TURUN YLIOPISTO
UNIVERSITY OF TURKU

Prediction of the Aggressiveness of the Pancreatic Neuroendocrine Neoplasms Using Positron Emission Tomography and Immunohistochemical Biomarkers

Susanna Majala

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ABSTRACT

Predicting the aggressive behavior of a heterogeneous group of pancreatic neuroendocrine neoplasms (panNENs) remains a clinical challenge. Some panNENs are indolent, and some behave aggressively and metastasize to regional lymph nodes or distant organs. Prediction of the aggressiveness of panNEN is the main goal of diagnostic workup and an essential basis for treatment planning.

This thesis was designed to assess prognostic factors of panNENs. The main aim was to investigate, in a prospective setting, whether the malignant potential of nonfunctional (NF) panNENs could be predicted using dual-tracer functional imaging with [^{68}Ga]-DOTANOC and [^{18}F]-FDG positron emission tomography/computed tomography (PET/CT). Further, the second aim of this study was to correlate immunohistochemical tissue levels of all five somatostatin receptors with the receptor density generated from [^{68}Ga]-DOTANOC uptake in a prospective series of NF-panNENs. The third aim of this study was to evaluate prognostic clinical factors predicting recurrence and survival in a large, immunohistochemically confirmed, national cohort of panNENs (FinPanNET study).

[^{18}F]-FDG uptake in the tumor correlated positively with the Ki-67 proliferation index (PI) and serves as a poor prognostic marker in patients with NF-panNEN. [^{18}F]-FDG-avidity in NF-panNEN indicates a preference for surgical management. Further, SSTR5 expression in tumor samples correlated positively with Ki-67 PI and is associated with better prognosis. When all five SSTRs were analysed, SSTR2 had the highest impact on [^{68}Ga]-DOTANOC PET signaling of panNENs.

In the 373 immunohistochemically confirmed panNEN patients, a tumor size ≥2.4 cm predicted poorer prognosis. After re-evaluation, the Ki-67 PI changed in one-third of cases, demonstrating the importance of immunohistochemical analysis for establinshing high-quality study cohorts of panNENs.

KEYWORDS: Pancreatic neuroendocrine neoplasm, pancreatic surgery, [^{18}F]-FDG, [^{68}Ga]-DOTANOC, positron emission tomography/computed tomography, prognosis, immunohistochemistry

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TIIVISTELMÄ

Haiman neuroendokriiniset kasvaimet (panNEN) ovat heterogeeninen ryhmä kasvaimia, joiden aggressiivisen käyttäytymisen ennustaminen on edelleen merkittävä kliininen haaste. Osa panNEN:sta on hyvänlaatuisia sattumalöydöksiä ja osa käyttäytyy aggressiivisesti ja leviää paikallisiin imusolmukkeisiin tai muihin elimiin. Diagnostiikan päätavoitteena on selvittää mitkä kasvaimet ovat aggressiivisia ja mitkä eivät, ja hoitoratkaisut perustuvat tähän arvioon.

Väitöskirjan tarkoitus oli selvittää panNEN-kasvainten ennusteellisia tekijöitä. Päätavoitteena oli arvioida prospektiivisesti, voidaanko toimimattomien panNEN-kasvainten (NF-panNEN) aggressiivisuutta ennustaa kaksoismerkkiaine-PET/TT-kuvantamisella, jossa käytettiin [^{68}Ga]-DOTANOC ja [^{18}F]-FDG merkkiaineita. Toisena tavoitteena oli verrata kaikkien viiden somatostatiinireseptorin (SSTR) immunohistokemiallista ilmentymistä [^{68}Ga]-DOTANOC merkkiaineen osoittamaan reseptoritiheyteen. Kolmantena tavoitteena oli arvioida panNEN-kasvainten uusiutumista ja potilaiden eloonjäämistä ennustavia kliinisiä tekijöitä suuressa, immunohistokemiallisesti varmistetussa kansallisessa panNEN-aineistossa (FinPanNET-tutkimus).

Kasvaimen [^{18}F]-FDG-kertymä korreloi positiivisesti Ki-67 proliferaatio-indeksin (PI) kanssa ja osoittautui huonon ennusteen merkiksi NF-panNEN-potilailla. Kävi ilmi että [^{18}F]-FDG-positiivisuus puoltaa kasvaimen kirurgista hoitoa. Lisäksi SSTR5-reseptorin ilmentyminen kasvaimessa liittyi korkeaan Ki-67 PI:in ja parempaan ennusteeseen. Kaikkien viiden somatostatiinireseptorin tarkastelu vahvisti, että SSTR2 on merkittävin reseptori panNEN-kasvainten [^{68}Ga]-DOTANOC PET-signaalin kannalta.

