Pancreatic Neuroendocrine Tumors

Surgical Treatment and Follow-up

JOSEFINE KJAER
Abstract

Pancreatic neuroendocrine tumors (Pan-NET), are rare, heterogenous and derive from the hormone producing cells in the pancreas. The functioning tumors that overproduce hormones cause clinical syndromes with specific symptoms due to the hormonal production. However, the majority of patients have non-functioning tumors, and in lack of symptoms, these more often present with, or develop, liver metastases. This thesis focuses on treatment of metastasized pan-NET, stage IV, from a surgical perspective. As some patients operated on for localized disease eventually experience recurrence, it would also be beneficial to be able to predict which patients that are at a higher risk for recurrence.

In paper I, outcome after primary tumor resection in pan-NET patients, stage IV, was evaluated. An association between primary tumor resection and prolonged survival was found in patients, both before and after propensity score match. In paper II, outcome after hepatic resection and thermal hepatic ablation of liver metastases, in patients previously subjected to primary tumor resection, was scrutinized. Survival rates were significantly higher in the hepatic resection/thermal hepatic ablation group, and in a multivariable analysis, hepatic resection/thermal hepatic ablation remained a significant positive prognostic factor for prolonged survival. In paper III, patients with unresectable liver metastases, eligible for liver transplantation were investigated. A very small group of all pan-NET stage IV patients was eligible for liver transplantation and even fewer patients met any of the current selection criteria for liver transplantation. The survival rates for these patients, only subjected to multimodal treatment, were comparable to the survival rates after liver transplantation, presented in previously published studies. In paper IV, an external validation of a prediction model for recurrence after resection of non-metastatic, non-functioning, grade 1-2 tumors, was performed. The model performed well in the validation and is available online.

To conclude, both primary tumor resection and surgical and ablative treatment of liver metastases in stage IV pan-NET, were associated with prolonged survival in analyses controlling for bias and possible confounders. However, the evidence base to perform liver transplantation in patients with pan-NET is weak. A prediction model for recurrence after radical surgery of non-metastatic pan-NET was externally validated with success. Our findings provide additional knowledge regarding treatment of stage IV pan-NET and could also help us predict which patients that will recur after surgery.

Keywords: Pancreatic neuroendocrine tumor, surgery, liver metastases, hepatic resection, liver transplantation, recurrence

Josefine Kjaer, Department of Surgical Sciences, Endocrine Surgery, Akademiska sjukhuset ing 70 1 tr, Uppsala University, SE-751 85 Uppsala, Sweden.

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ISSN 1651-6206
URN urn:nbn:se:uu:diva-490483 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-490483)
"They don’t know that we know they know we know!"

-Phoebe
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>c-Pan-NEN</td>
<td>cystic pancreatic neuroendocrine neoplasm</td>
</tr>
<tr>
<td>ENETS</td>
<td>European Neuroendocrine Tumor Society</td>
</tr>
<tr>
<td>ESMO</td>
<td>the European society for medical oncology</td>
</tr>
<tr>
<td>F-pan-NET</td>
<td>functioning pancreatic neuroendocrine tumor</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health related quality of life</td>
</tr>
<tr>
<td>GEP-NET</td>
<td>gastroenteropancreatic neuroendocrine tumors</td>
</tr>
<tr>
<td>GRH</td>
<td>growth related protein</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health related quality of life</td>
</tr>
<tr>
<td>IF-II</td>
<td>insulin-like growth factor</td>
</tr>
<tr>
<td>LT</td>
<td>liver transplantation</td>
</tr>
<tr>
<td>MEN1</td>
<td>multiple endocrine neoplasia type 1</td>
</tr>
<tr>
<td>MWA</td>
<td>microwave ablation</td>
</tr>
<tr>
<td>NCDB</td>
<td>national cancer database</td>
</tr>
<tr>
<td>NEC</td>
<td>neuroendocrine carcinoma</td>
</tr>
<tr>
<td>NEN</td>
<td>neuroendocrine neoplasm</td>
</tr>
<tr>
<td>NET</td>
<td>neuroendocrine tumor</td>
</tr>
<tr>
<td>NF-pan-NET</td>
<td>non-functioning pancreatic neuroendocrine tumor</td>
</tr>
<tr>
<td>NF-1</td>
<td>neurofibromatosis type 1</td>
</tr>
<tr>
<td>NME</td>
<td>necrolytic migratory erythema</td>
</tr>
<tr>
<td>Pan-NEN</td>
<td>pancreatic neuroendocrine neoplasm</td>
</tr>
<tr>
<td>Pan-NET</td>
<td>pancreatic neuroendocrine tumors</td>
</tr>
<tr>
<td>PCS</td>
<td>pancreatic cholera syndrome</td>
</tr>
<tr>
<td>PRRT</td>
<td>peptide receptor radionuclide therapy</td>
</tr>
<tr>
<td>PTHrp</td>
<td>parathyroid hormone related protein</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RFA</td>
<td>radiofrequency ablation</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristics</td>
</tr>
<tr>
<td>RRS</td>
<td>recurrence risk score</td>
</tr>
<tr>
<td>SEER</td>
<td>surveillance, epidemiology and end results</td>
</tr>
<tr>
<td>SI-NET</td>
<td>small intestine neuroendocrine tumor</td>
</tr>
<tr>
<td>SIRT</td>
<td>selective internal radiotherapy</td>
</tr>
<tr>
<td>TAE</td>
<td>trans arterial embolization</td>
</tr>
<tr>
<td>TACE</td>
<td>trans arterial chemo-embolization</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumor, Node, Metastases</td>
</tr>
<tr>
<td>TSC</td>
<td>tuberous sclerosis</td>
</tr>
<tr>
<td>UNOS</td>
<td>United Network for Organ Sharing</td>
</tr>
<tr>
<td>VHL</td>
<td>von Hippel-Lindau</td>
</tr>
<tr>
<td>VIP</td>
<td>vasoactive intestinal peptide</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>VMS</td>
<td>Verner–Morrison syndrome</td>
</tr>
<tr>
<td>WDHA</td>
<td>watery diarrhea–hypokalemia–achlorhydria</td>
</tr>
</tbody>
</table>
Introduction

Pancreatic neuroendocrine tumors are rare and constitutes a heterogenous group of tumors. Some of the tumors overproduce hormones, causing syndromes with very specific symptoms, some are indolent tumors, whereas others are more aggressive. Delayed detection of the tumors that do not overproduce hormones, the non-functioning ones, is not uncommon, and some present with metastatic disease at diagnosis. The treatment arsenal for these tumors consists of both systemic oncological treatments, however, surgical treatment and ablative methods constitutes the only two that offer potential cure. This thesis focuses on the surgical treatment in patients that present with or develop liver metastases. In paper I, primary tumor surgery is evaluated in patients with synchronous liver metastases. In paper II, treatment with liver resection and thermal hepatic ablations are evaluated in patients subjected to previous primary tumor resection. In paper III, patients with unresectable liver metastases, eligible for liver transplantation, were evaluated regarding survival rates. Finally, in paper IV, a prediction model for recurrence for patients with complete resection of non-metastatic, low-grade, non-functioning tumors, was externally validated.
Background

Nomenclature
Neoplasms arising from neuroendocrine cells in different parts of the body are called neuroendocrine neoplasms (NENs), and are divided into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated cancers, termed neuroendocrine cancers (NECs).\(^1,2\) The most common site for these neoplasms is the digestive tract, commonly denoted gastroentero-pancreatic neuroendocrine tumors (GEP-NETs), and the broncho-pulmonary system, but NETs may also have other origin, such as the ovaries and thymus.\(^3\)

Anatomy
The pancreas is a gland with both exocrine and endocrine function. The exocrine part produces the digestive enzymes α-amylase, lipase and protease, which are portioned through the ductal system into the duodenum. They are responsible for digestion of carbohydrates, fats and proteins.\(^4\) Neoplasms arising from the exocrine parts of the pancreas constitute cancers with a completely different pathophysiology, pattern of growth and prognosis.\(^5\)

Pancreatic neuroendocrine neoplasms (Pan-NENs) arise from the islet cells of the pancreas, also called the islet of Langerhans, named after Paul Langerhans (1849-1888) who first described these cells in 1869.\(^6\) These clusters of endocrine cells consists of five different endocrine cell types with hormone production, and are scattered throughout the exocrine parenchyma, constituting only 1-2% of the pancreas.\(^6,7\)

Grade and Stage
The World Health Organization (WHO) have used different grading systems over the years. The last update from 2017 divides pan-NENs into well-differentiated tumors, grades 1-3 (NET G1-3) depending on mitotic index and the proliferation index Ki67, and poorly differentiated neuroendocrine cancers, grade 3 (NEC G3).\(^8,9\) (Table 1)
The stages of pan-NENs are described by the tumor, node and metastases (TNM) system according to the European Neuroendocrine Tumor Society (ENETS) that has been used since 2006. The T1 tumors are classified as stage I, T2-3 as Stage 2, T4 or any T-tumor and N1 as Stage III, and all tumors with distant metastases as Stage IV. (Table 2)

WHO Classification

<table>
<thead>
<tr>
<th>WHO Classification (2017)</th>
<th>Ki67 index (%)</th>
<th>Mitoses/10 HPF</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET G1</td>
<td>&lt;3</td>
<td>&lt;2</td>
<td>Well</td>
</tr>
<tr>
<td>NET G2</td>
<td>3–20</td>
<td>2–20</td>
<td>Well</td>
</tr>
<tr>
<td>NET G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>Well</td>
</tr>
<tr>
<td>NEC G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>Poorly</td>
</tr>
</tbody>
</table>

WHO; World Health Organization, HPF; High Power Field (=2mm²)

Table 2. TNM-classification of Pan-NET according to ENETS

TNM Classification of Pan-NET

T—primary tumor

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the pancreas and size &lt;2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor limited to the pancreas and size 2–4 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to the pancreas and size &gt;4 cm or invading duodenum or bile duct</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland)</td>
</tr>
<tr>
<td></td>
<td>or the wall of large vessels (celiac axis or superior mesenteric artery)</td>
</tr>
<tr>
<td></td>
<td>For any T, add (m) for multiple tumors</td>
</tr>
</tbody>
</table>

N—regional lymph nodes

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph node cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

M—distant metastases

<table>
<thead>
<tr>
<th>M</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>Disease stages</td>
<td>Primary tumor</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
</tr>
<tr>
<td>IIa</td>
<td>T2</td>
</tr>
<tr>
<td>IIb</td>
<td>T3</td>
</tr>
<tr>
<td>IIIa</td>
<td>T4</td>
</tr>
<tr>
<td>IIIb</td>
<td>Any T</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
</tr>
</tbody>
</table>

