-17]. The operation can be performed as a one- or two-step procedure and always requires an accurate IOUS evaluation. Complete resection is associated with a 5-year survival rate of 60–80% compared with 30% in unresected patients [18-21]. However, due to the high incidence of multifocal and bilateral metastases, with liver involvement frequently exceeding 75%, a radical liver resection is possible in < 20% of patients [18]. However, recurrence is the rule, with a median time to progression of 16–20 months and a 5-year survival of 50–60% [22].

Debulking resections (R2) might be alternatively offered with palliative intent to all patients in whom 90% of the tumor burden can be safely removed, as part of a multimodal approach (combined or followed by other ablative therapy, peptide receptor radionuclide therapy, bio- and chemotherapy) [17]. Metastatic disease also can be treated by other interventional procedures [17, 23], mainly trans-arterial embolization (TAE), trans-arterial chemo-embolization (TACE), and radiofrequency ablation (RFA). Such procedures can be used as loco-regional ablative therapy per se or as an adjunct to palliative surgery. TAE or TACE are endovascular interventional radiology procedure that may be used to treat multiple or large liver metastases. Data regarding survival after TACE for metastatic PanNENs are still lacking although the procedure has been demonstrated as effective in reducing tumor size [24, 25]. RFA may

be performed either intraoperatively or via a percutaneous approach, with a low morbidity rate in either case, although its role is still limited to selected patients [26].

Cytoreductive surgery limited to the primary tumor in patients with unresectable metastases is proposed in selected cases to alleviate mass-related symptoms by reducing tumor burden. Moreover, the analysis of retrospective series has demonstrated a measurable advantage in terms of survival after debulking [27] .

Liver transplantation is limited to 1% of patients. The main criteria for this approach include the presence of multiple metastases not amenable of other invasive procedures, the absence of extra-abdominal disease, a low Ki-67 value, and stable disease 1 year after diagnosis. Nevertheless, outcomes after transplantation for PanNEN liver metastases are heterogeneous and the efficacy of this strategy is still unclear [3].

10.2.5 Laparoscopic Approach for PanNENs

Both distal pancreatectomy and enucleation can be safely performed laparoscopically. The advantages of minimally invasive surgery are less postoperative pain, a better cosmetic result, a reduced length of hospital stay, and a faster postoperative recovery; the rate of pancreatic fistula formation is comparable to that observed after open surgery. It has been demonstrated that laparoscopic resections are safe and feasible in patients with presumed benign PanNENs whilst they are still a controversial procedure for those with malignancies. Whereas the laparoscopic approach is optimal for insulinomas and small non-functioning tumors, the role of laparoscopic surgery for gastrinomas is probably limited [28, 29].

10.3 PanNEN in Multiple Endocrine Neoplasia Type 1 (MEN1) Syndrome

Patients with MEN1 usually develop synchronous or metachronous PanNENs of various types: gastrinomas (54%), insulinomas (18%), and non-functional tumors (80–100%). The association of PanNENs with hereditary diseases such as MEN1 changes the surgical strategy due to the tendency towards disease multicentricity and the high rate of recurrence. To date, whereas surgery remains mandatory in case of tumor-related symptoms and a functioning tumor (e.g., insulinoma), the role of surgical treatment in small (< 2 cm) non-functioning PanNENs or gastrinomas is still unclear [30-32]. Small non-functioning PanNENs are commonly asymptomatic and their incidence is increasing due to better detection following the widespread use of modern cross-sectional imaging techniques. In MEN1 patients, only a few small tumors develop liver metastases or influence survival. Most recent studies suggests the

active follow-up of small lesions and to operate only in the event of larger tumors (> 2 cm) and/or tumors growing or metastasizing during follow-up [32]. Similarly, since patients with small gastrinomas have excellent long-term survival also without surgical treatment and Zollinger–Ellison syndrome is easily controlled with medical treatment, surgery is commonly recommended only for lesion > 2 cm.

When surgery is indicated, the procedure ranges from enucleation to total pancreatectomy [6, 30]. The latter, although effective, is not generally recommended; instead, total pancreatectomy should be limited only to those patients in with multicentric lesions and a familial history of high mortality due to the disease. Enucleation is rarely the only needed procedure, mostly in small nonfunctioning PanNENs or benign functioning tumors such as insulinomas. Due to the high rate of multi-centric lesions, IOUS is always mandatory and it often leads to the decision to perform a subtotal distal pancreatectomy, with enucleation of those tumors located in the head of the pancreas or in the duodenal submucosa. When associated with an appropriate lymphadenectomy and duodenotomy for patients with suspected gastrinomas, the procedure is commonly called "Thompson's procedure." When a gastrinoma is associated, a pancreatico-duodenectomy generally results in a higher rate of cure (77–100%), although experience is poor since the procedure is rarely recommended [30, 33]. The associated high postoperative and long-term morbidity is commonly compared to the increasing evidence of good long-term survival (100% at 15 years) of patients with gastrinomas < 2 cm treated conservatively [31]. Pancreatico-duodenectomy may be advisable in patients with large tumors in the pancreatic head or duodenal tumor and in the presence of lymphadenopathy.

10.4 Conclusions

Despite recent advances in our understanding of neuroendocrine tumors, the appropriate surgical treatment of PanNENs remains challenging [34]. The optimal surgical strategy should be always tailored to the tumor's characteristics as well as the patient's symptoms, comorbidities, and life expectancy. Accordingly, these patients should be referred to highly experience centers in order to optimize the surgical indications and reduce operative morbidity. Moreover, proper communication with the patient and a multidisciplinary decision-making process are key elements in disease management, especially in advanced disease.