Kansallisessa 373 panNEN-potilaan tutkimuksessa ≥2.4 cm:n koko oli yhteydessä panNEN-potilaan heikompaan ennusteeseen ja suurempaan uusiutumisriskiin verrattuna sitä pienempiin kasvaimiin. Lisäksi uudelleenarvioinnin jälkeen Ki-67 PI muuttui kolmasosassa tapauksista, mikä osoittaa immunohistokemiallisen analyysin tärkeyden laadukkaassa panNEN-tutkimuksessa.

AVAINSANAT: Haiman neuroendokriinien kasvain, haimakirurgia, [^{18}F]-FDG, [^{68}Ga]-DOTANOC, positroniemissiotomografia/tietokonetomografia, ennuste, immunohistokemia

Table of Contents

Abbreviations **8**

List of Original Publications **10**

1 Introduction **11**

2 Review of the Literature **14**
2.1 Pancreas 14
2.1.1 Anatomy of the pancreas 14
2.1.2 Neuroendocrine part of the pancreas 15
2.2 Pancreatic neuroendocrine neoplasms (panNENs) 15
2.2.1 Incidence and pathogenesis 15
2.2.2 Histopathology 16
2.2.2.1 General histopathological features 16
2.2.2.2 Immunohistochemistry 18
2.2.3 Classification 18
2.2.3.1 World Health Organization 18
2.2.3.2 Tumor-Node-Metastasis (TNM) staging 19
2.2.4 Diagnosis 20
2.2.4.1 Clinical presentation 20
2.2.4.2 Biochemical diagnostics 22
2.2.4.3 Conventional Imaging 24
2.2.4.4 Functional Imaging 26
2.2.5 Preoperative diagnostic workup 29
2.3 Treatment 30
2.3.1 Surgery 30
2.3.1.1 Resection 31
2.3.1.2 Enucleation 32
2.3.2 Endoscopic Ultrasound-guided Radiofrequency Ablation 33
2.3.3 Medical Therapy 34
2.3.3.1 Somatostatin Analogs 34
2.3.3.2 Chemotherapy 35
2.3.3.3 Other Medical Therapy 36
2.3.4 Peptide Receptor Radionuclide Therapy 37
2.3.5 Surveillance 38
2.4 Prognosis of panNEN patients 39
2.4.1 Histopathology 39
2.4.2 Imaging 46
2.4.2.1 Conventional Imaging 46

2.4.2.2 Functional Imaging 47

3 Aims 51

4 Materials and Methods 52
4.1 Study subjects 52
4.1.1 Study I 52
4.1.2 Study II 53
4.1.3 Study III 53
4.2 Methods 55
4.2.1 Dual tracer PET/CT (Study I and II) 55
4.2.2 Immunohistochemical analysis (Study II and III) 56
4.2.3 Statistical analysis 58

5 Results 59
5.1 Positive [^{18}F]-FDG PET/CT predicts poor prognosis among nonfunctional panNEN patients (Study I) 59
5.2 Somatostatin receptor subtype 2 expression correlated with [^{68}Ga]-DOTANOC PET/CT imaging (Study II) 62
5.3 Somatostatin receptor subtype 5 expression correlated with Ki-67 proliferation index of panNEN (Study II) 63
5.4 Characterization of the national, multicentre FinPanNET clinical cohort of panNENs (Study III) 64

6 Discussion 67
6.1 Prognostic value of PET/CT 67
6.2 Correlation of SSTR immunohistochemical (IHC) analysis to PET/CT and the value of SSTR IHC expression to prognosis 69
6.3 Prognostic value of tumor size 71
6.4 Other clinical factors to predict prognosis 71
6.5 Strengths and limitations 73
6.5.1 Strengths 73
6.5.2 Limitations 73
6.6 Future prospects 74

7 Conclusions 76

Acknowledgements 77

References 81

List of Figures and Tables 108

Original Publications 111

Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
AJCC	American Joint Committee on Cancer
ALT	Alternative lengthening of telomeres
ATRX/DAXX	Alpha-thalassemia/mental retardation X-linked/death domain-associated protein
Ca19-9	Carbohydrate antigen 19-9
[^{18}F]-FDG	[^{18}F]-fluoro-2-deoxyglucose
[^{68}Ga]-DOTANOC	[^{68}Ga]-DOTA-1-Nal3-octreotide
[^{68}Ga]-DOTATATE	[^{68}Ga]-DOTA-Tyr3-octreotate
[^{68}Ga]-DOTATOC	[^{68}Ga]-DOTA-D-Phe1-Tyr3-octreotide
[^{18}F]-SITATE	[^{18}F]-SIFA*lin*-Glc-Asp2-PEG1-TATE
Chrom A	Chromogranin A
CI	Confidence interval
CT	Computed tomography
DSS	Disease-specific survival
EUS	Endoscopic ultrasonography
F	Functional
FDA	U.S. Food and Drug Administration
FN	False negative
FNA	Fine-needle aspiration
FNB	Fine-needle biopsy
FP	False positive
GEP	Gastroenteropancreatic
IHC	Immunohistochemical
LNM	Lymph node metastases
MEN1	Multiple endocrine neoplasia type 1
MiNEN	Mixed neuroendocrine-non-neuroendocrine neoplasm
MRI	Magnetic resonance imaging
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasm
NET	Neuroendocrine tumor

