CHAPTER 1

General introduction and outline of the thesis.
GENERAL INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) are classified as a rare disease since the prevalence of pNETs is 2/100,000. The incidence of pNET has been rising over the past decades, probably as a result of an increase in doctors' awareness and an increase of incidental findings on radiological imaging.1

Clinical presentation and diagnosis

Based on the hormonal overproduction causing clinical syndromes, pNET can be divided in functional and non-functional pNET.2,3 Insulinomas and gastrinomas are the most common functional pNET causing symptoms such as hypoglycemia or the Zollinger-Ellison syndrome, which causes diarrhea and atypical duodenal and small bowel ulcers. Small non-functional pNET are often detected incidentally but larger tumors cause symptoms such as abdominal pain, weight loss, anorexia and nausea. Most patients with larger non-functional pNETs, present with liver metastases at the time of diagnosis. A small subgroup of patients with pNET is known with hereditary tumor syndromes such as Multiple Endocrine Neoplasia Type 1 (MEN-1) or Von Hippel Lindau syndrome. These patients may develop multiple well-differentiated functional or non-functional endocrine tumors in the pancreas.

Like functional pNETs non-functional pNETs also secrete peptides such as chromogranin A, a glycoprotein which can be used as a serum tumor marker in patients with pNETs. Chromogranin A is often elevated in patients with pNETs but it may also be elevated in other situations such as impaired renal function, chronic atrophic gastritis or proton pomp inhibitor treatment. The diagnostic accuracy of chromogranin A is high in patients with metastatic disease and therefore it is often used as a tumor marker during follow-up of patients after surgical resection of pNETs or to evaluate treatment response in patients with metastatic disease.4

For the initial diagnosis a computerized tomography (CT) scan, magnetic resonance imaging (MRI) and an endoscopic ultrasound (EUS) are the most used imaging modalities. Since somatostatin receptors are highly expressed on most neuroendocrine tumors. Therefore, an additional somatostatin-receptor scintigraphy (Octreoscan) can be made for optimal staging. A single photon emission CT (SPECT) can be used to display the anatomic location of the uptake. A somatostatin-receptor scintigraphy is indicated for the detection and localization of the primary tumor and recurrent disease during follow-up. Furthermore it could select patients with locally advanced or metastatic disease for peptide receptor radionuclide therapy (PRRT).

Surgical treatment

As for many carcinomas, surgical resection is the only curative treatment of patients with pNETs. Based on tumor location and tumor size, different surgical procedures are available. In patients with a pNET in the pancreatic head, the tumor could be enucleated or a pancrea...
toduodenectomy could be conducted. In patients with a tumor in the pancreatic body or tail, an enucleation, central pancreatectomy or (spleen preserving) distal pancreatectomy can be performed. If a tumor enucleation is preferred, only the tumor will be removed with a small part of the pancreas (head, corpus or tail). An enucleation is particularly indicated in patients with benign disease such as pancreatic cysts or symptomatic intra pancreatic mucinous neoplasms, without any worrisome features. An enucleation is often performed in patients with insulinomas or small non-functional pNETs, since most of these tumors are benign. In patients with a larger tumor, a standard resection will be performed, which is also advised for small tumor nearby the main pancreatic duct in order to prevent complications such as pancreatic leakage. Since small pNET usually are less aggressive, a lymphadenectomy is usually not carried out.

Most of the aforementioned surgical procedures nowadays are performed laparoscopically as well, however the experience with laparoscopic pancreatic surgery for pNETS increases slowly. Compared to pancreatic adenocarcinoma, pNETs are less aggressive and therefore patients with metastases may benefit from surgery as well. In patients with limited metastatic liver disease, a combined resection of both the primary tumor in the pancreas as well as the liver lesions can be performed. Liver embolisation or radiofrequency ablation (RFA) can be combined with resection of the primary pNET and resection of the liver metastasis. In general, aggressive extended surgery is feasible in patients low proliferation index of the primary tumor and without other extra-abdominal disease.