T; primary tumor according to the TNM classification; N; lymph node metastases according to the TNM classification, M; metastases according to the TNM classification

Increase in Ki67, and thereby grade progression, may happen over time, and is difficult to predict for the individual patient.¹³ Changes in hormonal secretion, associated with poorer prognosis, has also been described.¹⁴

Incidence

Neuroendocrine tumors in general and pancreatic neuroendocrine tumors (pan-NET) in particular are relatively rare tumors. Global epidemiologic data are widely heterogeneously reported and therefore makes interpretation challenging. However, there is a coherence in both a rising incidence and prevalence of pan-NETs and NETs in general.²,¹⁵-¹⁷ In the largest epidemiologic study of NENs to date, based on the population in the US and the Surveillance, Epidemiology and End Results (SEER) database 1973-2012, the incidence of pan-NET was 0.48 cases per 100,000. In an age-adjusted analysis the incidence rates increased from around 0.2 per 100,000 in 1973 to over 0.8 per 100,000 which is a four-fold increase.¹ Relatively, the incidence increased the most in localized disease.¹ Pan-NENs constitute 7% of all NENs in the US.² There also seems to be a variable increase in incidence in different parts of the world as well as racial differences, which may be due to different national demographics, both environmental and biological factors.²,¹⁵-¹⁹

The reasons for the increasing incidence are debated. The more frequent use of cross-sectional imaging and the improvement in the radiological techniques leads to an increased detection of small tumors.¹,²,²⁰ Another explanation to the increased incidence may be an improved consistency and accuracy of reporting to registers.
Hormonal expression

As pan-NET arise from the islet cells, some of the tumors are hormone producing, causing clinical symptoms. These tumors are called functioning pan-NET (F-pan-NET) and constitutes around 40% of all pan-NETs.21,22 The F-pan-NETs presents with different syndromes, depending on which hormone or hormones, that are produced. The most common syndrome is insulinoma, which causes hypoglycemia, and gastrinoma that presents with Zollinger-Ellisson syndrome, causing peptic ulcer disease due to gastrin excess.23 Among the rare F-pan-NETs are VIPomas, causing a syndrome called Verner–Morrison syndrome (VMS), WDHA (watery diarrhea–hypokalemia achlorhydria) syndrome, or pancreatic cholera syndrome (PCS), due to excess of vasoactive intestinal peptide (VIP).23,24 Other rare F-pan-NETs are glucagonomas, causing glucose intolerance, weight loss and a specific rash called necrolytic migratory erythema (NME), somatostatinomas causing diabetes mellitus, cholelithiasis and steatorrhea, GRHomas, ACTHomas, serotoninomas causing carcinoid syndrome and PTHrp-omas causing hypercalcemia. Among the very rare F-pan-NET are tumors secreting renin, lutetinizing hormone, erythropoietin and insulin-like growth factor II (IF-II).23 The malignant potential varies among these syndromes where almost all insulinomas are benign and almost all gastrinomas are malignant.25

Genetic syndromes

Pan-NETs most often present as a sporadic tumor, but can also appear as part of a genetic syndrome. The most common syndrome is multiple endocrine neoplasia type 1 (MEN1), or Wermers syndrome, which is an autosomal dominant inherited disorder with >95% penetrance by age 40-50.26,27 The syndrome is caused by a mutation in a tumor suppressor gene, expressing the protein menin that regulates gene transcription, located in the long arm of chromosome 11 (11q13).24,28,29 The major clinical manifestations of MEN1 syndrome, besides pan-NET, present in 50-70% of the patients, are primary hyperparathyroidism, present in >95% of the patients and pituitary tumors present in 30-55% of the patients.27,30 Thereto, the syndrome is also associated with an increased risk of other proliferative lesions.30 The prevalence of MEN1 syndrome is reported as 1-10 in 100 000 individuals without gender bias.26,27 Patients with MEN1 often develop multiple pan-NET and duodenal NETs and are recommended to be closely monitored by biochemical screening and imaging according to current guidelines.27,31,32 Genetic testing is recommended in all patients with clinical suspicion of MEN1 to confirm the diagnosis, and in all first-degree relatives of MEN1 gene carriers.27,31

Von Hippel-Lindau (VHL) disease is an autosomal dominant neoplasia syndrome. VHL is a tumor suppressor gene on the short arm of chromosome
Germline mutations in the VHL gene lead to the development of several benign or malignant vascular tumors, and cysts in many organ systems such as the central nervous system and viscera.\textsuperscript{24,33} There are several familial phenotypes of VHL disease, where pan-NETs are present in Type 1 and type 2B. In total, 8-17% of all patients with VHL disease develop pan-NET.\textsuperscript{33}

Also, Pan-NETs occur in 10% of patients with Neurofibromatosis type 1 (NF-1) and there are also case reports proving pan-NET associated with Tuberous Sclerosis (TSC).\textsuperscript{22,23}

**Diagnosis**

**Pathology**

Histological diagnosis is mandatory for the pan-NET diagnosis. Specimen from surgical resection or by core biopsies are assessed on hematoxylin eosin (HE)-staining and shows specific growth pattern and positive synaptophysin and/or chromogranin A (CgA).\textsuperscript{3} In F-pan-NET, specific staining for peptide hormones is assessed, however, immunohistochemistry (IHC) and symptomatology does not always correlate. Proliferation index Ki67 and mitotic rate is used to grade the tumors. When applicable, tumors are assessed according to the TNM classification.\textsuperscript{35}

**Imaging**

Several radiological methods are available to depict pan-NET. The most commonly used, is contrast-enhanced computed tomography (CT), and with the advances in modern equipment, this imaging method has short scanning time and is highly accessible.\textsuperscript{36} Pan-NETs are typically hyper-enhancing during the arterial phase and remain mildly hyper attenuating during the venous and delayed phases.\textsuperscript{37} The sensitivity varies between 67-96% with a specificity of 96%.\textsuperscript{38} Small lymph nodes and bone metastases may be hard to detect, however, CT is superior to other methods in detection of small lung metastases.

Magnetic resonance imaging (MRI) is useful to detect liver metastases where the sensitivity is 75% with a specificity of 98%. To further characterize lesions in the liver, contrast-enhanced ultrasound (CEUS) can be used. Optimal imaging of small pan-NETs is endoscopic ultrasound (EUS) which also allows for biopsy.

Nuclear medicine imaging is the most specific method to detect pan-NETs, and is routinely performed at Uppsala University Hospital for all patients with suspicion of pan-NET. This entails the use of positron emission tomography (PET) with CT (PET-CT), where the radionuclide \textsuperscript{68}Ga is linked
to an SSA via a chelator; DOTATOC, DOTANOC or DOTATATE. $^{68}$Ga-DOTATOC-PET-CT detects pan-NETs with a sensitivity of 88-93% and a specificity of 88-95%.$^{38}$ Moreover, this imaging method detects almost all bone metastases.$^{23}$ However, due to the lack of somatostatin receptor (SSTR) expression in insulinomas, imaging with radiolabeled GLP-1 receptor analogues can also be used although the availability of this method is limited. For detection of tumors with Ki67>15% including NET G2-3, PET with 18F-fluoro-deoxyglucose (FDG) is recommended due to higher glucose metabolism and less SSTR expression.$^{3,35,38}$ Some centers have developed or use other specific PET amine precursor tracers, such as $^{11}$C-5-hydroxy-L-tryptophan ($^{11}$C-5-HTP) and $^{18}$F-DOPA, however, these are not widely used due to limited availability.$^{36}$

Biomarkers
Among biochemical markers, Chromogranin A in serum is used as a general NET marker. The levels in untreated patients are known to correspond to the tumor burden, however, it is a non-specific marker that is elevated in other tumor diseases, in patients treated with proton pump inhibitors (PPI) and in patients with renal insufficiency or atrophic gastritis.$^{21,35}$ Pancreatic polypeptide (PP) in serum is common in pan-NET patients and is often elevated in patients with NF-pan-NET. Specific markers for functioning tumors also include gastrin, VIP, ACTH, Calcitonin, glucagon, insulin, proinsulin and C-peptide.$^{35}$

Survival rates
Diverse OS for all patients with pan-NET has been reported with a median OS of 3.6 years and 5-year survival of 53%.$^{1,39}$ Median OS in localized pan-NET is favorable, almost 20 years. In disease with regional lymph nodes or distant metastases, the median OS is noticeably lower, 7.5 years and 2-2.5 years, respectively.$^{1,40}$ The expected 5-year survival rate in localized disease, regional disease and stage IV pan-NETs is 93%, 74% and 24% respectively according to the SEER database. In other studies, 5-year survival in stage IV pan-NET varies between 27 and 60%.$^{41,42}$

Treatment
Treatment of primary tumor, stage I-III
The only curative treatment for patients with pan-NET is surgical resection. However, the aggressiveness of the disease varies, from small indolent tu-
mors to small tumors with advanced metastatic disease, or in some patients large locally aggressive tumors. Factors, or predictors, associated with worse prognosis are higher WHO grade, age >55-60 years and presence of lymph node metastases.  

Generally, resection is recommended for all patients with functioning tumors. Regarding NF-pan-NET, the size of the primary tumor is correlated with risk of lymph node metastases, and thereby also constitutes a factor associated with poorer prognosis. Tumors less than 2 cm are generally considered small, and multiple studies has shown increased presence of lymph node metastases in tumors larger than 2 cm compared to tumors ≤2 cm. Cystic tumors, c-Pan-NENs, have been discussed to have different tumor biology than the solid tumors, and are associated with lower WHO grade. However, no difference in metastatic lymph node presence or survival between the two has been shown.  

According to the Swedish national guidelines, tumors <1 cm should be followed and in patients with tumors 1-2 cm, individual assessment regarding surgical treatment is recommended. Worldwide, patients with small asymptomatic tumors, NF-pan-NETs ≤2 cm, are often managed non-operatively, with a watch-and-wait strategy. However, surgery is recommended for young patients, and in those with signs of local invasiveness such as jaundice or dilation of the pancreatic duct, according to international guidelines.  

Depending on localization of the pancreatic tumor, different surgical approaches are required. For tumors in the pancreatic head, two principally different methods are used. Enucleation is a possible surgical technique when the tumor is small, does not invade the pancreatic duct and no metastatic lymph nodes are present. Otherwise, a pancreaticoduodenectomy (PPPD) or Whipple’s procedure is required. For tumors in the body or tail of the pancreas, a distal pancreatectomy with or without spleen-preserving technique is performed. When there are lymph node metastases, the spleen is usually removed to enable proper lymph node dissection.  

