GEP–NETS UPDATE

A review on surgery of gastro-entero-pancreatic neuroendocrine tumors

Stefano Partelli, Angela Maurizi, Domenico Tamburrino¹, Andrea Baldoni, Vanessa Polenta, Stefano Crippa and Massimo Falconi

Pancreatic Surgery Unit, Università Politecnica delle Marche, Via Conca, 71, 60126 Ancona, Italy and ¹Department of Surgery, University of Verona, Verona, Italy

Abstract

The incidence of neuroendocrine tumors (NETs) has increased in the last decades. Surgical treatment encompasses a panel of approaches ranging from conservative procedures to extended surgical resection. Tumor size and localization usually represent the main drivers in the choice of the most appropriate surgical resection. In the presence of small (<2 cm) and asymptomatic nonfunctioning NETs, a conservative treatment is usually recommended. For localized NETs measuring above 2 cm, surgical resection represents the cornerstone in the management of these tumors. As they are relatively biologically indolent, an extended resection is often justified also in the presence of advanced NETs. Surgical options for NET liver metastases range from limited resection up to liver transplantation. Surgical choices for metastatic NETs need to consider the extent of disease, the grade of tumor, and the presence of extra-abdominal disease. Any surgical procedures should always be balanced with the benefit of survival or relieving symptoms and patients’ comorbidities.

Introduction

Neuroendocrine tumors (NETs) arise from the cells present throughout the diffuse endocrine system. They comprise a broad family of tumors, the most common of which arise in the lungs and bronchi, small intestine, appendix, rectum, and pancreas. These neoplasms were previously regarded as rare, but in fact are increasing in incidence (3.65/100 000 individuals per year) (1) and occur as frequently as testicular tumors, Hodgkin’s disease, gliomas, and multiple myeloma (2). There are multiple classifications for NETs. The gastro-entero-pancreatic (GEP) NETs present as functioning or nonfunctioning tumors. Functioning tumors are commonly associated with a specific hormonal syndrome directly related to a hormone secreted by the neoplasm, such as insulinomas, gastrinomas with Zollinger–Ellison or carcinoid syndrome (3). Most of NETs share the characteristic of longer survival than adenocarcinomas originating from the same organs. As a consequence, surgery plays a key role not only for

Invited Author’s profile

Dr M Falconi is currently Associate Professor of Surgery and Chairman of the Pancreatic Unit, University Politecnica delle Marche (Ancona, Italy). He studied medicine at the University of Verona, specializing in general surgery, gastroenterology, and endoscopy. He has participated in international medical research projects in such diverse places as Germany, Spain, Ecuador, and Japan. A member of many medical societies, including IAP, EPC, and EHPBA, Prof. M Falconi is currently on the executive committees of ENETS and IAP.
localized tumors but also for advanced NETs. Tumor grading and tumor stage represent the main prognostic factors of NETs. Well- and moderately differentiated NETs defined by a value of Ki67 $<$20% have a significantly better survival compared with poorly differentiated neuroendocrine carcinomas. Similarly, a small tumor size, along with the absence of metastases, is associated with a lower risk of recurrence after surgery (4). Subsequently, surgical treatment of NETs is strictly related to the localization of NETs, the grade of tumor, and the stage of disease. Surgery can be a valid option in all stages of disease ranging from conservative approach to radical operations that include multiple organs resection and also liver transplantation (LT). This article aims to elucidate the best surgical management of patients with GEP NET and to address the role of different surgical procedures.

**Management of localized disease**

The management of localized GEP NET depends mainly on tumor size, tumor localization, and patients' comorbidities. Surgical resection is often the best treatment for the majority of localized NETs, although a conservative approach is currently advocated for small, incidentally discovered tumors. Small, benign neoplasms are usually readily curable by surgical resection with a favorable prognosis, although all these tumors should always be considered as potentially malignant (3). The main European and North American guidelines recommend surgical resection for localized NETs irrespective of tumor grading (5, 6, 7).

