The role of surgery and transplantation in neuroendocrine tumours

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Abstract

Surgery represents the only chance of cure for a patient with a neuroendocrine tumour (NET). The main indications for surgery lie in the risk of developing metastatic disease with increasing tumour diameter and for a functioning NET also in control of the hormonal syndrome. However, only a small minority of patients presents with a potentially resectable primary NET without metastatic disease. An R0-resection is mandatory, which may be achieved in selected cases by tissue sparing surgical techniques.

Most patients unfortunately present with a locally advanced or metastatic disease. For patients with an advanced functioning NET, control of the hormonal syndrome may also represent a surgical indication. Various cytoreductive techniques or, in highly selected cases, liver transplantation can be applied. For locally advanced non-functioning tumours, there is an indication for surgery in large tumours which tend to create local complications because of bleeding or bowel obstruction. Especially in ileal NETs aggressive surgical therapy is recommended because of prevention of long term complications, which may improve survival. (Acta gastroenterol. belg., **2009**, 72, **39-43**).

Key words : neuroendocrine tumours, surgery, transplantation, radiofrequency ablation.

Introduction

Determining the role of surgery in neuroendocrine tumours (NETs) in a simple flowchart is impossible, because we are confronted with localized or metastatic disease, hormone secreting and non-secreting tumours. Therefore, every patient needs specific tailored therapy in a multidisciplinary approach. In this review we will focus on some surgical principles in the management of localized and metastastic NETs.

Localized neuroendocrine tumours of the pancreas : minimal invasive versus aggressive surgery

A localized functioning or hormone secreting lesion is the most straightforward indication for surgical resection. By this resection, the patient can be cured from the hormonal syndrome and from the risk to develop metastatic disease (1). The indication for surgery lies in the symptoms as a consequence of the hormone production. Nowadays, most surgeons advocate tissue sparing or minimal invasive surgery for a pancreatic NET with a lower malignant potential such as insulinoma. For a hormone secreting tumour in the pancreatic tail a laparoscopic enucleation or pancreatic tail resection could be performed (2) ; for a lesion in the pancreatic head, we prefer enucleation or a duodenum preserving pancreatic head resection (Fig. 1). In the last mentioned technique, the pancreatic head can be enucleated from the encircling duodenal C, leaving the bowel itself, the bile duct with its surrounding tissue and the blood supply to these structures intact. During surgery for this kind of tumours, intraoperative ultrasound is mandatory to localize the primary tumour, to exclude other small lesions in the rest of the pancreas and to detect (small) liver metastases. This is even more true during laparoscopy when palpation of the pancreas can not be performed. But even in open surgery, it is nowadays no longer acceptable to depend on palpation to have a complete surgical removal (3).

For pancreatic gastrinoma on the other hand, there is a tendency to perform more aggressive surgery such as pancreaticoduodenectomy because of possible duodenal localization and reported primary location in lymph nodes (4). Gastrinomas are also considered to have a higher malignant potential than insulinoma (5). With improving results of pancreatic surgery, pancreaticoduodenectomy could be preferred over duodenotomy and palpation of the duodenal wall to ascertain a complete resection. Norton *et al.* report the highest rate of cure with this technique : 68% (6). If a neuroendocrine tumour can not be localized pre- or intraoperatively, pancreatic tail resection without localisation is no longer recommended. Adjuvant therapy after curative resection has not been studied.

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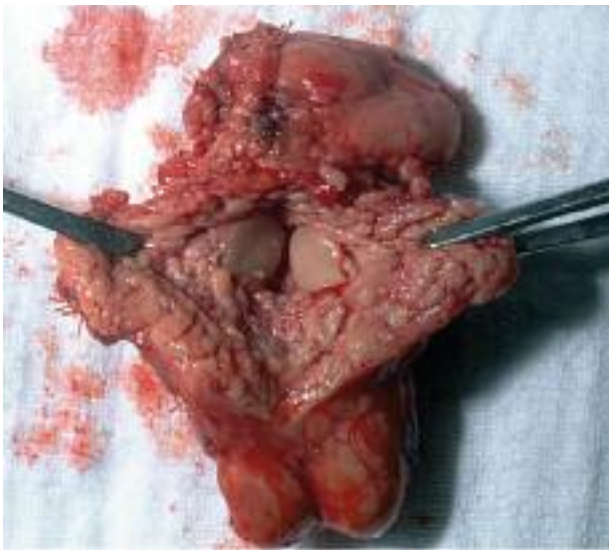

Fig. 1. — Patient with a insulinoma centrally located in the pancreatic head, undergoing duodenum preserving pancreatic head resection.