NF	Non-functional
NPV	Negative predictive value
OS	Overall survival
panNEN	Pancreatic neuroendocrine neoplasm
panNET	Pancreatic neuroendocrine tumor
PD	Pancreatoduodenectomy
PFS	Progression-free survival
PET	Positron emission tomography
PI	Proliferation index
POPF	Postoperative pancreatic fistula
PP	Pancreatic polypeptide
PPV	Positive predictive value
RFA	Radiofrequency ablation
RFS	Recurrence-free survival
SEER	Surveillance Epidemiology and End Results
SSA	Somatostatin analog
SSTR	Somatostatin receptor
SUV_{max}	Maximum standardized uptake value
S-CgA	Serum circulating chromogranin A
Sv	Sievert
SYP	Synaptophysin
TN	True negative
TP	True positive
TTV	Total tumor volume
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Majala, S., Seppänen, H., Kemppainen, J., Sundström, J., Schalin-Jäntti, C., Gullichsen, R., Schildt, J., Mustonen, H., Vesterinen, T., Arola, J. and Kauhanen, S. Prediction of the aggressiveness of non-functional pancreatic neuroendocrine tumors based on the dual-tracer PET/CT. *EJNMMI Res*. 2019; 9:116.

II Majala, S., Vesterinen, T., Seppänen, H., Mustonen, H., Sundström, J., Schalin-Jäntti, C., Gullichsen, R., Schildt, J., Kemppainen, J., Arola, J. and Kauhanen, S. Correlation of Somatostatin Receptor 1-5 Expression, ^{68}[Ga]Ga-DOTANOC, ^{18}[F]F-FDG PET/CT and Clinical Outcome in a Prospective Cohort of Pancreatic Neuroendocrine Neoplasms. *Cancers*. 2022; 14(1):162.

III Majala, S.*, Elonen, L.*, Kaprio, T., Vesterinen, T., Kauhanen, S., Sammalkorpi, H., Parviainen, H., Schalin-Jäntti, C., Schildt, J., Laukkarinen, J., Ahola, R., Nieminen, L., Rinta-Kiikka, I., Ronkainen, J., Sipilä, K., Nortunen, M., Karjula, H., Huhta, H., Pohjanen, V-M., Mäkinen, M., Söderström, M., Kemppainen, J., Mrena, J., Kuopio, T., Koivula, A-S., Rantanen, T., Pulkkinen, J., Sironen, R., Haglund, C., Arola, J. and Seppänen, H. Predictors of Long-term Survival for Patients with Pancreatic Neuroendocrine Neoplasm in FinPanNET: Nationwide Biobank Study with Histopathological Re-evaluation. *Br J Surg*. 2025 Oct;112(10):znaf197.

*Authors have an equal contribution

1 Introduction

Pancreatic neuroendocrine neoplasms (panNENs) are a rare but increasingly diagnosed, heterogeneous group of tumors with highly variable biological behavior and malignant potential. The detection of small, early-stage panNENs has increased in recent decades due to the improved and more frequent use of radiological imaging (Dasari et al., 2025). Some panNENs exhibit an indolent, slowly-progressive nature, whereas others are aggressive, rapidly metastasizing tumors with poor outcomes comparable to pancreatic adenocarcinoma. Surgical resection remains the only potentially curative treatment for localized panNENs, but pancreatic surgery carries a risk of major complications (Kokkinakis et al., 2022). Surveillance is a potential option for incidentally discovered panNENs smaller than 2 cm, but carries a risk of metastasis and remains controversial regarding the accurate patient selection (Partelli, Massironi, et al., 2022; Ricci et al., 2022). By surveillance, it is possible to avoid the morbidity of surgery in indolent cases, whereas optimally selected operative management minimizes the risk of tumor progression in aggressive diseases (Zhang et al., 2016). Therefore, accurate assessment of tumor aggressiveness is essential for guiding treatment decisions made by multidisciplinary teams in tertiary centers.

Preoperative prediction of a panNEN's behavior is challenging. The most powerful prognostic factors for panNENs include the World Health Organization (WHO) grade, lymph node metastases, and distant metastases (Bilimoria et al., 2008). However, even within the same grade or stage, individual outcomes can vary widely (Durante et al., 2009). The European Neuroendocrine Tumor Society (ENETS) recommends a biopsy whenever feasible (Falconi et al., 2016; Kos-Kudla et al., 2023; Perren et al., 2017). However, the deep and central location of the pancreas within the retroperitoneum, along with its proximity to major vascular structures, complicates accessibility. Furthermore, a single biopsy may fail to capture the highest-grade region of a heterogeneous tumor (Pyo et al., 2023). Consequently, there is great interest in non-invasive prognostic biomarkers and imaging techniques capable of assessing tumor aggressiveness before treatment decisions are made.