Treatment of primary tumor, stage IV  
In patients with distant metastases, stage IV, resection of the primary tumor in asymptomatic patients with NF-pan-NET is controversial and the management of these tumors differs among centers in the world. There are contradictory results from previous studies where some suggest oncological benefits for the patients undergoing primary tumor resection and other that does not. Review articles and meta-analyses often conclude an association between primary tumor surgery and improved survival, however, they are all mainly based on almost the same, few studies. Although numerous studies have been carried out, investigating the effect of primary tumor surgery in a metastasized setting, conclusions regarding survival benefit are hard to draw due to the small sample sizes, lack of data on included patients’
comorbidity, lack of comparison between groups and the heterogeneity of the included patients.\textsuperscript{62-64}

Relevant studies including >50 patients are shown in Table 4. Studies with complete overlap in patients and analyses were excluded,\textsuperscript{16,65-67} as well as studies including mixed NETs.\textsuperscript{68} Five-year survival after primary tumor resection varies between 43 and 73\% compared with 16 to 42\% in the non-resected groups.
Table 4. Outcome after primary tumor surgery in stage IV69-79

<table>
<thead>
<tr>
<th>Authors</th>
<th>PT resection (n)</th>
<th>no PT resection (n)</th>
<th>Study period</th>
<th>Patient cohort</th>
<th>Data of comorbidity</th>
<th>Median OS (months)</th>
<th>OS (5-year, 10-year)</th>
<th>p-value</th>
<th>Adjusted analyses performed</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solorozano69</td>
<td>16</td>
<td>80</td>
<td>1988-1999</td>
<td>Single center</td>
<td>no</td>
<td>36</td>
<td>49%</td>
<td>16%</td>
<td>0.06</td>
<td>yes</td>
</tr>
<tr>
<td>Addeo79</td>
<td>51</td>
<td>-</td>
<td>1995-2020</td>
<td>Single center</td>
<td>no</td>
<td>65</td>
<td>61%, 29%</td>
<td>-</td>
<td>no CG</td>
<td>yes</td>
</tr>
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<td>Nguyen71</td>
<td>20</td>
<td>31</td>
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<td>63</td>
<td>60%</td>
<td>30%</td>
<td>0.025</td>
<td>no</td>
</tr>
<tr>
<td>Bertani72</td>
<td>63</td>
<td>30</td>
<td>1994-2013</td>
<td>2 center study</td>
<td>yes</td>
<td>111</td>
<td>43%</td>
<td>27%</td>
<td>0.003</td>
<td>yes</td>
</tr>
<tr>
<td>Bettini73</td>
<td>19</td>
<td>32</td>
<td>1990-2004</td>
<td>Single center</td>
<td>no</td>
<td>69</td>
<td>40%*</td>
<td>42%*</td>
<td>0.741</td>
<td>no</td>
</tr>
<tr>
<td>Partelli73</td>
<td>73</td>
<td>75</td>
<td>2000-2011</td>
<td>4 center study</td>
<td>no</td>
<td>89</td>
<td>73%</td>
<td>36%, 16%</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>Chawla74</td>
<td>351</td>
<td>3887</td>
<td>1998-2012</td>
<td>NCDB database</td>
<td>yes</td>
<td>72</td>
<td>59%</td>
<td>19%</td>
<td>&lt;0.001</td>
<td>yes</td>
</tr>
<tr>
<td>Lin76</td>
<td>35</td>
<td>28</td>
<td>1998-2016</td>
<td>Single center</td>
<td>no</td>
<td>72</td>
<td>54%</td>
<td>32%</td>
<td>0.01</td>
<td>yes</td>
</tr>
<tr>
<td>Ye77</td>
<td>392</td>
<td>1582</td>
<td>2004-2015</td>
<td>SEER-database</td>
<td>no</td>
<td>78</td>
<td>60%*</td>
<td>35%*</td>
<td>25%<em>, 10%</em></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mou78</td>
<td>214</td>
<td>322</td>
<td>2000-2017</td>
<td>SEER-database</td>
<td>no</td>
<td>73</td>
<td>68%</td>
<td>22%</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>Keutgen79</td>
<td>303</td>
<td>579</td>
<td>1973-2011</td>
<td>SEER-database</td>
<td>no</td>
<td>65</td>
<td>55%*</td>
<td>18%*</td>
<td>&lt;0.001</td>
<td>yes</td>
</tr>
</tbody>
</table>

PT; primary tumor, N; number of patients, OS; Overall Survival, CG; Control Group; ns; not specified; NCDB; National Cancer Database (USA), *Not reported in tables or manuscript but estimated visually from Kaplan-Meier curve
Treatment of liver metastases

As most pan-NETs are non-functioning, which may cause delay in diagnosis, it is common for patients to either present with or develop distant metastases.\cite{TreatmentOfLiverMetastases} The only cure for pan-NET is complete surgical resection and although the aim for treatment of liver metastases may be curative, the high frequency of micro metastases often makes long term disease free survival (DFS) difficult to achieve. Other aims of treatment may be debulking in an attempt to prolong survival or to relieve hormonal symptoms.\cite{SurgicalTreatmentOfPanNETLiverMetastases} When there is a concern regarding liver failure post-resection, due to insufficient residual liver volume, often considered <30% functional liver, portal vein embolization can be performed a month before the planned liver resection, to induce hypertrophy of the liver parenchyma.\cite{SurgicalTreatmentOfPanNETLiverMetastases} Surgical treatment of pan-NET liver metastases includes different types of hepatic resections, but also local thermal ablative techniques (THA) such as radiofrequency ablation (RFA), microwave ablation (MWA) and transcutaneous alcohol ablation.\cite{SurgicalTreatmentOfPanNETLiverMetastases} At our institution, RFA was replaced with MWA and this method has been offered since 2009. In a setting of more extensive liver tumor load, embolization of the hepatic artery may be performed, such as selective internal radiotherapy (SIRT) using Yttrium-90 ($^{90}$Y)-microspheres, trans arterial embolization with embolizing particles (TAE), or together with a chemotherapeutic agent (TACE). In highly selected patients with unresectable liver metastases, some centers perform liver transplantation, although this is controversial.\cite{LiverTransplantationForLiverMetastases}

No randomized trials (RCT) have been performed to evaluate hepatic resection or THA compared to watchful waiting, or other oncologic treatments for patients with metastasized pan-NET. Several studies evaluating treatment of liver metastases of mixed NETs, do not report sub-analyses of primary tumor origin, and many studies also lack an unbiased control group. To draw any firm conclusions from these studies is therefore almost impossible, as the prognosis for pan-NET is evidently worse than for the more common SI-NET, that often constitutes the main parts of these mixed cohorts.\cite{NoRandomizedTrialsForLiverMetastases} Table 5 shows the outcome in studies on patients with pan-NET and liver metastases subjected to hepatic resection and/or THA. Based on the survival rates after hepatic resection and THA in these studies, there may seem to be a survival benefit compared to patients not subjected to this treatment, however, due to the objections brought forth above, the evidence base is not very solid.
Table 5. Outcome after hepatic resection and THA for liver metastases\textsuperscript{74,87,97-101}

<table>
<thead>
<tr>
<th>Authors</th>
<th>NET (Pan-NET with LM)</th>
<th>Hepatic resection (n)</th>
<th>Controls (n)</th>
<th>THA</th>
<th>Study period</th>
<th>Patient cohort</th>
<th>Resection</th>
<th>No resection</th>
<th>Resection</th>
<th>No resection</th>
<th>p-value</th>
<th>Adjusted analyses performed</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamberlain\textsuperscript{97}</td>
<td>34</td>
<td>20</td>
<td>17</td>
<td>0</td>
<td>1992-1998</td>
<td>Single center</td>
<td>-</td>
<td>-</td>
<td>80%</td>
<td>-</td>
<td></td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Woltering\textsuperscript{97}</td>
<td>800</td>
<td>89</td>
<td>50</td>
<td>0</td>
<td>2003-2016</td>
<td>Single center</td>
<td>-</td>
<td>-</td>
<td>67%, 51%</td>
<td>-</td>
<td></td>
<td>no</td>
<td>67</td>
</tr>
<tr>
<td>Partelli\textsuperscript{104}</td>
<td>166</td>
<td>91</td>
<td>75</td>
<td></td>
<td>2000-2011</td>
<td>4 center</td>
<td>97</td>
<td>36</td>
<td>76%</td>
<td>36%</td>
<td>&lt;0.001</td>
<td>yes</td>
<td>41</td>
</tr>
<tr>
<td>Birnbaum\textsuperscript{98}</td>
<td>43</td>
<td>9</td>
<td>17</td>
<td>17</td>
<td>1995-2012</td>
<td>4 center</td>
<td>90</td>
<td>-</td>
<td>66%</td>
<td>-</td>
<td></td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>House\textsuperscript{99}</td>
<td>36</td>
<td>31</td>
<td>5</td>
<td>2</td>
<td>1988-2003</td>
<td>Single center</td>
<td>78</td>
<td>17</td>
<td>65%, 10%</td>
<td>20%, 0%</td>
<td>0.06</td>
<td>no</td>
<td>44</td>
</tr>
<tr>
<td>Kleine\textsuperscript{100}</td>
<td>41</td>
<td>9</td>
<td>6</td>
<td></td>
<td>1990-2009</td>
<td>Single center</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>yes</td>
<td>40</td>
</tr>
<tr>
<td>Zerb\textsuperscript{101}</td>
<td>66</td>
<td>22</td>
<td>36</td>
<td>15</td>
<td>2004-2007</td>
<td>24 centers</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>yes</td>
<td>21</td>
</tr>
</tbody>
</table>

OS; Overall Survival, n; number of patients
Liver transplantation

In patients with complete resection of the primary tumor and loco-regional lymph node metastases, liver transplantation (LT) has been suggested as a therapeutic method in an attempt to prolong survival rates. However, it is a controversial treatment and there are no globally accepted selection criteria for LT in these patients. North America Neuroendocrine Tumor Society (NANETS) does not include LT as a recommended treatment for patients with pan-NET. In centers and countries that perform LT in these patients, the selection varies. The most commonly used criteria for LT are the Milan criteria, LT criteria according to the European Neuroendocrine Tumor Society (ENETS) guidelines and LT criteria according to the United Network for Organ Sharing (UNOS) guidelines. The different LT criteria all require complete resection of the primary tumor, stable disease during at least six months and absence of extra-abdominal metastases. However, there are small differences regarding age, and additional criteria regarding lymph node metastases and Ki67% between the different guidelines. As in reports on survival rates after treatment of liver metastases, many studies of LT present survival rates of cohorts for mixed NET-types. Five-year survival rates range from 47.0-97.2% with the highest rates being quite remarkable. In these studies the majority of patients suffered from SI-NETs, which in a previous study, exclusively on SI-NET patients, eligible for LT but who instead were subjected to multimodal treatment, were shown to have excellent 5-years survival rates of 97%. In the few studies presenting sub-analyses of survival rates for patients receiving LT for metastasized pan-NET, the numbers are much lower and range from 27-53%. The opinions regarding the value of LT for pan-NET patients are diverse, and some of the studies reporting remarkable survival rates have probably fueled the discussion and convinced some surgeons that LT may benefit selected patients. However, the study presenting the best survival rates after LT may be criticized because of a major inherent methodological design flaw, where the survival is calculated from time of primary tumor resection, which in median was 18.5 months prior to the LT-surgery. Consequently, an immortal time bias was incorporated in the LT group, overestimating the benefit of LT. Thereto, this design caused the patients with progression while on waiting list, to end up in the non-transplant group, selecting the patients with progression, and thereby worse prognosis, into the control group. Another concern regarding this study is that complications and postoperative mortality was not presented at all, creating concerns regarding generalizability of the results, when other multicenter studies have presented 90-day mortality after LT reaching up to 10%.
Table 6. Criteria for LT