For localized non-functioning NETs on the other hand, the attitude is somewhat different, because these lesions do not secrete hormones per definition and therefore usually give only symptoms when there is a large mass invading surrounding organs (7). For lesions more than 3 centimetres, a more aggressive approach should be considered since nodules beyond this diameter tend to metastasize to lymph nodes and to the liver. Here a formal oncological resection as pancreaticoduodenectomy or pancreatic tail resection with lymph node clearance should be considered depending on the localization of the primary tumour. Solorzano *et al*. report a median survival of 7,1 year in patients with localized disease who underwent a potentially curative resection. Patients who could not be resected because of metastatic disease have a median survival of only 2,1 year (8).

Aside from the presence of liver metastases, the completeness of the resection of the primary tumour is a major prognostic factor in the survival of the patient. The median survival of patients with a complete surgical resection (110 months) is significantly better than that of patients without resection (34 months) (9).

Is there still a role for surgery in locally advanced or metastatic disease ?

The majority of patients suffer from metastatic or locally advanced disease, not resectable with curative intent. The development of hepatic metastases reduces the 5-year survival significantly from 70-80 to 30-40% (10).

Pancreatic NETs are considered irresectable when there is gross arterial invasion of the coeliac trunk or the superior mesenteric artery. As in pancreatic adenocarcinoma, partial portal vein involvement is not considered a contraindication for surgery. Large pancreatic NETs also have the tendency to invade nearby organs (e.g. NETs of the pancreatic tail invading stomach, kidney or colon). In the decision to resect such large upper abdominal masses, the symptoms of the patient must be weighed against the morbidity of these extensive procedures.

In patients with a functioning tumour, surgery may have a role in controlling the symptoms due to the hormone production that are refractory to somatostatin analogues. There is also a suggestion that surgical therapy in liver metastases may improve survival (11-15). Chamberlain compared different treatment modalities for hepatic metastases of NETs. He concluded that there were no 5 year survivors in the medically treated group whereas 51% of the group with hepatic arterial embolization and 76% of the surgically treated group reached 5 year survival (14). Sarmiento et al report on a large series of 170 patients who underwent hepatectomy for functioning and non-functioning NETs. Although recurrence rate was 84%, the 5 year survival was 61% and 10 years survival 35%. There was no difference between ileal and pancreatic NETs (15). Hepatectomy may also be effective in preventing the development of carcinoid heart disease.

For non-functioning metastatic or locally advanced neuroendocrine tumours, the role of surgery is more limited. Only when the patient develops complications in other organ systems, as gastric outlet obstruction, duodenal erosion or biliary obstruction or intestinal bowel obstruction, there is an indication for surgical intervention (7).

Surgical approach of liver metastases : focus on radiofrequency ablation

Surgical strategies for treating liver metastases imply liver resection, radiofrequency ablation and possibly liver transplantation in highly selected cases.

The introduction of radiofrequency ablation (RFA) has been a major step forward in treating liver metastases (10,17). In this technique, a needle is placed in the liver metastases, which are then heated to an ablative temperature (Fig. 2). The needle can be introduced into the lesion under ultrasound or CT-guidance. The localization of the lesion implies which route of access to follow and whether this needle can be placed percutaneously, by laparoscopic access or through a formal laparotomy.

Lesions in the upper posterior segments of the liver (segments VII, VIII and IVA) can usually not be reached by the percutaneous technique, because of the overlying lung and pleura. Ablation in these segments can be performed by laparoscopy (sometimes in lateral decubitus) with laparoscopic ultrasound as guidance tool. The RFA technique can obviously also be applied through laparotomy. This more invasive route of access is preferred when several liver metastases are treated during the same session.