In this context, functional imaging with positron emission tomography/ computed tomography (PET/CT), which integrates functional and anatomical

information, has emerged a valuable tool in panNEN evaluation. Well-differentiated panNENs characteristically overexpress somatostatin receptors (SSTRs) on the cell surface, allowing highly selective imaging with radiolabelled somatostatin analogs (SSAs), such as [^{68}Ga]-DOTANOC. [^{68}Ga]-SSA PET/CT is considered the gold standard for detecting and staging panNENs, with reported sensitivity of 78–96% and specificity of 79–97% for identifying primary and metastatic lesions (Bauckneht et al., 2020; Etchebehere et al., 2014; Naswa et al., 2011; Sharma et al., 2015; Wild et al., 2013). In contrast, [^{18}F]-fluorodeoxyglucose (FDG) PET/CT is traditionally used for evaluating high-grade panNENs and neuroendocrine carcinomas (NECs), as [^{18}F]-FDG uptake generally reflects more aggressive and dedifferentiated tumor biology. Importantly, retrospective studies have demonstrated that [^{18}F]-FDG PET/CT provides independent prognostic information even among well-differentiated panNENs (Binderup et al., 2010; Cingarlini et al., 2017). Evidence suggests that [^{18}F]-FGD PET/CT can even outperform histological grading in prognostication (Binderup et al., 2010). The latest clinical guidelines recommend performing both [^{68}Ga]-SSA and [^{18}F]-FDG PET/CT in selected patients with intermediate or high-grade (G2/G3) panNEN. Furthermore, the dual-tracer PET/CT may capture tumor heterogeneity, and composite scoring systems like NETPET-score have been validated as a powerful predictor of patient outcomes (Chan et al., 2017). In this thesis, the prognostic accuracy of dual-tracer functional imaging with [^{68}Ga]-DOTANOC and [^{18}F]-FDG was explored in a prospective setting.

Beyond imaging, immunohistochemical (IHC) analysis remains a cornerstone in the diagnosis of panNENs. Neuroendocrine neoplasms (NENs) arise from neuroendocrine cells distributed all over the body, and morphologically, NENs have various “outfits”. NENs express general neuroendocrine markers such as chromogranin A (Chrom A) and synaptophysin (SYP), confirming their neuroendocrine differentiation. Because panNENs are rare, patient cohorts are often collected over extended periods reaching from the 20th century on, with uncertain confirmation of neuroendocrine differentiation with modern immunohistochemical techniques. Our aim in Study III was to establish a national, retrospective, immunohistochemically confirmed cohort of surgically treated panNENs—the FinPanNET cohort—and to evaluate prognostic factors associated with recurrence and survival.

The aim of this thesis was to assess the prognosis of surgically treated panNENs using dual-tracer PET/CT and IHC analysis of SSTRs and neuroendocrine biomarkers. The study material comprised a prospective cohort of panNEN patients imaged with two tracers, [^{68}Ga]-DOTANOC and [^{18}F]-FDG (Studies I and II) and a national retrospective cohort of 373 patients from the FinPanNET study (Study III). In Study I, a prospective cohort of panNEN patients underwent dual-tracer PET/CT with [^{68}Ga]-DOTANOC and [^{18}F]-FDG. We assessed the ability of dual-tracer

imaging to predict tumor grade and patient outcomes. The main hypothesis was that the high [^{18}F]-FDG-avidity would correspond to a high Ki-67 proliferation index (PI) and poor prognosis, whereas high SSTR expression, reflected by high [^{68}Ga]-DOTANOC uptake on PET/CT, would indicate a lower Ki-67 PI and more favourable outcomes. In Study II, dual-tracer PET/CT findings were correlated with SSRT1–5 expression assessed by IHC analysis. In Study III, we analysed prognostic factors in the national FinPanNET cohort of 373 surgically treated, IHC-confirmed panNEN patients reanalysed over a 30-year period. The purpose of this thesis was to improve the understanding of the functional imaging and molecular characteristics of panNENs and to support the development of more personalized management strategies in the future.

2 Review of the Literature

2.1 Pancreas

2.1.1 Anatomy of the pancreas

Pancreas is a soft, glandular organ measuring roughly 20 cm in length, weighing around 100 grams. Anatomically, it is divided into three main segments: the head (caput), the body (corpus), and the tail (cauda). The central position of the pancreas near the major abdominal blood vessels creates a challenge to surgical exposure (Figure 1). The great proximity and shared blood supply with second part of the duodenum make the separation of these two structures impractical. Due to the close anatomical relationship between of body and tail of the pancreas and the splenic vessels, splenectomy is generally performed during left pancreatectomy for