<table>
<thead>
<tr>
<th></th>
<th>Tumor grade</th>
<th>Primary tumor drainage</th>
<th>Stable disease</th>
<th>Hepatic tumor burden</th>
<th>Ki67 index</th>
<th>Primary tumor surgery</th>
<th>Age</th>
<th>Extrahepatic disease</th>
<th>Additional criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milan Criteria</td>
<td>G1-2</td>
<td>Portal</td>
<td>&gt;6 months</td>
<td>&lt;50%</td>
<td>x</td>
<td>6 months</td>
<td>&lt;55</td>
<td>None</td>
<td>x</td>
</tr>
<tr>
<td>ENETS Guidelines</td>
<td>G1-2</td>
<td>x</td>
<td>&gt;6 months</td>
<td>&lt;50%</td>
<td>&lt;10%</td>
<td>6 months</td>
<td>x</td>
<td>None</td>
<td>x</td>
</tr>
<tr>
<td>UNOS Guidelines</td>
<td>G1-2</td>
<td>x</td>
<td>&gt;6 months</td>
<td>&lt;50%</td>
<td>x</td>
<td>6 months</td>
<td>&lt;60</td>
<td>None</td>
<td>If lymph nodes on PET-scan, negative follow-up scan after 3 months</td>
</tr>
</tbody>
</table>
Systemic therapy

Systemic therapy with somatostatin analogues are effective to alleviate symptoms from F-Pan-NETs and may prolong time to progression. The mTOR inhibitor, everolimus, and the tyrosine kinase inhibitor, sunitinib, may prolong progression-free survival. For patients with well differentiated, progressive disease, with adequate somatostatin analogue receptor expression, peptide receptor radionuclide therapy (PRRT) is used. Chemotherapy is indicated for intermediate- and high-grade Pan-NETs.

In a neoadjuvant setting, PRRT and/or first line chemotherapy may be used. Streptotozin/5-Fluorouracil or Temozolomide/Capecitabin may be administered in an attempt to shrink the primary tumor before resection in selected patients.

Follow-up

For patients with stage IV pan-NET, follow-up is determined based on the treatments the patients receive and how well the patient responds to the treatment. In the patients with stable disease, cross-sectional imaging is performed every 6-12 months and if needed, the follow-up interval is shortened.

For patients with non-metastatic, low-grade tumors, there is a lack of consensus on the optimal surveillance after complete resection. The European Society for Medical Oncology (ESMO) recommends follow-up with imaging every 3-6 months and recommends a lifelong surveillance, the NANETS guidelines states initial imaging every 3-6 months and then every 6-12 months for a total of 10 years, the National Comprehensive Cancer Network (NCCN) recommends imaging every 6-12 months but does not state for how long, and the ENETS guidelines recommends imaging every 3-9 months. Other groups recommend no follow-up in specific low-risk groups with small grade 1 tumors without lymph node metastases.

Prediction model for recurrence

The prognosis for patients with curative resected NF-pan-NETs are known to be favorable. It is also known that patients with higher Ki67 have an increased risk of recurrence. In order to identify risk factors for recurrence, a study investigating tumor characteristics and recurrence rates, presented a scoring system to predict recurrence. The three independent risk factors for recurrence after resection of grade 1-2 sporadic NF-pan-NET identified in this study was tumor grade, presence of lymph node metastases and perineural invasion. These risk factors represent 40, 24 and 24 points respectively in the scoring system, based on the calculated HR in the Cox regression analysis. The aim of this prediction model was to identify patients with high
risk of recurrence, patients that would benefit from adjuvant therapy and help as guide to individualize follow-up.\textsuperscript{48}

Three other prediction models for recurrence have been developed; The US Neuroendocrine Tumor Study Group created a validated model including all GEP-NETs with a C-index of 0.74, an international group created a validated model including risk factors such as number of positive nodes and range in Ki67 index with a C-index of 0.84, and a US and Italian collaboration including risk factors such as symptomatic tumors, tumor size \(>2\) cm, and Ki67 index (\(<3\%, 3–20\%, >20\%)\textsuperscript{126-128
Aims

The overall aim of this thesis was to evaluate treatment of metastasized pan-NET, stage IV, from a surgical perspective. In localized disease the intent is almost always curative and the strategy is surgical resection. However, in stage IV disease, the intent, which may be curative or palliative, the treatment strategy is not always as clear. The possible benefits with surgical treatment must always be weighed against the risks for complications, and preferably the scientific literature can guide us in the correct direction. Studies I-III were performed in attempt to add to this growing body of literature.

As some patients operated on for localized disease eventually experience recurrence, it would be beneficial to be able to predict which patients that are at a higher risk for recurrence, which would aid in development of new treatment strategies and follow-up regimens.

The specific aims were:

I. To evaluate outcomes in patients with stage IV pan-NET who underwent resection of the primary tumor compared with those managed nonoperatively, while also accounting for the variability in the extent of metastatic disease and comorbidity.

II. To evaluate outcomes after surgery and thermal hepatic ablation of Pan-NET liver metastases, and to compare the outcomes for these patients with those of a control group of pan-NET patients not subjected to liver surgery or thermal hepatic ablation, and to control for any possible confounders.

III. To determine the survival in a cohort of patients with stage IV pan-NET who meet the Milan criteria, ENETS guidelines and UNOS guidelines for LT, but instead received multimodal treatment.

IV. To validate the risk score for recurrence, in an international cohort of patients with complete resection of grade 1-2, NF-pan-NET, with an additional validation in tumors > 2cm, and also to update the prediction model to be more applicable in a daily setting.
Material and Methods

Study population
All four studies are retrospective cohort studies. All patients treated for pan-NET at Uppsala University Hospital, from the year 1985, were assessed for eligibility. Collaborations were made with Brigham and Women’s Hospital/Dana-Farber Cancer Institute in Boston, USA and Sahlgrenska University Hospital in paper I and solely with Sahlgrenska University Hospital in paper II. Paper IV is a multicenter study, with seven international referral centers included. The retrospective patient data were prospectively collected at each participating center.

Study design and comparison of groups
Due to the rareness of pan-NET, prospective RCTs are desirable, but hard to perform. In default of this, retrospective studies are important, not the least to be able to use the results to optimize the design of a future prospective RCT.

A few things need to be considered when comparing outcomes in non-randomized study groups. First of all, the time period needs to be defined. With a rare disease, like pan-NET, the time period needs to be increased to be able to include enough patients to have sufficient power in the statistical analyses. This itself has its boundaries considering the changes in treatments and advances over time in different fields, for example in the radiologic and oncologic field. To be able to evade these problems, multicenter studies can be helpful. This is the reason for the collaborations in paper I-II and IV. Besides this, there are other advantages with multicenter studies, such as an increase of the generalizability of the results, improved networking for future collaborations and sharing of resources.

Further, to be able to compare the outcome of a group subjected to an intervention, with a control group, a time zero needs to be defined. If this is not accomplished, you risk incorporate immortal time bias in the intervention group and the outcome will favor the intervention group and the result will be skewed and unreliable\cite{129,130}. Time zero is defined in study I-III.

To assess the effect of a treatment, comparable groups are needed. Below mentioned baseline characteristics are presented in paper I-III. When there are differences between the groups, there are statistical methods that can
reduce these differences, for example with matching and multivariable analyses discussed later on.

Baseline data
Patient records were scrutinized for patient characteristics such as age, sex, time period, hormonal expression, genetics, albumin and chromogranin A in serum and comorbidity. There are a few possible ways to assess comorbidity and in study I-III Charlson comorbidity Index (CCI) was used due to its validated prognostic indicator for mortality.\textsuperscript{131,132} Data of tumor characteristics were also collected regarding size of primary tumor, WHO grade (according to pathology reports), number of liver metastases and occurrence of extra-abdominal metastases. Both the surgical and the oncological treatments were noted and time zero was defined accordingly. The patients were followed until death, if possible, otherwise until their last clinical appointment.

Outcome and survival analyses
In our studies, including patients with liver metastasized pan-NET, overall survival (OS) was used. Generally, overall survival rates are often used in patients with short life expectancy, whereas disease-specific survival (DSS) or cause-specific/cancer-specific survival (CSS) more often are used in studies where patients have longer life expectancy with risk of dying due to multiple other diseases. For pan-NET, the life expectancy is quite long, even in a metastatic setting, and one could therefore argue that DSS should be preferred. However, to use DSS, the cause of death needs to be determined, and regardless cause, it is hard to be sure that the cause of death is not related to the metastatic disease. We could assume that all patients died from causes related to their stage IV pan-NET and call it DSS, however, to avoid subjectivity, we chose OS as outcome for survival. In our interpretation of our analyses, however, we assumed that the patients died of a cause related to their metastatic disease.

Another outcome presented in paper I and II is progression-free survival (PFS) which refers to how many patients that were alive and without tumor progression. Another way could be to present time to progression (TTP) which only refers to the time from time zero to progression, and do not relate to if the patients are alive or not. DFS is used in paper II, which can be used in a setting where curative intent is aided.

Progression can be defined in different ways. In paper I, progression was defined as clinical progression, determined by changes in oncological or surgical treatments. A limitation of this definition is that patients with toxic reactions to the oncologic treatment may have been interpreted as progression. In paper II, we used the radiology reports to determine progression according to the RECIST 1.1 criteria. According to these criteria, complete
response is defined as non-detectable disease, partial response is defined as 30% decrease of sum of longest diameters (SLD), no new lesions, and stable disease as neither progression or response. Progressive disease is defined as 20% increase of SLD, but minimum increase of 5mm, or new lesions.\textsuperscript{133,134} In an ideal world, the combination of clinical and radiology progression would be optimal and probably even more accurate.