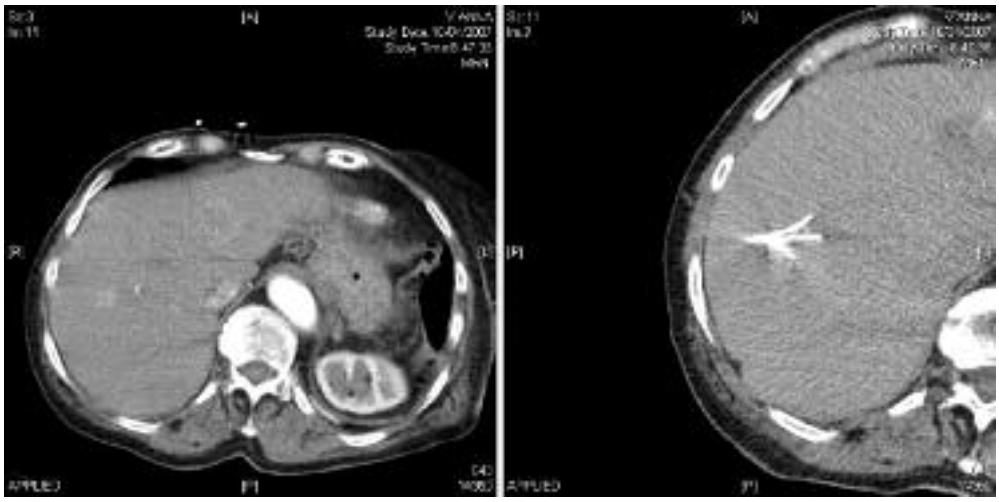

Fig. 2. — Patient with an insulinoma treated with radiofrequency ablation to obtain hormonal control (left). Umbrella shaped radiofrequency needle unfolded in the liver metastasis (right).

The size of the dominant liver tumour is a strong predictor for survival. Patients who underwent RFA for lesions more than 3 centimetres had a worse prognosis, associated with a higher frequency of local recurrence. Patients should therefore be referred for RFA as early as possible (18-19). Patients with a foregut or pancreatic neuroendocrine tumour recur more often, possibly related to the higher Ki67 index (20).

Radiofrequency also has its limitations, and liver surgery should not be omitted in treating liver metastases of NETs. Lesions immediately under the liver capsule e.g. are not considered good candidates for RFA, since they tend to bleed from the necrotic zone afterwards, sometimes with breakthrough towards the peritoneal cavity and massive haemorrhage as a consequence. Lesions in liver segment I are also not good candidates for ablation because of the nearby hilar vascular and biliary structures. For these two categories, a liver resection is preferred.

Since liver metastases from NETs are frequently bilobar, a combination of liver resection and RFA is often the best approach. In treating hormone producing liver metastases, a close interaction between radiologist and surgeon is necessary to determine the best approach for a specific lesion.

Some authors advocate that there is only an indication for surgery when at least 90% of the hormone producing tissue can be removed (12). In our opinion, this cut-off is too strict, since in some patients temporary relief can be achieved with radiofrequency of the largest metastases with reduction less than 90%, but this intervention can be repeated.

Resection of the primary tumour in the presence of extensive liver metastases

Even in the presence of extensive liver metastases, the prophylactic resection of ileal NETs is advocated, also when asymptomatic (16,21). These patients develop in the long term typical abdominal complications such as small bowel ischemia and intestinal obstruction due to fibrotic entrapment. The metastases in the mesentery of the small bowel encase the mesenteric vessels leading to venous obstruction and later also arterial impairment (22,23). In these patients, debulking should be preferred over bypass surgery, because the latter will not deal with the vascular complications. During the bowel resection, the liver metastases can also be treated with radiofrequency ablation.

The importance to remove the primary tumour is also stressed by Helmann *et al*. (24). Patients with the primary resected had a significantly better median survival (7.4 versus 4.0 years) than patients without resection. This difference is independent of the presence of liver metastases. The resection of mesenteric metastases leads also to a significant improvement of median survival (7,9 versus 6,2 years).