Pancreatic surgery is often associated with minor but also major complications. The main complications after pancreatic surgery are pancreatic fistula, delayed gastric emptying and postoperative bleeding. Based on the international study group of pancreatic surgery (ISGPS) criteria, these complications can be divided in grade A, B and C in which a grade A has often no clinical relevance. In grade B or C pancreatic fistula, the clinical condition is more severe with signs of infections, persistent drainage and even sepsis, reoperation or death in grade C pancreatic fistula. Especially pancreatic fistula are a common complication after pancreatic surgery in patients with pNET. The Clavien-Dindo grading system also defines the severity of the complications in terms of re-interventions and organ failure. A long-term complication, especially after pancreatoduodenectomy, is pancreatic insufficiency, either endocrine or exocrine or both. Endocrine insufficiency is characterized by development of diabetes mellitus and exocrine insufficiency is characterized by complaints of steatorrhea, weight loss and abdominal pain.

Pathology and prognosis
In the past decades, much has changed regarding the classification and nomenclature in patients with a neuroendocrine tumor. Besides the TNM classification, the World Health Organisation (WHO) grading system of 2010 is often used to express tumor proliferation. Tumor grading is based on the number of mitosis per unit area and the proliferation index by
the Ki67 index, (table 1).

<table>
<thead>
<tr>
<th>Tumor grade</th>
<th>Mitotic Count per 10 high power fields (HPF)</th>
<th>Ki67 Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>&lt; 2</td>
<td>&lt; 2%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2-20</td>
<td>3-20%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt; 20</td>
<td>&gt; 20%</td>
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Table 1. Tumor grading neuroendocrine tumors

Prognosis is mainly dependent on the presence of distant metastases. The median survival of patients with distant metastasis is 23 months. The median survival of patients with regional and localized disease is 70 and 124 months, respectively. Patients with tumor grade 1 have a much better prognosis compared to patients with a tumor grade 3. In patients with extended liver resection, the 5-year survival ranges from 47-76%.

**Follow-up**

The aim of follow-up is to evaluate physical symptoms and to detect recurrent disease since there are several treatment options for patients with tumor recurrence. According to the European Neuroendocrine Tumor Society (ENETS) guidelines, a follow-up program is not required in patients with a pNET grade 1 who have undergone a radical resection.

In general, the follow-up program of patients with grade 2 pNETs consists of the determination of chromogranin A levels in combination with radiological examinations such as ultrasound, MRI/CT and octreotide scintigraphy on a yearly basis. In patients with grade 3 tumors, the follow-up program should be intensified to every 6 months.

In patients affected by hereditary tumor syndromes, follow-up should be performed with a 6 to 12 months interval to evaluate symptoms related to hyperparathyroidism or pituitary disease. Extended biochemical evaluation is needed such as ionized calcium, serum PTH and prolactin. Patients with curative resected gastrinoma will be evaluated on a yearly basis. In patients with a curative resected insulinoma, a follow-up program should only be continued after 6 months if symptoms recur.

**Recurrent disease**

Patients with recurrent disease after curative resection can be offered various treatments. Besides surgical resection of metastasis and embolization /RFA of liver lesions, several other treatment options may be provided.

First, somatostatin analogues are often used to treat metastatic symptoms caused by the hormone hypersecretion. Somatostatin analogues will reduce the secretion of these hormones.
Furthermore, recently the CLARINET study showed also a significant antitumor effect. Compared to patients treated with a placebo. Patients treated with somatostatin analogue (Lanreotide 120mg) had a significant prolonged progression free survival17. The new developed analogue Pasireotide might also be an effective antiproliferative drug18.

Secondly, chemotherapy can be recommended in patients with tumor-related symptoms, high tumor load in the liver or tumor progression. Frequently, combinations such as Streptozotocin/5-FU, temozolomide/capecitabine or Cisplatin/etoposide can be given 19,20.

Thirdly, peptide receptor radionuclide therapy (PRRT) can be a treatment option in patients with a high uptake on the Octreoscan. With the use of radioactive labeled somatostatin analogues, tumor cell death could be obtained and therefore symptoms may relief, tumor load may be reduced and often stable disease could be achieved21,22.