**Pancreatic NETs**

The incidence of small, incidentally discovered pancreatic NETs has increased significantly in the last decade with the widespread use of high-quality imaging techniques (8). Incidental diagnosis of pancreatic NETs is associated with a significantly better survival after curative resection compared with patients with symptoms (9). Moreover, Bettini et al. (10) demonstrated that patients with incidental diagnosis associated with a tumor size $<$2 cm had a 5-year overall survival of 100% with a minimal risk of recurrence. On the basis of these experiences, the European Neuroendocrine Tumor Society (ENETS) guidelines now recommend a ‘wait and see’ policy in selected patients with asymptomatic sporadic pancreatic NETs (5). This management should be considered only in the presence of a low-grade (G1) NET. Consequently, tumor grading should always be assessed by fine-needle aspiration or biopsy (11). Although a follow-up protocol has not been investigated, a yearly imaging-based observation with a first control after 6 months from diagnosis seems to be reasonably safe. Preliminary reports have demonstrated the safety of this conservative approach (9, 12, 13). Lee et al. (12) retrospectively analyzed 134 patients with pancreatic NET $<$2 cm. Of those, 57 underwent surgery with a risk of complications of nearly 50%. The remaining 77 patients were conservatively managed and they were all free of progression disease. In addition, Gaujoux et al. (13) published a bi-institutional study where they observed 46 patients with small, incidentally discovered pancreatic NETs. Overall, eight patients (17%) underwent surgery after a median time of 41 months. All resected tumors were T stage 1 ($n=7$) or 2 ($n=1$), node negative with neither vascular or peripancreatic fat invasion.

On the other hand, surgery still represents the treatment of choice for pancreatic NETs $>$2 cm and/or for symptomatic forms. Radical surgery for pancreatic NETs includes both typical and atypical pancreatic resections. Typical resections differ according to tumor site: lesions of the pancreatic head are treated with a pancreaticoduodenectomy, while lesions of the body and tail with a distal pancreatectomy. Currently, when performed in high-volume centers, pancreatic typical resections have an acceptable mortality rate ($<$5%), although the percentage of complications is still significant ranging from 40 to 50% (14, 15). Typical pancreatic resections are also associated with a high incidence of exocrine and endocrine insufficiency (16). Risk of long-term pancreatic impairment has increased the use of parenchyma-sparing techniques or atypical resections such as enucleation and middle pancreatectomy that consists of the resection of the central part of the gland. Currently, these procedures are limited only for small functioning tumors ($<$2 cm) (17). In particular, surgery still plays an important role in the management of insulinomas. Recurrence after surgery for insulinomas is exceptional and these neoplasms can be safely resected with enucleation that can be performed both with an ‘open’ approach and laparoscopically (18, 19). The role of lymphadenectomy for patients with pancreatic NET is still unclear (20). Lymph node metastases occur only in the 30% of patients affected by these tumors (20), but the association between node metastases and poorer survival is still debated (4).

**Gastric NETs**

Borch et al. (21) studied a total of 65 patients with gastric NETs of different types from 24 hospitals and managed with a differentiated treatment in relation to type. The conclusion of this study is that the
type of gastric NETs is helpful in the prediction of malignant potential and long-term survival and it is a guide to management. Three types of gastric NETs are generally recognized: type 1 (associated with chronic atrophic gastritis), type 2 (associated with Zollinger–Ellison syndrome), and type 3 (sporadic) (22). Types 1 and 2 gastric NETs are both associated with hypergastrinemia. Treatment options for types 1 and 2 gastric NETs <2 cm or smaller include: i) endoscopic mucosal resection, if feasible, with biopsy of the tumor and adjacent mucosa and ii) observation (23, 24, 25). Currently, there is no evidence that endoscopic resection is superior to endoscopic surveillance. However, when tumor invades behind the submucosa, positive resection margins after endoscopic mucosal resection, multiple tumors >1 cm or regional lymph node metastasis, local resection, or gastrectomy should be performed (23). Gastric resection procedures include total gastrectomy and sparing procedures such as partial gastrectomy or antrectomy. Antrectomy plays a role in avoiding gastrin stimulation and is effective in nearly 80% of type 1 gastric NETs (26, 27). Surgery in type 2 tumors is focused on removing the source of hypergastrinemia, either by excision of mostly duodenal gastrinomas via duodenotomy or by pylorus-preserving pancreaticoduodenectomy. Patients with non-metastatic gastric NET and normal gastrin levels (type 3) present usually more aggressive tumors and they should be treated with radical resection of the tumor with meticulous regional lymphadenectomy (24, 28).