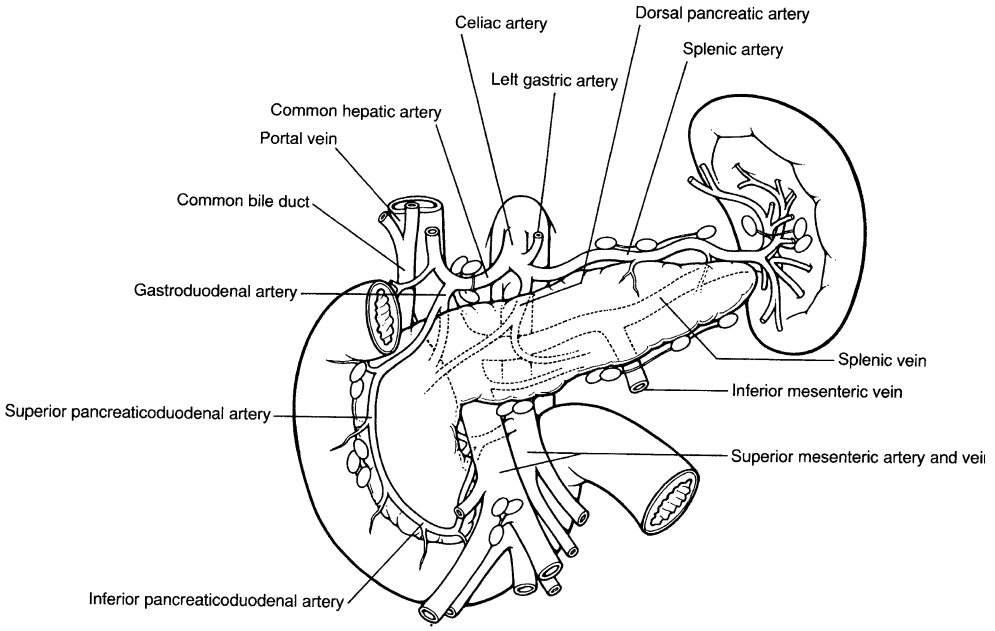


Figure 1. Regional anatomy of pancreas including vascular relationships Reprinted with permission from *Essential operative techniques and anatomy*, 4th edition, LWW, 2013.

malignant conditions (Scott-Conner & Dawson, 2013). The blood supply to the spleen can be preserved in cases of benign tumors or in selected cancer cases as well.

2.1.2 Neuroendocrine part of the pancreas

Pancreatic neuroendocrine neoplasms (panNENs) develop from pancreatic islet cells. Although they comprise only 1% of the mass of pancreatic tissue, their endocrine secretions have indispensable metabolic effects. Neuroendocrine cells are interspersed within small blood vessels, forming clusters that comprise the islets of Langerhans, which are spread throughout the exocrine pancreas. In the islets of Langerhans, five different types of cells produce biologically active peptides.

Islets of Langerhans consist of 60% insulin-producing β-cells, 30% glucagon-producing α-cells, and the remaining 10% of somatostatin-producing δ-cells, pancreatic polypeptide (PP) cells, and ghrelin-producing cells (Cabrera et al., 2006). These cells are diffusely located throughout the islets, and work synchronously to maintain euglycemia (Kim et al., 2009). Especially, β-cells have been extensively studied in the context of diabetes, as the disease is caused by decline or dysfunction of β-cells. The contribution of islet cells varies across the pancreas parts, leading to unequal functional consequences following different types of pancreatic resections (Menge et al., 2009).

2.2 Pancreatic neuroendocrine neoplasms (panNENs)

2.2.1 Incidence and pathogenesis

PanNENs were first identified over a hundred years ago by Nicholls, who described those as “simple adenomas of the pancreas arising from islets of Langerhans” (Nicholls, 1902). PanNENs constitute 1 to 3% of all pancreatic neoplasms (Yao et al., 2008). Following ductal adenocarcinoma, PanNENs are the second most frequently occuring pancreatic tumor (Hruban, 2007). In recent years, the incidence of panNENs, similar to that of all gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs), has increased, reaching 1 per 100 000 (Dasari et al., 2017; Hallet et al., 2015; Hauso et al., 2008; Modlin et al., 2003; Sonbol et al., 2022; Yao et al., 2008). The incidence of PanNENs increased 4.3-fold from 2000 to 2021 (Dasari et al., 2025). The increased utilization of cross-sectional imaging techniques has resulted in earlier detection of nonfunctional (NF) panNENs (Cheema et al., 2012). However, the incidence of functional (F-) panNENs has decreased from 2000 to 2017 (Luo et al., 2023). The prevalence of panNENs is fairly high due to better

survival rates, with 5-year survival rates of 85% and 78% for G1 and G2 tumors, respectively, compared to other pancreatic tumors (Siegel et al., 2017). However, among all GEP-NEN sites, panNENs are associated with the lowest 5-year survival rate (Man et al., 2018; Nunez-Valdovinos et al., 2018). Due to variable prognosis, panNENs have become a central focus of ongoing research. The heterogeneity of panNENs makes predicting aggressiveness and management very complex, and it remains an unmet clinical challenge.