Definition of a local recurrence or metastatic lesion, was either a lesion histologically confirmed with fine needle aspiration or biopsy or by radiology.

Complications from given treatment were categorized according to Clavien Dindo classification.\textsuperscript{135}

In paper III, patients were retrospectively assessed according to different criteria for LT. For patients that met criteria for LT according to Milan criteria, ENETs guidelines and UNOS guidelines, time zero was defined as the date when the patient was eligible for LT and survival was calculated from this time. For patients that did not meet the criteria for LT, time zero was set when the following criteria were met; first appointment at Uppsala University Hospital, primary tumor resected and LM present. Patients were sorted into following groups; all patients meeting the inclusion criteria, patients meeting the Milan criteria, patients meeting the criteria according to the UNOS guidelines, and the ENETs guidelines. One patient could therefore be included in more than one of the groups.

**Statistical analysis**

**General statistics**

For descriptive data at baseline and follow-up, median with interquartile range (IQR) or mean with standardized difference (SD) were used. Differences in proportions of groups were analyzed with Chi2-test and Fisher’s Exact test as appropriate.

Survival rates and cumulative incidence were computed with Kaplan–Meier analysis with corresponding 95% confidence interval (CI) and log-rank test to compare survival between the groups. Kaplan–Meier analyses were truncated when a third of the cohort remained at risk. Both univariate and multivariable analysis were performed by Cox proportional hazard regression and presented as hazard ratio (HR) with corresponding 95% CI.

A p-value of <0.05 was considered statistically significant in all statistic test. All analyses were performed in SPSS (IBM, Armonk, New York, USA).
Propensity score and multivariable analyses

In paper I, comparable groups were achieved by a propensity score matched analysis. A logistic regression, based on baseline characteristics, was used as a balancing score to match the two groups by a ratio of 1:1. \(^{136,137}\) With this method, it is possible to assess the balance between the groups after matching, using standardized mean difference (SMD). A caliper width of maximum 0.1 was chosen and an SMD <10% was considered to equal an insignificant difference between groups. \(^{138,139}\) A propensity-score matched analysis has its advantages where comparable groups are created regarding the variables in the logistic regression analysis, and it is also illustrative for the reader and intuitive to understand the comparison of the matched groups, which almost mimics the study design of an RCT. However, the study cohort decreases in size, and it is possible that patients that would be crucial for the results, are in fact excluded from the analysis. There is also a risk that an important confounder is not adjusted for, or that an important variable is one that cannot be observed. If an important variable is missing, the analyses can be suboptimal but there is also a risk of overcorrecting, to include an irrelevant variable.

In paper II, a multivariable cox proportional hazard regression analysis was performed to assess the variables or interventions associated with risk for death. First, univariate regression analysis of the variables chosen, based on perceived clinical importance and/or previous studies, was performed. For the adjusted cox regression analysis, only variables with \(P<0.100\) for the hazard ratio (HR) on crude analysis were included.

Additional statistics for paper IV

The scoring system for prediction of recurrent disease in grade 1 and 2 NF-pan-NET by Genc et al. was used. \(^48\) Three groups of risk for recurrence were constituted based on the scores, the low-risk group that included patients with 0-24 points, medium-risk group with 40-48 points and the high-risk group with 64-88 points. Predicted probabilities for 5-year RFS were calculated based on the survival function from the Cox regression model in the original study; \((b = 0.853 \exp(LP))\) and coefficients (intercept \(−0.809\); tumor grade \(−1.403\); positive lymph nodes \(−0.892\); perineural invasion \(−0.867\)). Predicted risk was calculated as 1-RFS.

To assess the accuracy of the model, discrimination and calibration was used. Discrimination evaluates if the model can accurately predict if an event will happen to a patient or not. The statistical test is Harrel’s C-statistics which is presented with a 95% CI. Thereto, a receiver operating characteristics (ROC) curve for the prediction of 5-year RFS specifically was constructed, and the area under the curve (AUC) was calculated. Calibration, or goodness of fit, estimates the accuracy of which the model estimates the
absolute risk of an event happening. A model with poor calibration will ei-
ther underestimate or overestimate an outcome. The predicted 5-year risk of
recurrence with observed risk for all groups were plotted in a calibration
plot. These calculations were also performed in the subgroup of patients with
tumor size >2 cm.

Power calculations
Power calculations were performed in study I-II. The power of 80% and an
alpha of 0.05 were chosen to detect a hazard ratio of 0.5 in study I and 0.4 in
study II.

Ethical Considerations
All four studies were approved by the former Swedish Ethical Review Board
no 2012/160 and no 1007/17 for Paper I-II, and by The Swedish Ethics Re-
view Authority no 2020-05645 for Paper I-III.
Results

Paper I

A total of 733 patients with stage IV disease were assessed for eligibility, 335 patients from Uppsala University Hospital, 63 patients from Sahlgrenska University Hospital and 335 patients from Brigham and Women’s Hospital/Dana-Farber Cancer Institute. After exclusion, 194 patients remained. (Fig 1) Median follow-up time was 3.9 years and 115 patients died.

Figure 1. Flow-chart of the enrolled patients

Analyses of survival and PFS was calculated before and after propensity-score matching. The unmatched surgery group (unmatched SG) had younger patients and less intrahepatic and extrahepatic spread than the unmatched non-SG. Median and 5-year survival for the unmatched SG patients was higher, 7.8 years (IQR 4.1–10.6) and 67.0% (95% CI, 79.0), respectively, compared with 5.0 years (IQR 2.8–8.4) and 51.6% (95% CI, 42.2-61.0) in the unmatched non-SG, (log-rank, p = 0.018). The median PFS in the unmatched SG was 1.4 years (IQR 0.6–3.4) compared to 1.6 years (IQR 0.6–2.9) in unmatched non-SG, (log-rank, p = 0.218). (Fig 2)
Figure 2. Kaplan-Meier curves of OS before and after Propensity Score Matching
Complication rates with Clavien Dindo of 2 or higher in the unmatched SG were 29.2%. Of these, 21.5% suffered a complication classified as Clavien Dindo ≥3.

A 1:1 propensity score match resulted in 50 patients in each group. Differences in baseline characteristics were minimal after matching. OS was calculated and in the matched SG median and 5-year survival was 7.4 years (IQR 4.1–10.5) and 65.4% (95% CI, 51.5-79.3), respectively, compared with 4.6 years (IQR 3.5–6.5), (log-rank p = 0.043), and 47.8% (95% CI, 30.6-65.0) in the matched non-SG (logrank, p = 0.043). The median 3-year PFS in the matched SG was 27.7% (95% CI, 15.5-40.2) versus 24.8% (95% CI, 11.5-38.1) in the matched non-SG (log-rank, p = 0.458).

Systemic treatments, surgical and ablative treatments were given in both groups. There was no difference in the number of lines of systemic therapy and types of systemic therapy received between the groups, but more liver resection and thermal ablative treatment was performed in the matched SG.

Paper II

Of the 714 patients treated for pan-NET during the time period, 108 patients met the criteria for inclusion and constituted the liver surgery/THA group (n=57) and the control group (n=51).

Figure 3. Flow-chart of the enrolled patients

There were no significant differences in the baseline characteristics between the groups. Five-year overall survival in the liver surgery/THA group was
70.6 % (95% CI 0.57-0.84) and in the control group 42.4 % (95% CI 40.7-59.1). Median overall survival for surgery/THA was 9.1 years (95% CI 6.5-11.7) years versus 4.3 years (95% CI 3.4-5.2) in the control group, (log rank P 0.016). (Figure 4)

![Figure 4. Kaplan-Meier curves of OS the liver surgery/THA group and the control group](image)

Using univariable Cox regression analyses with overall survival as dependent variable, four variables had p<0.100: WHO grade, age, time period and liver surgery/THA. In adjusted analysis including all these four variables, only liver surgery/THA, was associated with a decreased hazard ratio (0.403, 95% CI 0.208-0.782, p=0.007) whereas age greater than 70 years and increasing WHO grade were associated with an increased hazard ratio.

Fourteen patients (24.6 per cent) suffered from complications after liver surgery/THA whereof nine patients had a grade III complication and one patient a grade V complication. Two patients died within 90 days in the liver surgery/THA group versus three patients in the control group.

Liver metastases were evaluated according to RECIST criteria 1.1 at 2 and 5 years. Response in the liver surgery/THA group was found in 38.2% of the patients at 2 years and in 20.5% at 5 years, and in the control group, 22.0% at 2 years and 10.0% at 5 years. PFS at 2 and 5 years, in the liver surgery/THA group, was 54.5% and 27.3% respectively, and 42.0% and 22.5% respectively in the control group, (p=0.361).
Paper III

In total, 519 patients with pan-NET at Uppsala University Hospital from 2000 to 2021 were screened for inclusion. After excluding patients with no liver metastases (n=176), primary tumor not resected (n=228), non-Swedish personal number, NET/NEC G3 tumors (n=11), patients with age >75 years (n=2) and extra abdominal disease (n=4), 41 patients remained. (Fig 5)

Figure 5. Flow-chart of the enrolled patients

Four groups were constituted; All patients that met the inclusion criteria in our study (n=41), patients meeting the Milan criteria for LT met (n=11), the criteria for LT according to ENETS guidelines met (n=8) and the criteria for LT according to UNOS guidelines met (n=13).

OS for all patients was 9.3 years (95% CI 6.8-11.7) and five-years survival was 64.7% (95% CI 48.2-81.2). Patients meeting the Milan criteria for LT had a five-year survival of 64.9% (95% CI 32.2-97.6), for the ENETS guidelines 85.7% (95% CI 59.8-100.0) and for the UNOS guidelines 55.4% (95% CI 26.0-84.8). (Fig 6)
Figure 6. Kaplan-Meier curves for OS in the groups of patients meeting the different criteria for LT

Paper IV

A total of 374 patients were included, and after exclusion of 32 patients due to missing data, 342 patients remained. In this cohort, more patients had grade 2 tumors compared to the derivation cohort (43.6% vs 34.1%). Median follow-up time was 50.5 months (IQR 22.3-103.0) and 58 patients had a recurrence during this period of time. The majority of patients developed liver metastases only (n=45), and 13 patients developed recurrence in multiple sites.