Finally, two new biologicals have been used in randomized clinical trials with beneficial effects. Everolimus is an oral inhibitor of mTOR (mammalian target of rapamycin) and mTOR stimulates cell growth, proliferation and angiogenesis. Inhibition of mTOR causes a antiproliferative effect in patients with advanced pNET23. Sunitinib is a multitargeted tyrosine kinase inhibitor and by the inhibition of growth factors such as vascular endothelial growth factor (VEGF) or platelet-derived growth factors receptors (PDGFRs) tumor growth can be delayed. In a recent study, daily administration of Sunitinib improved progression free survival in patients with advanced pNET24.

Aim and outline of the thesis
In current European guidelines, surgical management of patients with pNET is mostly descriptive rather than leading2,3. The aim of the thesis is to complement the scientific evidence in several topics in the surgical management of patients with pNET.

The studies on postoperative outcome and survival after the surgical management of patients with pNET are limited to cohort studies or case series, no results of randomized trials have been published. In chapter 2 we have performed a systematic review in order to combine all the available evidence on postoperative outcome/complications and survival after surgery for pNETs. The postoperative outcome was defined as pancreatic fistula, delayed gastric emptying, postoperative hemorrhage and in-hospital mortality. The postoperative outcome was analyzed for each surgical procedure separately as well as a proportion analysis. In addition, a survival analysis was performed on both the 5-year overall survival and 5-year disease specific survival after surgical resection in patients with or without synchronously resected liver metastasis. In the literature, a tumor enucleation is often described as a low risk operation with only an increased risk of pancreatic fistula. In chapter 3 we have analyzed the postoperative outcome in patients with pNET of the Academic Medical Center in Amsterdam and the Erasmus Medical Center in Rotterdam to determine if outcome after tumor enucleation was better compared to the other surgical procedures. We have analyzed the postoperative
complications for each surgical procedure separately with both ISGSPs- and Clavien-Dindo criteria together with the in-hospital stay, need for re-interventions and re-admissions for each surgical procedure.

A relatively new technique is the laparoscopic pancreatic tail resection. In chapter 4 we have investigated whether a laparoscopic procedure is safe compared to an open procedure, based on postoperative outcome. Since the surgical technique is likely to be comparable in patients with pNET and other diagnosis such as pancreatic adenocarcinomas, we combined the different diagnosis in one cohort.

Some studies suggest, that the diagnosis pNET can be a risk factor for pancreatic fistula due to the texture of the pancreas25. In chapter 5 we tested this hypothesis. Therefore, we have compared the morbidity in patients with pNET after pancreatic surgery to other types of pathology.

Postoperative hemorrhage is another severe complication after pancreatic surgery causing a high mortality13. Pancreatic fistula is a well-known risk factor for postoperative hemorrhage. Therefore, in chapter 6 the outcome after postoperative hemorrhage and the need for re-intervention was analyzed.

During the pre-operative workup or follow-up, a somatostatin receptor scintigraphy can be performed to detect the primary tumor or recurrent disease after curative resection. Somatostatin receptor scintigraphy is often performed as second test after a CT scan. It is unclear if patients benefit from this extra additional imaging. Therefore, in chapter 7 we have determined the additional value of somatostatin receptor scintigraphy during pre-operative staging and follow-up after standard imaging. Main endpoints were a change in TNM classification or a change in management after the somatostatin receptor scintigraphy.

Chromogranin A (CgA) is often used as a biochemical tumor marker in patients with pNETs. Since CgA is mostly used to detect recurrent disease or evaluate tumor response, no evidence is available for the determination of CgA in patients with resectable non-functioning pNETs. Therefore, in chapter 8 we have analyzed the diagnostic accuracy and additional value of CgA in this selected group of patients.

In most studies on long-term follow-up, the group of patients with resected pNET is inhomogeneous. Studies included patients with hereditary syndromes, well differentiated / poorly differentiated tumors, functional/non-functional pNET, with or without liver metastases. Follow-up programs are not uniform and not based on risk profiles. In chapter 9 we have identified risk factors for recurrent disease within 5 years after pancreatic resection in patients with a grade 1 and 2 pNETs without synchronous metastases or hereditary syndromes. Based on our findings, we have developed a nomogram to predict recurrent disease and to identify high-risk patients for recurrent disease.
REFERENCES