References

1. Rindi G, Kloppel G, Alhman H et al (2006) TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 449:395-401
2. Kulke MH, Anthony LB, Bushnell DL et al (2010) NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas 39:735-752

3. Falconi M, Bartsch DK, Eriksson B et al (2012) ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms of the Digestive System: well-differentiated pancreatic non functioning tumors. Neuroendocrinology 95:120-134
4. Norton JA, Fraker DL, Alexander HR et al (1999) Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 341:635-644
5. Norton JA, Jensen RT (2004) Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. Ann Surg 240:757-773
6 Crippa S, Zerbi A, Boninsegna L et al (2012) Surgical management of insulinomas: short- and long-term outcomes after enucleations and pancreatic resections. Arch SurgMar 147:261-266
7. Norton JA (1994) Neuroendocrine tumors of the pancreas and duodenum. Curr Probl Surg 31:77-156
8. Falconi M, Plockinger U, Kwekkenboom DJ et al (2006) Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 84:196-211
9. Bettini R, Partelli S, Boninsegna L et al (Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery 150:75-82
10. Falconi M, Zerbi A, Crippa S et al (2010) Parenchyma-preserving resections for small nonfunctioning pancreatic endocrine tumors. Ann Surg Oncol 17:1621-1627
11. Falconi M, Mantovani W, Crippa S et al (2008) Pancreatic insufficiency after different resections for benign tumors. Br J Surg 95:85-91
12. Aranha GV, Shoup M (2005) Nonstandard pancreatic resections for unusual lesions. Am J Surg 189:223-228
13. Boninsegna L, Panzuto F, Partelli S et al (2011) Malignant pancreatic neuroendocrine tumor: Lymph node ratio and Ki67 are predictors of recurrence after curative resections. Eur J Cancer [Epub ahead of print]
14. Akerstrom G, Hellman P (2007) Surgery on neuroendocrine tumors. Best Pract Res Clin Endocrinol Metab 21:87-109
15. Fendrich V, Langer P, Celik I et al (2006) An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. Ann Surg 244:845-851
16. Schurr PG, Strate T, Rese K et al (2007) Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. Ann Surg 245:273-281
17. Sutcliffe R, Maguire D, Ramage J et al (2004) Management of neuroendocrine liver metastases. Am J Surg 187:39-46
18. Chamberlain RS, Canes D, Brown KT et al (2000) Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 190:432-445
19. Chen H, Hardacre JM, Uzar A et al (1998) Isolated liver metastases from neuroendocrine tumors: does resection prolong survival? J Am Coll Surg 187:88-92
20. Sarmiento JM, Heywood G, Rubin J et al (2003) Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 197:29-37
21. Bettini R, Mantovani W, Boninsegna L et al (2009) Primary tumor resection in metastatic nonfunctioning pancreatic endocrine carcinomas. Dig Liver Dis 41:49-55
22. House MG, Cameron JL, Lillemoe KD et al (2006) Differences in survival for patients with resectable versus unresectable metastases from pancreatic islet cell cancer. J Gastrointest Surg 10:138-145
23. Touzios JG, Kiely JM, Pitt SC et al (2005) Neuroendocrine hepatic metastases: does aggressive management improve survival? Ann Surg 241:776-783
24. Yao KA, Talamonti MS, Nemcek A et al (2001) Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. Surgery 130:677-682
25. Langergraber G, Gupta JK, Pressl A et al (2004) On-line monitoring for control of a pilot-scale sequencing batch reactor using a submersible UV/VIS spectrometer. Water Sci Technol 50:73-80
26. Mazzaglia PJ, Berber E, Milas M, Siperstein AE (2007) Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. Surgery 142:10-19

27. Capurso G, Bettini R, Rinzivillo M et al (2011) Role of resection of the primary pancreatic neuroendocrine tumor only in patients with unresectable metastatic liver disease: a systematic review. Neuroendocrinology 93:223-229
28. Mabrut JY, Fernandez-Cruz L, Azagra JS et al (2005) Laparoscopic pancreatic resection: results of a multicenter European study of 127 patients. Surgery 137:597-605
29. Fernandez-Cruz L, Blanco L, Cosa R, Rendon H (2008) Is laparoscopic resection adequate in patients with neuroendocrine pancreatic tumors? World J Surg 32:904-917
30. Jensen RT, Berna MJ, Bingham DB, Norton JA (2008) Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. Cancer 113:1807-1843
31. Norton JA, Alexander HR, Fraker DL et al (2001) Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg 234:495-505
32. Triponez F, Goudet P, Dosseh D et al (2006) Is surgery beneficial for MEN1 patients with small ≤ 2 cm), nonfunctioning pancreaticoduodenal endocrine tumor? An analysis of 65 patients from the GTE. World J Surg May 30:654-662
33. Lopez CL, Falconi M, Waldmann J et al (2012) Partial pancreaticoduodenectomy can provide cure for duodenal gastrinoma associated with multiple endocrine neoplasia type 1. Ann Surg [Epub ahead of print]
34. Rindi G, Falconi M, Klersy C et al (2012) TNM Staging of neoplasms of the endocrine pancreas: results from a large international cohort study. J Natl Cancer Inst 104:764-77