The 5-year RFS was 83.0% (95% CI 78.0–88.0%), resulting in a 5-year risk of recurrence of 17.0%. Patients in the low- and high-risk groups, developed fewer recurrence than predicted. The predicted 5-year risk of recurrence in the low-risk group was 8.1%, in the medium-risk 26.1% and in the high-risk group 65.3%. (Fig 7) Agreement between predicted and observed 5-year risk of recurrence with an intercept of 0 and a calibration slope of 0.74 is shown in Figure 8. The AUC for prediction of 5-year recurrence was 0.74 and the Harrel’s C-statistic was 0.77 (95% CI: 0.71–0.83), as compared to 0.81 (95% CI: 0.75–0.87) in the derivation cohort. The risk groups had a corresponding 5-year RFS of 95.8% (95% CI: 92.8–99.2), 76.1% (95% CI: 65.0–89.1) and 53.4% (95% CI: 40.9–69.8) for low, medium, and high-risk patients, respectively.
In the cohort of 163 patients with tumors >2 cm, 5-year RFS was 74.2% (95% CI: 66.8-80.8). The nomogram predicted lower 5-year risk in all three risk groups. Agreement between predicted and observed 5-year risk of recurrence with an intercept of 0.05 and a calibration slope of 0.7 is shown in Figure 8. The AUC for prediction of 5-year recurrence was 0.7 and the Harrel's C-statistic was 0.79 (95% CI: 0.7–0.9). For a NF-Pan-NET >2 cm, the risk groups had a 5-year RFS of 89.8% (95% CI: 81.5–98.9), 74.4% (95% CI: 60.0–92.2), and 50.6% (95% CI: 36.1–70.7) for low-, medium-, and high-risk patients, respectively.

Figure 7. Kaplan-Meier curves of 5-year RFS in total cohort (a) and tumors > 2cm (b)

Figure 8. Calibration plot of predicted versus observed 5-year RFS in resected 1-2 NF-Pan-NET for the low-, medium- and high-risk patients in the total cohort (a) and tumors > 2cm (b)
Discussion

This thesis focuses on surgical treatment of pan-NET stage IV. Although this rare disease has been studied for decades, to this date, no RCTs have been performed evaluating surgical treatment. Published retrospective studies are challenged by selection bias, small study cohorts and prolonged study periods, due to the rareness of the disease. Modern imaging technique, patient care, surgical technical and oncological has advanced over time, and data from historical controls may thus be unreliable. The treatment intent and treatment strategies for these patients is ambiguous and the evidence base for recommending surgical treatment is debatable. The included studies in this thesis, control for some of the bias and possible confounders in earlier publications, and the aim was to broaden the evidence base for the treatments offered to these patients.

Primary tumor resection

Based on the available data, different options are possible for a patient with stage IV pan-NET. When the primary tumor is resectable, there is usually an indication for primary tumor resection of functioning tumors due to symptoms caused by the overproduction of hormones. The liver metastases can then, be treated either with liver resection, ablative methods or oncological treatment, depending on the tumor load and distribution of the metastases.\textsuperscript{22,23,103}

In stage IV NF-pan-NET, the management of the primary tumor, regarding survival benefit, is not as clear. Review articles and meta-analyses based on data from previous studies, suggest that primary tumor resection is associated with prolonged survival and should therefore be considered in all patients without contraindications for surgery.\textsuperscript{57-64} Unfortunately, these studies are all retrospective, limited by immortal time bias, selection bias and lacking prognostic data, most importantly of comorbidity, which makes it difficult to draw firm conclusions. In Table 4 (see page 21), studies on primary tumor resection in stage IV patients, are listed.\textsuperscript{69-79} The 5-year survival rates vary between 40\% and 73\% in the resected group and between 16\% and 42\% in the non-resected group. The survival was thus quite heterogenous both between and within the two groups. Several studies in larger cohorts, were based on the SEER database, which has three major weaknesses. First,
the database lacks data on comorbidity. Information on patient comorbidity is crucial when assessing if a patient is a suitable candidate for surgery or not, and lack of this information in a retrospective cohort study allows an undetected selection of healthier patients for primary tumor surgery. Secondly, the study periods of the SEER-database studies overlap and therefore the same patients are included in several studies.\textsuperscript{77-79} Third, the lack of information regarding resectability, includes patients with unresectable primary tumors in the control group, selecting a group of patients with more advanced disease in the control group.

Of the studies presented in Table 5, only two reports data on comorbidity. The study by Chawla et al., includes 4038 patients from the NCDB database, whereof 351 patients were treated with primary tumor resection.\textsuperscript{75} In a multivariable regression model, primary tumor resection was associated with prolonged survival. Unfortunately, the follow-up in the non-resected group was tangibly shorter, only 14 months compared to 51 months in the primary tumor resection group, making it hard to interpret the differences between the groups. The largest, non-database study, is the two-center study by Bertani et al., including 93 patients with resectable tumors from 1994-2013.\textsuperscript{72} Comorbidity was assessed by the ASA classification, which might be considered a blunter tool for assessment, in comparison to CCI. Even so, a Cox regression analysis of 14 different cofactors showed an association of prolonged survival for patients undergoing primary tumor resection, and an association of poorer survival for increasing grade, Ki67 and increased liver tumor burden.

In our propensity score matched study, based on data from patients from three large NET centers in Sweden and in the US, all patients with irresectable tumors and those inoperable for other reasons, were excluded, and thereto, comorbidity was matched for in the propensity score matched analysis.\textsuperscript{140} We found that primary tumor resection was associated with improved OS, both before and after propensity score matching. Baseline variables that pre-match had a large disparity, were minimalized after matching and the few variables with suboptimal matching conferred to more liver metastases and more severe comorbidity in the group subjected to primary tumor resection, making the results even stronger. Our study contributes to the general knowledge about primary tumor surgery in stage IV patients by showing that comorbidity does not seem to be the primary explanation to why the patients going through primary tumor resection had higher survival rates. The patients in the matched group subjected to primary tumor resection underwent surgical and ablative treatment of liver metastases to a greater extent, but since survival was longer in this group, these patients were also able to be treated during a longer period of time. Regardless, both solely and in combination with surgical/ablative treatment of the liver metastases, primary tumor resection was associated with prolonged survival in these patients.
All pancreatic surgery is of course considered major surgery; however, a proximal resection is associated with higher complication and morbidity rates and patients with tumors of the pancreatic head should probably have a stronger indication for surgery than those with a body or tail-tumor. Most studies regarding stage IV pan-NET do not analyze these two groups separately although at least one cohort included only body and tail tumors for just this reason.\(^{72}\)

The indications for the primary tumor surgery may differ among GEP-NET. In a similar study as ours, of SI-NET, primary tumor resection in stage IV patients did not prolong survival.\(^{141}\) In SI-NET patients there are often indication for surgical treatment of the primary tumor and lymph node metastases due to an obstructive or ischemic situation. In pan-NET patients it is quite unusual that the primary tumor causes local problems. However, pan-NET is a more aggressive disease, and the patients are thus more likely to die from the disease rather than with the disease. Moreover, in contrast to the chemotherapy resistant SI-NET tumors, some pan-NETs do respond to systemic treatment with chemotherapy, which in turn may lead to a more beneficial post-resective situation, supporting more aggressive surgical management.

Limitations of this study include a modest cohort size, a long study period, and possible inherent bias of a retrospective design. Moreover, the chosen method with propensity score matching is not without flaws. The matching does not control for selection bias and there is always a risk of important unobserved variables, not included in the matching, that may affect the result. Also, some of the unmatched patients could be important for the outcome but are, due to the matching, excluded from the analysis. Further, unknown differences between the centers could affect the baseline variables, for example differences regarding the choice of radiological methods and varying available data between centers.

An RCT would be needed to further verify these findings. However, because of the obvious difficulties due to the low incidence of the disease and the relatively long survival of patients with pan-NET, an RCT would be challenging to carry through.

Treatment of liver metastases

Many patients either present with, or develop liver metastases during the course of their disease. For these patients, many treatments are available, although, the only potential cure is surgical resection or ablative methods.\(^{17,80,120}\) Several retrospective studies have been conducted, however, cohorts of mixed NETs lacking sub-analyses of primary tumor origin, makes the results difficult to interpret. The studies listed in Table 5 represent the few studies that report sub analyses for pan-NET, and as seen, all studies but three, include less than 50 patients.\(^{87,98-100}\) The largest, four-center study by
Partelli et al. included 166 patients whereof 91 patients underwent resection of liver metastases. Survival rates were significantly higher in the resection group, and resection remained significant as a prognostic factor of better survival in the multivariable analysis. However, this study does not present any data on comorbidity, potentially allowing for selection of healthier patients for liver surgery. Another study by Woltering et al., included 89 patients whereof 50 patients underwent liver resection. However, this study does not present survival for the non-resected group, and no comparing or adjusted analyses are presented. Therefore, this study does not facilitate selection of patients for hepatic surgery.

In our study, we compared the outcome in patients subjected to liver resection and/or THA with those subjected to other medical treatment. We selected patients who all had undergone resection of the primary tumor. Patients who underwent liver surgery and/or THA lived longer, with a 5-year survival of 70.6%, versus 42.4% in the control group. In the performed multivariable analysis, liver surgery/THA remained a significant positive prognostic factor for survival.

The results from our study, in combination with the results from our previous study that shows an association between primary tumor resection and survival benefits in stage IV patients, further strengthen the belief that these patients, if possible, preferably should be managed more surgically aggressively. However, it is important to remember that our studies include highly selected patients, the sample sizes are small and the study period is long. These are all effects of the rareness of the disease and limits interpretation of the results. The advances in radiology and changes in other available treatments also may affect the results. To reduce these biases, the multivariable analysis subdivided the patients into different time periods. However, important confounders may have been overlooked.

As discussed above, the benefit of different treatments seems to vary between different GEP-NETs. A similar study of treatment of liver metastases with resection or RFA, in SI-NET patients, showed contradictory results compared to our study on pan-NET patients. Another difference between pan-NET and SI-NET in a metastatic setting, is the presence of micrometastases, that has been shown, are present to a larger extent in SI-NETs, 67% compared to 32% in pan-NETs. This, in combination with the different chemotherapies available for pan-NET, which may eradicate residual microscopic disease, could explain part of the difference.

So how do we identify patients who would benefit from resection or THA? It is known that micro metastases are common, and that they are more frequent in patients with many LM. Perhaps there is a cutoff in the number of LM separating patients who would benefit from resection and ablative methods, from those who would not, and instead be more suitable for PRRT or systemic treatment. There are many questions to be discussed regarding
this group of patients, and an individual assessment is crucial to select the optimal treatment for the patient.

An RCT would of course be desirable in order to further investigate the benefit of liver surgery and/or THA, however, as discussed above, it would be challenging to carry through. Results from this study could, however, be valuable in designing such a trial. The endpoint for a future RCT may be radiologic regression of tumor load after surgery, biochemical response or reduced need for oncologic treatment. However, the most important endpoints for the patients are most likely; improved quality of life, symptom relief and increased survival, all of which are difficult to study in such a rare disease.