NETs of the duodenum, papilla of Vater, small intestine, and colon ▶ For localized lesions arising in the duodenum, endoscopic resection is recommended, when feasible. In particular, endoscopic resection is recommended for duodenal NETs <1 cm, whereas the optimal treatment for lesions measuring between 1 and 2 cm is more controversial, with some recommending endoscopic removal and others recommending surgical treatment (29). Transduodenal local excision with or without lymph node sampling and pancreaticoduodenectomy are other options for primary treatment of non-metastatic duodenal NETs >2 cm. Nevertheless, the optimal approach remains unclear as the biological behavior of these NETs remains largely unknown (30, 31). Although ileum/jejunum NETs often present with metastases at diagnosis, surgical treatment has become increasingly important for their management (32). For patients presenting with tumors in the jejunum/ileum, surgical resection of the bowel with regional lymphadenectomy is recommended (30). Mesenteric lymph node metastases are common also with small tumors (33). These metastases will often grow conspicuously large and may be mistaken to represent the primary tumor. As tumor spread to the lymph nodes and liver can occur also in patients with small primary tumors, surgery of the primary tumors should adhere to oncological principles. This involves clearance of lymph node metastases by dissection around the mesentery (30). The surgical procedure should include careful examination of the entire bowel, because multiple synchronous lesions may be present. Surgery at an early stage of the disease is favorable when growth is less extensive in the mesentery (32, 34). Colon NETs should be treated with an appropriate right or left-sided hemicolectomy or sigmoidectomy (35).

Appendiceal NETs ▶ Appendiceal NETs are often identified incidentally, during appendectomy performed for appendicitis (36). Most NETs of the appendix have well-differentiated histology, and for most tumors <2 cm and confined to the appendix, simple appendectomy is sufficient because metastases are uncommon (37). However, some controversy exists regarding the management of appendiceal NETs measuring below 2 cm with more aggressive histologic features (38, 39). According to Moertel et al. (36), patients with larger tumors and metastasis are younger than those with smaller and clinically benign tumors. As a result of a retrospective analysis of 1570 appendiceal NETs, performed by Sandor et al. (39), it was highlighted that careful evaluation and postoperative follow-up are of paramount importance because of the increased risk of coexisting neoplasms and the uncommon presentation of metastatic disease. Patients with an incomplete resection or tumors larger than 2 cm are at risk for locoregional or distant metastases and they should undergo re-exploration with right colectomy (37). Right colectomy is also considered as the treatment of choice for appendix goblet cell tumors as the risk of metastases is very high (40).

Rectal NETs ▶ The treatment of rectal lesions is based on the size of the primary tumor. If the lesion is 2 cm or less, endoscopic or transanal excision is recommended (41, 42). Given the higher risk of invasion with larger tumors, examination under anesthesia and/or endoscopic ultrasound (EUS) before the procedure should be considered for tumors 1–2 cm in size. Tumors larger than 2 cm, those with invasion of the muscularis propria, or those associated with lymph node metastases should be treated with low anterior resection or, in rare cases, an abdominoperineal resection (42).
**Surgery of advanced NETs**

Several treatment modalities are available in the management of advanced NETs. These treatments include somatostatin analogs, peptide receptor radionuclide therapy, targeted therapies (everolimus and sunitinib), and chemotherapy (43). In this setting, surgery should always be included in a multimodal approach.

Surgical management of advanced and/or metastatic NETs is still controversial. While patients with hormonal symptoms can be relieved with cytoreductive procedures, the role of surgery for patients with non-functioning disease is more debated. In particular, it is still unclear about the role of primary tumor resection and the impact of liver metastases (LM) resection on survival. As most of NETs have a low aggressive behavior, a tendency to promote aggressive surgery, even in the presence of LM, exists. Generally, when R0 resection is achievable, an aggressive approach for well-differentiated NETs, possibly with a Ki67 <10%, is widely used (44, 45, 46). Some patients present with locally advanced tumors with local infiltration of the portal vein or stomach. For these patients, a pancreatic resection extended to nearby organs might be a valuable option (47). Nevertheless, the choice of surgery is often influenced not only by the improvement in survival but also by the risk-benefit balance regarding morbidity and mortality. ENETS guidelines identified some essential prerequisites before performing surgery in patients with LM from digestive NETs (48). These criteria include: i) the presence of well-differentiated lesions (Ki67 <5%); ii) the absence of right heart insufficiency; iii) the absence of extra-abdominal disease; and iv) the absence of diffuse peritoneal carcinomatosis (48). Under these circumstances, we recognize two different phases in the management of these patients, which are the primary tumor resection and the surgical treatment of liver lesions.