PanNENs exhibit a slight male predominance (55%) and are most commonly diagnosed between the third and sixth decades of life (Halfdanarson et al., 2008). An earlier manifestation of panNENs is typically observed in hereditary syndromes. Familial conditions are associated especially with panNENs, but most of the panNENs (about 90%) are sporadic. The most recognized genetic syndrome is multiple endocrine neoplasia type 1 (MEN1), which is present in approximately 65% of gene-related panNENs. MEN1 is characterized by the following manifestations: primary hyperparathyroidism (>95%), panNENs (25–80%), pituitary tumors (20–40%), and adrenocortical adenomas (10–15%). MEN1 is an autosomal dominant familial neoplasia syndrome resulting from an inactivating mutation of the MEN1 gene, which functions as a tumor suppressor, and is mapped to chromosome 11q13. Most commonly, MEN1 patients manifest with NF-panNENs followed by gastrinomas and insulinomas (Skogseid & Doherty, 1999). Alterations in the MEN1 gene represent a key initiating event in approximately one-third of sporadic NF-panNENs, insulinomas, and gastrinomas, and are detected irrespective of tumor diameter or metastatic status (Hessman et al., 1999; Hessman et al., 1998). Approximately two-thirds of patients with MEN1 actually experience mortality due to MEN1-related causes, with panNEN accounting for the primary cause of death in 40–45% of cases (Ito et al., 2013). An active surgical approach has been suggested for MEN1 patients having panNEN (Skogseid & Doherty, 1999). However, the prognosis of panNENs diagnosed with MEN1 syndrome did not differ from patients with sporadic panNEN (Chiloiro et al., 2018). PanNENs may also be associated with more rare syndromes like Von Hippel-Lindau, tuberous sclerosis, and neurofibromatosis 1 (Recklinghausen`s syndrome).

2.2.2 Histopathology

2.2.2.1 General histopathological features

PanNENs were originally identified as rare tumors characterized by histopathological features distinct from those of classical pancreatic adenocarcinomas (Bosman, 2010). Macroscopically, panNENs are usually small, encapsulated, solitary tumors of 1–5 cm in diameter. Microscopically, panNEN cells

are typically small, featuring uniform round or oval nuclei and a finely to coarsely granular chromatin pattern, commonly referred to as 'salt and pepper'. Unlike the more common gland-forming adenocarcinomas, panNENs are characterized by loss of epithelial tubular gland structures and by their diffuse expression of neuroendocrine markers. The histopathological profile of well-differentiated panNENs is characterized by a well-developed, organoid growth pattern, varying degrees of fibrotic stroma in which necrosis is rare. The organoid pattern is highly diverse and can be divided into either solid or trabecular architecture. Some histological architectures are associated with the secretion of certain hormones. For instance, insulin-producing insulinomas often have a solid-nested architecture with amyloid, and tumors expressing glucagon are often characterized by a trabecular-reticulated with cystic features (*Digestive System Tumours, WHO Classification of Tumours*, 2019; Konukiewitz et al., 2011).

Poorly differentiated neuroendocrine carcinomas (NECs) exhibit a solid, sheet-like architecture of tumor cells characterized by irregular nuclei, high mitotic activity, and fewer secretory granules compared to well-differentiated neuroendocrine tumors (NETs) (Figure 2). Expression of typical neuroendocrine markers is lower among NECs than in well-differentiated NETs. However, immunohistochemistry is crucial to distinguish panNEC from G3 pancreatic neuroendocrine tumors (panNETs).

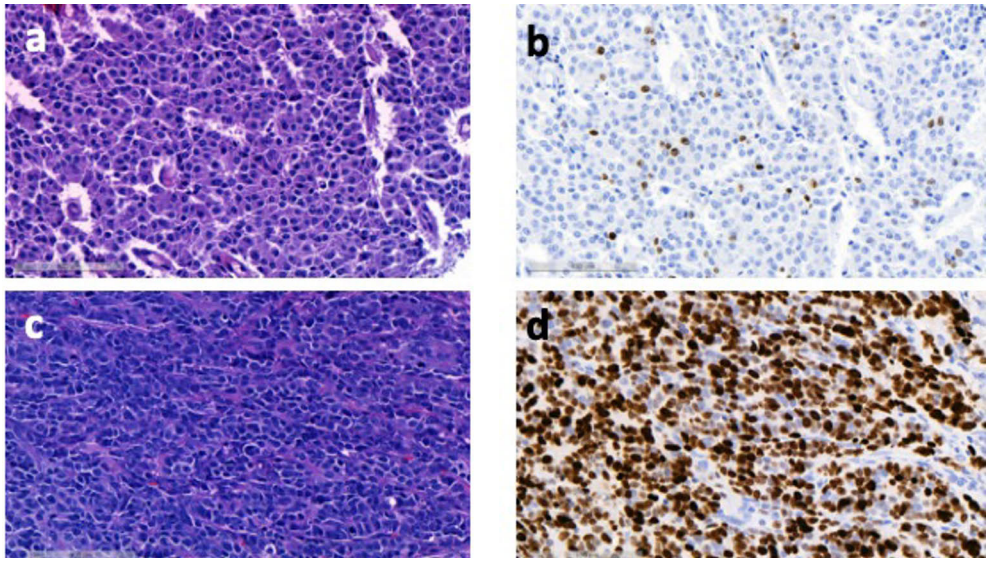


Figure 2. Representative figures of hematoxylin & eosin staining and Ki-67 staining of well-differentiated (G1) neuroendocrine tumor (**a**, **b**) and poorly differentiated neuroendocrine carcinoma (**c**, **d**).