An important question is whether we need to draw a line between patients who can be potentially cured, and those with a palliative situation. We know that recurrence after liver surgery and THA, is common in the long-term perspective. In our cohort, all patients who were followed more than five years developed a recurrence, even though the patients at some point seemed to be tumor-free. Perhaps treatment in most of these patients should be considered as palliative, with prolonged survival and reduced symptoms, rather than cure, as the primary goal. With the advances in both oncological treatment and contemporary technical surgical advances, the patients will possibly live longer regardless of the choice of treatment, with curative or palliative intent. This makes it even harder to draw conclusions of which approach is the best, without having any RCT to rely on. Another important question for the surgeons will probably be how to weigh what is surgically technically possible and what is oncologically sound to do.

Liver transplantation
Liver transplantation in an attempt to prolong survival for patients with pan-NET is controversial. Several studies reporting long-term survival after LT, include NETs of mixed origin, and often without specifying the survival rates according to primary tumor origin. The study with the highest survival rates of 97.2%, by Mazzaferro et al., does not present any sub-analyses of survival for pan-NET, and does not report the of follow-up time for these patients. A major study design flaw also needs to be addressed; calculation of survival is measured from time of diagnosis, not from time of LT, adding an immortal time bias of median 18.5 months, overestimating the survival in the patients subjected to LT. Moreover, patients with disease progression, originally planned for LT, ends up in the non-transplant group, resulting in a super selected group of patients without progression for a median of 18.5 months before LT. The few studies specifying survival rates for pan-NET alone, have other obvious limitations, such as selection bias of younger patients with lower TNM-stage and tumor grade.
In our study we retrospectively assessed the survival of patients eligible for LT, but instead receiving only multimodal treatment. One noticeable finding was that an extremely low fraction of the originally included patients were eligible for LT. Only 3.1% of the included patients met the criteria for LT, which of course is a highly selected group of patients. Thereto, the survival rates of these selected patients were comparable to, or even higher than most reported survival rates after LT. This makes the clinical implication of LT for pan-NET patients questionable. Perhaps these results show that a highly selected group of patients like this, will experience a good prognosis regardless of the surgical intervention or medical treatments they receive.

LT has its drawbacks for the patients. Not only are they subjected to substantially extensive surgery, with its per- and postoperative risks, but also to lifelong treatment with immunosuppressives with of rejection, infections and development of malignancies. Also, health related quality of life (HRQoL) has not been evaluated, which is important in the patient perspective.

As previously discussed, this study is limited by its small cohort. There is also a challenge, in the retrospective setting, assessing patients eligible for surgery. The guidelines used to select the patients eligible for LT, are narrow and may have influenced the selection in a way that patients who would have benefitted from LT were sorted out from the analysis. To further gain knowledge of the benefit of LT in pan-NET patients, a large international multi-center study over a long time-period would be necessary. However, the burden of proof regarding the benefit of LT should lay on the surgeons performing the surgery. This study present baseline survival rates for patients receiving multimodal treatment in stage IV patients eligible for LT. Should LT be recommended, proof of beneficial survival rates need to be presented.

**Prediction model for recurrence**

Due to the increased incidence of pan-NET, and the fact that many patients develop liver metastases, a prediction model for recurrence in patients with non-metastatic tumors after resection, would be valuable to guide in both treatment strategies and the follow-up regimen. The model, previously developed by Genc et al., was updated and externally validated.

Our multicenter study assessed external validity of the previously published prediction model for 5-year risk of recurrence after surgical curative resection in sporadic grade 1-2 NF-pan-NETs. The risk factors included in the study was tumor grade, presence of lymph node metastases and perineural invasion in the pathology report. Since there are no unanimous guidelines on how to follow these patients and since the management of patients with pan-NET vary among different centers and countries, risk stratification is vital in these rare tumors. A prediction model for recurrence could help cli-
nicians to differentiate between patients who would potentially benefit from more intense follow-up, from those who might not need as close surveillance. This is important for a couple of reasons. First, to follow patients more often than needed is both a waste of medical resources and could cause the patient unnecessary radiation. Second, the worry this can cause the patients and the patients’ family is not negligible. Secondly, the prediction model may identify patients with high-risk of recurrence, who would benefit from adjuvant therapy.

This model performed well in the external validation cohort, with a C-statistic of 0.77 and an AUC of 0.74. It is easy to use which will facilitate the implementation in a clinical setting. One of the previously presented prediction models with a C-statistics of 0.74 included all GEP-NETs which makes this model less applicable to use for pan-NET, as the various NET types have different prognoses. The model with the highest C-statistics, of 0.84, uses a Ki67 range which probably is a more powerful predictor, but argued that it is not available in all centers. The third prediction model available is not externally validated and uses an RRS, and no c-statistics was calculated or ROC curve performed.

The prediction model was successfully externally validated, however, there are some limitations in our study. All patients with missing data were excluded from the study and selection bias is always incorporated in a retrospective design. Furthermore, differences between the validating centers regarding histological examination, preoperative investigation and surgical approaches could influence both the selection of patients and the strength of the prediction model. It is however a strength that the study comprises a multi-institutional and an international collaboration of high-volume hepatopancreatobiliary and NET expert centers.

The next step before developing and implementing this prediction model further, is a validation of all the available prediction models in a large multi-institutional study. A prospective and international validation with an adjuvant treatment protocol for patients with a predicted high recurrence risk would be desirable.
Conclusions

I. Resection of the primary tumor in patients with stage IV pan-NET with low- to intermediate-grade disease was associated with prolonged overall survival compared to nonoperative management and a surgically aggressive regime should be considered when resection is not contraindicated.

II. Liver surgery and/or thermal hepatic ablation of pan-NET liver metastases was associated with longer overall survival and acceptable mortality and morbidity rates and should thus be considered in pan-NET patients with reasonable tumor burden with the intent to improve survival.

III. In patients with stage IV pan-NET, grade 1 and 2, with no extra abdominal disease, the 5-year survival rates exceed previously published survival rates in after LT for pan-NET, hence, the evidence base for this treatment is virtually non-existent.

IV. External validity of the prediction model for recurrence after curative surgery for grade 1–2, NF-pan-NET, showed accurate overall performance using three easily accessible parameters.
Future perspectives

The future perspective, from my point of view, is how to better study this rare disease. In order to assess the impact of surgery, two major limitations must be overcome. First, confounding by indication, which always is a factor in a retrospective setting. Therefore, an RCT would be the best way forward to assess the impact of surgery, both of the primary tumor and the liver metastases, in pan-NET patients. Secondly, the rareness of the disease makes such a trial very hard to perform. However, recent national development such as national centralization of surgery for pan-NETs is underway. This gives a future opportunity to implement such studies nationally and abroad.

Regarding prediction models, a systemic review comparing all existing prediction models for recurrence after curative resection of grade 1 and 2 pan-NET is ongoing. The models will be tested in a large multicenter database to evaluate which model has the highest C-statistics and which model may be the most applicable in daily setting. The data will also be used to study the effects of spleen resection versus spleen-reserving distal pancreatectomy.
Sammanfattning på svenska


Eftersom majoriteten av tumörerna inte är hormonproducerande, så kallade ickefunktionella, upptäcks många tumörer redan i ett metastaserat stadium, stadium IV. Den onkologiska vinsten med att operera bort primärtumören hos dessa patienter är inte klarlagt. Syftet med studie I var att jämföra överlevnaden hos stadium IV-patienter som genomgått primärtumörskirurgi med de som endast fått onkologisk behandning och samtidigt kontrollera för variabiliteten i tumörbörda och komorbidityt. Studien var en multicenterstudie där patienter mellan åren 1985 och 2019, från Akademiska Sjukhuset i Uppsala, Sahlgrenska Sjukhuset i Göteborg och Brigham and Women’s Hospital/Dana-Farber Cancer Institute i Boston, USA screenades för inklusion. I den slutliga analysen inkluderades 194 patienter med sporadisk sjukdom, WHO-grad 1–2 tumör mellan år 2000 och 2019. Som förväntat var det relativt stora skillnader mellan grupperna, med yngre patienter med mindre tumörbörda i gruppen som genomgått primärtumörskirurgi. Överlevnaden var också klart högre i denna grupp, med medianöverlevnad på 7,8 år (IQR 4,1–10,6) jämfört med 5,0 år (IQR 2,8–8,4) och 5-årsöverlevnad på 67,0% (95% CI, 55,0–79,0) jämfört med 51,6% (95% CI, 42,2–61,0) (log-rank, $P = 0,018$). För att skapa jämförbara grupper och kontrollera för bland annat tumörbörda och komorbiditet, utfördes en 1:1 Propensity-scorematchning som resulterade i 50 patienter i varje grupp. Skillnaden mellan grupperna var minimala efter matchning och när överlevnaden beräknades på nytt, bestod skillnaden i överlevnad mellan grupperna med medianöverlevnad i primärtumörskirurgigruppen på 7,4 år (IQR 4,1–10,5) jämfört med 4,6 år (IQR 3,5–6,5) i kontrollgruppen och 5-årsöverlevnad på 1:1 Propensity-scorematchning som resulterade i 50 patienter i varje grupp. Skillnaden mellan grupperna var minimala efter matchning och när överlevnaden beräknades på nytt, bestod skillnaden i överlevnad mellan grupperna med medianöverlevnad i primärtumörskirurgigruppen på 7,4 år (IQR 4,1–10,5) jämfört med 4,6 år (IQR 3,5–6,5) i kontrollgruppen och 5-årsöverlevnad på
65,4% (95% CI, 51,5–79,3) jämfört med 47,8% (95% CI, 30,6–65,0) (log-rank, \( P = 0,043 \)). Konklusionen av denna studie är att primärtumörsuirurgi hos patienter med sporadisk metastaserad pan-NET, WHO-grad 1–2, är associerad med förlängd överlevnad och att man bör överväga detta hos patienter som inte har kontraindikation för resektion.


Syftet med studie II var att utvärdera effekten av leverkirurgi och värmeablation och jämföra utfallet med en kontrollgrupp som inte erhållit denna behandling, och samtidigt kontrollera för möjliga confounders. Av de 714 patienter behandlade under diagnosen pan-NET mellan 1985 och 2018, på Akademiska Sjukhuset i Uppsala och Sahlgrenska Sjukhuset i Göteborg, kunde 108 patienter som hade levermetastaser och genomgått primärtumöroperation, mellan 1995 och december 2017, analyseras. Femårsöverlevnaden i leverkirurgi/THA-gruppen var 70,6% (95%CI 57–84) och i kontrollgruppen 42,4% (95%CI 40,7–59,1) (log-rank \( P = 0,016 \)). Medianöverlevnaden för leverkirurgi/THA-gruppen var 9,1 (95%CI 6,5–11,7) år jämfört med 4,3 (95%CI 3,4–5,2) år i kontrollgruppen. En univariabel Cox regressionsanalys, med överlevnad som beroende faktor, visade fyra variabler med \( p <0,1 \); WHO-grad, ålder, tidsperiod och leverkirurgi/THA. I en multivariabel analys med dessa variabler var leverkirurgi/THA associerat med minskad hazard ratio på 0,403 (95%CI 0,208–0,782) \( (p = 0,007) \). Konklusionen av denna studie är att leverkirurgi/THA är associerad med förlängd överlevnad med acceptabla risker för komplikationer och bör erbjudas till patienter med rimlig tumörbörda.