**Surgery of primary tumor**

At the time of diagnosis, more than 80% of LM are bilobar (49) and curative resection is not possible. Synchronous liver and pancreatic resection seem to be associated with a better survival, although the risk of recurrence remains high (50, 51, 52). The removal of primary tumor in the presence of unresectable LM is still debated. Potential advantages may be to relieve symptoms and to increase survival. In particular, in patients with symptomatic non-functioning pancreatic NET and unresectable LM, a marked reduction of symptoms and a lower rate of progression in those with resection of the primary compared with the unresected cohort were demonstrated (53). Published recommendations differ for small intestine and pancreatic NETs. Indeed, while ENETS suggests the removal of the primary tumor to make the only persisting problem for intestinal NETs (30), the resection of the primary tumor in metastatic pancreatic NETs is not recommended, except for selected low-risk patients with life-threatening symptoms due to complications (5). Concerning intestinal NETs, a systematic review by Capurso et al. (54) demonstrated a possible benefit of resection of the primary lesion in patients affected by small intestinal NETs with unresectable LM. They demonstrated a clear trend toward longer survival in patients who underwent surgical resection in all studies, with a median overall survival ranging from 75 to 139 months compared with 50–88 months in patients who did not have resection (54). Regarding pancreatic NETs, another systematic review by Capurso et al. (55) evaluated the potential benefits or harms of surgical resection of the primary lesion without concomitant resection of metastases. This systematic review included three studies (56, 57, 58), one prospective study with a relatively small sample size and an other two retrospective studies. The overall survival data did not differ significantly in the two studies (56, 58), whereas the third study (57) did not report data on overall survival. Nevertheless, the 5-year survival rate seemed generally higher in patients who had their primary tumor resected, with a difference of 30% in one study, of 33% in a second (57), and no difference in a third study (56). Given the absence of randomization in the examined studies, a bias toward a more aggressive approach in patients with a better overall performance status, a less advanced disease, or possibly with location of the tumor in the body or tail of the pancreas seems likely. When synchronous resectable LM is present, a combined surgical approach is a valid option.

**Surgery of LM**

Curative resection (R0/R1) is associated with a better long-term survival in all series and survival rates of 60–80% can be achieved (48). However, the overall survival after hepatic resection has been reported in 46–86% at 5 years and 35–79% at 10 years (49, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72). This wide heterogeneity reflects the selection bias that is present in the majority of series. In addition, Elias et al. (73) reported that fewer than 50% of the LM were detected.
by preoperative imaging modalities compared with a final pathological count. These results suggest that NET LM are frequently more extensive than identified, even intraoperatively, and that a real curative R0/R1 resection is difficult to achieve. Mayo et al. (74) reported one of the largest series of patients who underwent surgical management for neuroendocrine LM. Median survival in this study was 125 months, but disease recurred in nearly all the patients, confirming that a real curative resection is far from being achieved in metastatic NETs. In order to select patients who will really benefit from surgery, an accurate preoperative imaging work-up is necessary. Indeed, the main criterion in the assessment of possible surgical resection for LM from NETs is morphological and it regards the localization of lesions. Frilling et al. (75) defined the role of aggressive surgical resection in relation to localization patterns of neuroendocrine hepatic metastases. In this study, three different patterns of metastatic spread were identified: single metastasis of any size (type 1); isolated metastatic bulk accompanied by smaller deposits, with both liver lobes always involved (type 2); and disseminated metastatic spread, with both liver lobes always involved, single lesion of varying size, and virtually no normal liver parenchyma (type 3). All patients with type 1 metastases underwent R0 resection, none of patients with type 2 metastases were suitable for staged hepatic resection, and the 21% of type 3 patients underwent LT. Patients with type 1 LM had a significantly better survival than patients with types 2 and 3 metastases. This advantage is mainly related to the higher probability of performing a curative resection for unilobar metastases. On the other hand, the management of bilobar LM is often challenging. In this setting, Kianmanesh et al. (76) evaluated the feasibility of a two-step surgical approach. This technique includes a first step when primary tumor and all left-sided LM are resected while a portal vein ligation is performed to induce hypertrophy in the left liver. Two months later, in the absence of tumor progression, a second step including a right or extended right hepatectomy is planned. This surgical approach proved to be safe with a 5-year disease-free survival of 50% and represents a valid option in the management of bilobar LM from NETs (76). As disease progression is a common occurrence, a multimodality treatment approach for progressive disease is necessary (77). For small NET LM, radiofrequency ablation has been proven as safe and effective in prolonging survival and relieving symptoms (78, 79).