PanNEN may present with coexisting high-grade adenocarcinoma or acinar cell carcinoma. If one component exceeds 30% of the total tumor cells, such a tumor is classified as mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN). If the non-neuroendocrine component consists of adenocarcinoma and neuroendocrine component of NEC, the old term “mixed adenoneuroendocrine carcinoma (MANEC) may be used (Bosman, 2010).

2.2.2.2 Immunohistochemistry

Well-differentiated panNEN cells contain secretory granules and exhibit strong immunoexpression of neuroendocrine biomarkers, such as SYP. These biomarkers can be detected by means of immunohistochemistry. Although conventional morphological analysis alone may be sufficient to recognize panNEN, IHC analysis is always essential to confirm the diagnosis. PanNENs usually express SYP, Chrom A, and insulinoma-associated protein 1 (INSM1) (McHugh et al., 2020; Perren et al., 2017; Tanigawa et al., 2018). Labeling for p53 and retinoblastoma 1 (RB1) is strongly suggested to separate G3 panNENs from panNECs. SSTR2 may also be useful (Rindi et al., 2022). Only 16% of NECs express SSTR2, and 70% of NECs show an abnormal expression pattern (complete loss or >20 %) of p53 and/or RB1 (los of expression) (Konukiewitz et al., 2017). Overall, the frequency of mutations, for instance the KRAS mutation, is substantially higher in NECs than in NETs (Hijioka et al., 2017; Vijayvergia et al., 2016). Well-differentiated panNENs typically express SSTRs, which form the basis of SSA functional imaging and SSA medical therapy (see below). The epithelial nature of panNEN must be proven by cytokeratin, for instance, by pancytokeratin (CKPan) staining to rule out a neuroectodermal tumor such as paraganglioma. Organ-specific markers are useful in establishing the diagnosis of panNEN and particularly useful in determining the primary tumor site when liver metastases are present without known origin: TTF-1 positivity is in favor of primaries of the lung, serotonin and CDX2 are found in primary tumors from midgut, for instance, small intestine, and ISL1 in primaries of pancreas and duodenum (Agaimy et al., 2013; Schmitt et al., 2008).

2.2.3 Classification

2.2.3.1 World Health Organization

In the most widely accepted classification of panNENs, the World Health Organization (WHO) separates panNENs into two major categories: well-differentiated pancreatic neuroendocrine tumors (panNETs) and poorly differentiated pancreatic neuroendocrine carcinomas (PDNECs) (Table 1) (*Digestive*

System Tumours, WHO Classification of Tumours, 2019). Moreover, the WHO classifies well-differentiated PanNENs, panNETs, into three main categories: grades 1, 2, and 3 based on Ki-67 PI and/or mitotic count per 10 high-power fields (Table 1). Ki-67 is an antigen that stains only rapidly dividing cells, not resting cells. Tumor grade predicts how fast the tumor grows, and differentiation predicts the behavior of the tumor.

Table 1. The 2022 WHO classification and grading for neuroendocrine neoplasms of the gastrointestinal and hepatopancreatobiliary tract. Modified from Rindi et al., 2022.

Terminology		Grade	Differentation	kI-67 proliferetion index*	Mitotic count#
NET	G1 NET	Low	Well-differentiated	<3%	<2
	G2 NET	Intermediate	Well-differentiated	3–20%	2–20
	G3 NET	High	Well-differentiated	>20%	>20
NEC	SCNEC LCNEC	High	Poorly differentiated	>20%	>20
MINEN		Variable	Well- or poorly differentiated	Variable	Variable

* Ki-67 proliferating index is determined by counting ≥500 cells in the regions of highest labelling (hot- spots); #Mitotic rates are expressed as the number of mitoses/2 mm^2 determined in 50 fields of 0.2 mm^2; the final grade is based on the proliferation index that places the neoplasm in the higher-grade category.
Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; SCNEC, small cell neuroendocrine carcinoma; LCNEC, large-cell neuroendocrine carcinoma; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm.

In the 2019 WHO classification, a novel subgroup, well-differentiated high-grade NET (G3), was incorporated into the spectrum of well-differentiated NETs (Nagtegaal et al., 2020).