Den enda potentiellt botande behandlingen av pan-NET är kirurgi, oavsett tumörstadium eller WHO-grad. Även om levermetastaser kan behandlas med leverkirurgi, åstadkommer man sällan bot, trots man lyckas recessera de
metastaser man kunnat identifiera preoperativt. Detta beror sannolikt på kvarvarande mikrometastaser som man kunnat visa finns hos 32% av patienter med levermetastaser från pan-NET. Hos patienter med komplett resektion av extrahepatisk sjukdom har levertransplantation (LT) diskuterats med avsikt att förlänga överlevnaden. Det finns inga globalt accepterade kriterier för LT. De mest använda är Milan kriterierna, kriterierna enligt European Neuroendocrine Tumor Society (ENETS) guidelines och kriterierna enligt the United Network for Organ Sharing (UNOS) guidelines. Alla kriterierna innebär radikal kirurgi av primärtumören, stabil sjukdom >6 månader, tumörgrad enligt WHO 1–2 och inga extraabdominella metastaser. Små skillnader avseende ålder, tilläggskriterier avseende lymfkörtelmetastaser och Ki67% finns dock.

Syftet med studie III var att utvärdera överlevnaden hos patienter med pan-NET stadium IV, som uppfyller de vanligaste kriterierna för LT men som endast behandlades med multimodal behandling. Alla patienter diagnosticerade och behandlade på Akademiska Sjukhuset i Uppsala mellan 2000 och 2021 screenades för inklusion (n=519). Patienter utan levermetastaser, som inte genomgått primärtumörsirurgi, ålder >75, grad 3 tumörer samt patienter med extraabdominella metastaser exkluderades och då återstod endast 41 patienter. Dessa bedömdes sedan enligt de olika transplantationskriterierna. Medianöverlevnaden för alla 41 patienter i analysen var 9,3 år och 5-årsöverlevnaden var 64,7%. Subanalyserna för de grupper som representerar vilka kriterier som patienterna uppfyllde visade en 5-årsöverlevnad för Milankriteriegruppen på 64,9%, ENETS-gruppen på 85,7% och UNOS-gruppen på 55,4%.

De flesta studier som presenterar överlevnadssiffror efter levertransplantation inkluderar NET av olika ursprung och i dessa varierar 5-årsöverlevnaden mellan 47,0 och 97,2%. I de subanalyser av patienter med pan-NET i de studier som presenterar det, är 5-årsöverlevnaden mellan 27 och 53%. Även om kohorterna i litteraturen och den i vår studie inte är helt jämförbara, överstiger inte överlevnadssiffrorna efter levertransplantation, de i vår studie, där patienterna endast behandlats med multimodal behandling. Därför koncluderar vi att det inte finns tillräckliga evidens för att erbjuda patienter denna behandling.

för prediktion av återfall skapades och i denna räcker det med att ha en av ovan nämnda riskfaktorer för att bedömas som en högriskpatient för återfall.

Studie IV är en extern validering av detta nomogram som predikterar återfall. Totalt inkluderas 374 patienter från sju centra i Europa, USA och Australien, och efter exklusion, återstod 342 patienter. Medianuppföljningen var 50,5 månader (IQR 22,3–103,0) och 58 patienter fick recidiv under denna period. Majoriteten utvecklade endast levermetastaser (n=45), och 13 patienter utvecklade recidiv på multipla lokaliseringer. Recurrence free survival (RFS), beräknades och visade en 5-års RFS på 83,0% (95% CI 78,0–88,0%), resulterande i en 5-årsrisk för recidiv på 17%. Patienter i låg- och högriskgruppen utvecklade färre recidiv än förväntat där den predikterade 5-årsrisken för recidiv i lågriskgruppen var 8,1%, i mediumriskgruppen 26,1% och i högriskgruppen 65,3%. Sambandet mellan predikterad och observerad 5-årsrisk för recidiv med skärningspunkt på 0 ger kalibreringsslutning på 0,74. Area under curve (AUC) för prediktion av recidiv på 5 år var 0,74 och Harrel’s C-statistic var 0,77 (95% CI 0,71–0,83). Risken för motsvarande 5-års RFS var 95,8% (95% CI 92,8–99,2), 76,1% (95% CI 65,0–89,1) och 53,4% (95% CI 40,9–69,8) för respektive låg-, medium- och högriskpatienter. Konklusionen är att den externa valideringen av detta nomogram för prediktion av recidiv hos patienter med grad 1–2, ickefunktionella pan-NET, visade sig välfungerande med användning av dessa tre lättillgängliga parametrar.
Min huvudhandledare, Olov Norlén, som först och främst övertalade mig att skriva denna avhandling och som sedan hejade på mig under! Du är en av de smartaste personerna jag känner, och förhoppningsvis har en del av ditt sätt att tänka smittat av sig på mig under dessa år. Våra handledningsstunder har kantats av spännande diskussioner om forskning men också av ordvitsar, padeltaktik och väldigt många skratt. Du har följt mig i mina upp- och nedgångar, och även när du inte tycker att jag varit särskilt klipsk, har du fått mig att fokusera framåt!

Min bihandledare, Peter Stålberg, för din visdom inom forskning, endokrinkirurgi och livet. Du är som en storebror jag aldrig haft, den tryggaste personen med de bästa råden men samtidigt är du kung av ironi och den som retas mest av alla! Utan dig och din vägledning skulle jag inte ha börjat med endokrinkirurgi och denna avhandling skulle aldrig ha blivit skriven.

Claes Juhlin, Kristiina Kask, Peter Stålberg och Bengt Isaksson, tidigare, och nuvarande Verksamhetschefer på Kirurgkliniken, och Per Hellman och Liisa Byberg, tidigare och nuvarande Prefekt på Institutionen för kirurgiska vetenskaper, för att ni givit mig möjlighet att skriva denna avhandling.

Min kliniska handledare, Helene Siilin, och ST-studierektor Hella Hultin för att ni har guidat mig genom min ST och lindrat min värsta frustration över att få operera för lite.

Till kollegor och medförfattare på Onkologisk Endokrinologi, för fint samarbete, och till Anders Thornell för ditt hård arbete och dina peppande ord!

Mina kollegor på endokrinkirurgiska sektionen för att ni gör det dagliga arbetet intressant och roligt - ni är bäst! Per Hellman, för din kunskap inom endokrinkirurgi och forskning, dina fantastiska berättelser och ditt uppmuntrande sätt att vara. Branislav Klimacek, eller som jag brukar kalla dig, Tom Cruise, du är den mest arbetsamma, samarbetsvilliga och roliga kollegan man kan önska sig. Jag kommer att sakna dig när du är i London!
Matilda Annebäck, du är en fantastisk kollega och vän och den piffigaste människa jag någonsin träffat. Allt blir bättre när du är med, oavsett om vi befinner oss i operationssalen, i en skidbacke eller på en vattenskoter!

Till Anders Sundin, för din expertis inom NET-radiologin, dina kloka ord och för att du alltid tar dig tid att svara på mina frågor!

Till mina fina kollegor på kirurgkliniken - ni gör alla att det är roligt att gå till jobbet! Särskilt tack till Fredrik Linder, för att du lärde mig operera bräck, för härliga skidresor, padelmatcher och många skratt. Gustav Linder, för bästa afterskin, löjligt roliga samtal och för att jag får ge dig smash-tips! Håkan Andréasson, för att du ställt upp när jag behövde det som mest. ST-kollegorna Sara Artursson, Nina Farrohnia, Janniz Jönsson, Henrik Benoni, Malin Enblad, Tobias Åkerström, Maria Söderström, Martin Löffling Skogar, Peter Cashin, Boris Bajic, Abhishek Roshan och Lina Holmberg för att ni fyllt min vardag med klokheter och tokigheter!
Tidigare kollegan och vänner John Möller, för att du lärde mig operera en galla, hur man firar fredag och för att du alltid citerar böcker och filmer jag aldrig kommer att läsa eller se. Jag saknar dig på Akademiska!

Fredrik Berglund och Niklas Lundblad, mina fantastiska vänner från norr, tänk så mycket roligt vi haft! Vi ses alldeles för lite men ni betyder mer än ni kan ana.

Helena, min fina vän sedan läkarutbildningen. Du är en av de kloktaste personer jag känner, och den tryggaste och mest jordnära vän som finns! Tack för alla härliga minnen,äventyr och upptåg jag fått dela med dig! Jag är så glad att jag har dig!

Inga, min bästa vän! Vad skulle jag gjort utan dig? Världen skulle vara en bättre plats om alla hade en Inga! Tack för allt.

Min mamma och pappa, Marianne och Bertil, mina största supportrar! Ni är de mest generösa föräldrar man kan ha och ni har alltid fått mig att känna mig älskad, trygg och fått mig att tro på mig själv! Pappa, jag hoppas att du tycker min avhandling är ”rätt höffsad”!

Fredrik, mitt livs kärlek! Du är den bästa människan jag någonsin träffat, den snällaste, mest generösa och kärleksfulla! Du inspirerar mig att bli en bättre människa och stöttar mig på alla tänkbara sätt! Livet är bättre med dig och du borde alltid ha funnits i det. I vårt nästa liv måste vi träffas tidigare! Jag älskar dig.
Min son Vincent, du är det bästa som någonsin hämt mig. Du gör mig stolt varje dag och jag älskar dig mer än ord kan beskriva!
References


141 Daskalakis, K. et al. Association of a Prophylactic Surgical Approach to
142 Kjaer, J. et al. Long-term outcome after resection and thermal hepatic
ablation of pancreatic neuroendocrine tumour liver metastases. BJS Open 5,
143 Kjaer, J., Norlen, O., Hellman, P. & Stalberg, P. Author s Reply: Overall
Survival in Patients with Stage IV Pan-NET Eligible for Liver
144 Thiis-Evensen, E. Letter to the Editor: Overall Survival in Patients with Stage
IV Pan-NET Eligible for Liver Transplantation. World J Surg,
145 Kjaer, J. et al. Overall Survival in Patients with Stage IV Pan-NET Eligible
022-06736-1 (2023).
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