Liver transplantation

NET metastases represent at this moment an indication of LT. The review of the European Liver Transplant Registry (ELTR) data reveals that the transplant experience in NET patients is limited and ill defined (80). Moreover, all usable information about the value of LT in the treatment of NETs comes from small, single-center series and from two multicentric retrospective studies (81, 82). Considering their former experience with hepatocellular cancer, the Milan group improved the results of LT for NETs by prospectively applying strict inclusion criteria. These criteria include the following: i) well-differentiated NETs (Ki67 <5%); ii) portosystemic tumor drainage; iii) patient age <55 years; iv) stable disease for at least 6 months; v) pre-transplant R0 primary tumor resection; vi) hepatic tumor involvement <50% of the liver volume; and vii) absence of extra-hepatic disease (83). Recently, Le Treut et al. (84) have described a large retrospective cohort of 213 patients who underwent LT for NETs, which represents by far the largest cohort in the literature. At a mean follow-up of 56 months, 17% of patients died from early or late complications of LT and the 5-year overall survival rate was 52% with a disease-specific survival rate of 30%. These results demonstrate that LT is a valid option in well-selected patients with neuroendocrine LM, although post-operative mortality is still high.

Surgery of NETs in multiple endocrine neoplasia type 1 patients

Surgical management of NETs in affected patients is often challenging, especially for the presence of multifocal pancreatic neoplasms. Nearly 80% of patients with multiple endocrine neoplasia type 1 (MEN1) had multiple duodenal and/or pancreatic NETs. These tumors include non-functioning NETs (80–100%), gastrinomas (54%), and insulinomas (18%) (85). Surgery is mandatory for i) functioning tumors, ii) tumors with resectable LM, iii) tumors with size >2 cm, and iv) for symptomatic non-functioning NETs (86). Atypical, parenchyma-preserving procedures are always preferred in respect of total pancreatectomy even in the case of multifocal NETs (87). On the contrary, total pancreatectomy is highly recommended in the presence of a familial history of disease-related mortality (85). Pancreatic NETs <2 cm are associated with a very low risk of metastases and mortality (88). For this reason, for patients with MEN1 affected by pancreatic NETs <2 cm, a careful watching policy is recommended. In these patients, it seems
Surgical treatment of gastrinomas in MEN1 patients is still debated (90). A conservative approach, with medical treatment of hypergastrinemia, is recommended (91). On the contrary, other authors suggest a surgical treatment for tumors >3 cm in size or when a biochemical diagnosis is unequivocal (92, 93). Nevertheless, patients who are conservatively treated have a risk of LM of 23–29% compared with 3–5% of those patients who undergo radical surgery (94, 95). The extension of surgery in these patients is also a matter of debate. Thompson (96) suggests a procedure that includes duodenotomy, enucleation of all pancreatic NETs, and locoregional lymphadenectomy. Other authors recommend a Whipple’s pancreaticoduodenectomy because this procedure is associated with a rate of cure of 77% (97, 98, 99, 100). We recommend a Whipple’s pancreaticoduodenectomy for gastrinomas in MEN1 patients.

Primary hyperparathyroidism (HPT) is associated with MEN1 syndrome in the 80–90% of cases (101). HPT in patients with MEN1 syndrome is usually more aggressive than sporadic HPT and often involves multiple glands (102). Surgery is the treatment of choice for HPT in patients with MEN1 syndrome (103, 104). Many authors recommend a subtotal parathyroidectomy (including at least three glands) or, alternatively, a total parathyroidectomy with autotransplantation (103, 105, 106). A limited resection can be associated with a high risk of recurrence, but an extended operation can cause a permanent hypocalcemia in 13–47% of cases (107). Nevertheless, a measurable risk of recurrence is present also after subtotal parathyroidectomy (108, 109, 110) and then a subtotal parathyroidectomy (including at least three glands) seems to be the most appropriate treatment for HPT in MEN1 patients.

Conclusions

Surgical treatment of NETs represents a key phase in the multimodal management of these tumors. Before planning a surgical approach, tumors, characteristics (size, localization, and grading) should always be considered along with patients, comorbidities and expectations. A more conservative approach for small, asymptomatic NETs is recommended. In particular, for tumors <2 cm involving the gastro-enteric tract, endoscopic or limited resection is usually recommended. For asymptomatic small pancreatic NETs, a careful follow-up policy is recommended both for sporadic and inherited forms because of the high risk of complications. For metastatic NETs, surgery plays a role when liver involvement is limited, in the presence of low-grade tumors, and in the absence of extra-abdominal lesions.

Declaration of interest

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