A recent paper of Hung *et al*. (25) also strongly suggests to resect symptomatic pancreatic neuroendocrine tumours even when unresectable hepatic metastases are present. They performed surgical resection in patients with symptoms due to a pancreatic NET while the hepatic metastases were treated with arterial embolization or lanreotide. Although a small number of patients included, nearly all of them reported improved quality of life after resection. Because of the relatively low risk of pancreatic surgery nowadays, and the slow progression of hepatic lesions, surgery can be an opportunity to eliminate symptoms caused by the primary tumour.

Liver transplantation and NETs

In the survival of a patient with a pancreatic NET, the evolution of the liver metastases is a major prognostic factor (9). Reviewing the literature on liver transplantation for metastatic NETs, overall and disease free

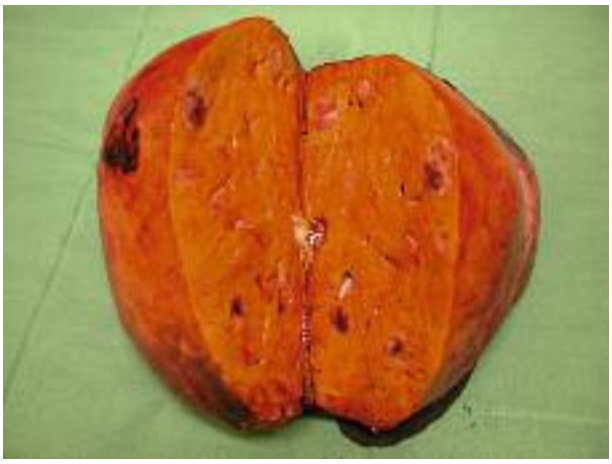

Fig. 3. — Liver specimen with multiple metastases of a neuroendocrine tumour in a young patient undergoing orthotopic liver transplantation.

survival were not convincing (26-29). Therefore, several predictors of long-term survival have been defined. Age over 50 and combining the liver transplantation with large resections of the primary represent adverse prognostic factors (30-31). Survival of patients with low Ki67 grade and regular E-cadherin staining of the primary tumour is significantly longer (32).

Nowadays, the transplantation society is progressing towards a consensus where liver transplantation is considered for highly selected patients with diffuse liver metastases (Fig. 3). These lesions can not be treated by liver surgery or RFA, because the liver remnant, and therefore liver function, would be too small.

Mazzaferro defined the following in and exclusion criteria (33). Liver transplantation can be considered for patients with a) a low-grade NET, b) a primary NET drained by the portal system that has been removed with a curative resection, c) metastatic involvement to the liver parenchyma < 50%, d) stable disease for at least 6 months during the pre-transplant period and e) age below 55 years. Exclusion criteria are : a) small-cell carcinoma and high-grade neuroendocrine carcinomas, b) other conditions contraindicating liver transplantation and c) non-gastrointestinal NETs or tumours not-drained by the portal system. Patients fulfilling these selection criteria may benefit from liver transplantation as a curative rather than a palliative therapeutic option.

Occasionally, liver transplantation has been performed in irresectable disease with otherwise untreatable hormonal syndromes or large tumour mass. These patients benefit with regard to symptom relief and even survival, but are frequently confronted with recurrent disease. In a time of organ shortage, transplantation as a palliative treatment is very debatable.

Summary and research agenda

Defining the role of surgery in a multimodal pathology as NET, is a complex process. Close interaction between surgeon, gastroenterologist, oncologist, radiologist, and specialist in nuclear medicine with experience in the field of NET, is mandatory to determine which patient may benefit from which intervention.

Progress has been made in the surgical management of patients with NET by the evolutions in pancreatic surgery and the introduction of radiofrequency ablation for the treatment of liver metastases. There is also evidence in favour of resection of the primary tumour even in the presence of extensive liver metastases.

The role of transplantation is still under investigation. Some prognostic factors and selection criteria have been defined to improve the chance of cure. This rather aggressive approach can only be supported in highly selected patients because of organ shortage and the continuous risk of recurrent disease.

Since randomized trials on surgical therapy are obviously not applicable in this disease, registries (such as the DNET, www.bgdo.be/DNET) may offer a possibility to increase our knowledge of the best surgical approach.

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