2.2.3.2 Tumor-Node-Metastasis (TNM) staging

The Tumor-node-metastasis (TNM) staging system is a prognostic classification used for all kinds of malignancies. The European Neuroendocrine Tumor Society (ENETS) classifications, published in 2006, and the American Joint Committee on Cancer (AJCC) 8th edition, published in 2018, are two widely used systems in staging panNENs (Table 2) (Rindi et al., 2006; You et al., 2019). The modified ENETS staging is a mixture of these two systems, maintaining ENETS TNM definitions and adopting the 7th edition AJCC staging (Luo, Javed, et al., 2017).

Table 2. AJCC 8th edition staging definitions, modified ENETS (mENETS) staging definitions, and ENETS staging definitions, and for PanNENs.

		AJCC 8th Edition Staging System	mENETS	ENETS
PRIMARY TUMOR (T)	T1	Tumor limited to pancreas, <2 cm		
	T2	Tumor limited to pancreas, 2–4 cm		
	T3	Tumor limited to pancreas, >4 cm, or invading to duodenum or common bile duct		
	T4	Tumor invades adjacent structures*		
LYMPH NODES (N)	N0	No regional lymph node metastasis		
	N1	Regional lymph node metastasis/metastases		
METASTASES (M)	M0	No distant metastasis		
	M1	Distant metastasis/metastases		
	M1a	metastasis confined to liver		
	M1b	metastasis in at one extrahepatic site#		
	M1c	both hepatic and extrahepatic metastases		
STAGE	I	T1, N0, M0 (A) T2, N0, M0 (B)	T1, N0, M0 (A) T2, N0, M0 (B)	T1, N0, M0
	II	T3, N0, M0 (A) T4, N0, M0 (B)	T3, N0, M0 (A) T1-3, N1, M0 (B)	T2, N0, M0 (A) T3, N0, M0 (B)
	III	Any T, N1, M0	T4, any N, M0	T4, N0, M0 (A) Any T, N1, M0 (B)
	IV	Any T, Any N, M1		

* stomach, spleen, colon, adrenal gland, or the wall of large vessels (celiac axis or superior mesenteric artery) # lung, ovary, nonregional lymph node, peritoneum, and bone AJCC, American Joint Commettee of Cancer; ENETS, European Neuroendocrine Tumor Society, mENETS modified European Neuroendocrine Tumor Society.

2.2.4 Diagnosis

2.2.4.1 Clinical presentation

Neuroendocrine neoplasms (NENs) are tumors that originate from neuroendocrine cells found in all organs, especially in the lung, gastrointestinal tract, and pancreas. NENs arising from the gastrointestinal (GI) tract and pancreas are histopathologically categorized under the same diagnostic entity;

gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs). However, panNENs exhibit distinct clinical characteristics from GI NENs and should be approached as a separate group. PanNENs are divided into functional (F-panNENs) or nonfunctional (NF-panNENs) tumors depending on whether they secrete hormones that produce symptoms or not. F-panNENs secrete particular hormones or peptides leading to specific hormonal syndromes (Table 3). Most of panNENs, about 60–90%, are nonfunctional and do not secrete active hormones. Histologically F-panNENs and NF-panNENs are indistinguishable from each other (Bosman, 2010).

Up to half of patients with NF-panNEN and are detected incidentally on imaging study. Although NF-panNENs are often asymptomatic, they are frequently diagnosed at an advanced stage, as synchronous or metachronous metastases are observed in 50–70% of patients (Ferrone et al., 2007; Franko et al., 2010). Liver is the most frequent site of metastases. Patients with panNEN may have symptoms or signs related to the compressive effect of the tumor or its metastases: obstructive jaundice, abdominal pain or mass, or acute pancreatitis caused by the main pancreatic duct compression.

F-panNENs secrete hormones and cause clinical syndromes due to hormonal hypersecretion. Insulinomas are the most common type, occurring in 60% of female patients, are typically benign, and are diagnosed between 40 and 45 years of age. Hypoglycemic symptoms, like weakness, tremor and sweating, are caused by insulin hypersecretion. Because of the early onset of clinical symptoms, insulinomas are usually small at the time of diagnosis, ranging 5–20 mm (Mehrabi et al., 2014). Other F-panNENs include glucagonomas, gastrinomas, VIPomas, somatostatinomas, and several rarer subtypes (Table 3).

The carcinoid syndrome, most frequently associated with midgut NENs, arises due to the secretion of serotonin and additional vasoactive peptides, resulting in a characteristic symptom profile. Due to the hepatic filtration via the portal vein, the carcinoid syndrome is generally observed only in panNEN cases with hepatic metastases. The carcinoid syndrome requires the presence of liver metastases, as the portal vein circulation allows the liver to clear the secretory products from the digestive system before arriving in the systemic circulation. The carcinoid syndrome in panNEN patients is uncommon, but a relatively high incidence rate (23%) has also been reported in a cohort with an overall metastatic rate of 67% (Soga, 2005). The classical symptoms of carcinoid syndrome are cutaneous flushing of the face, head, and upper chest, gut hypermobility with secretory diarrhea, asthmatic-like wheezing and dyspnea, and significant blood pressure changes or hypotension.

Table 3. The most common panNEN-associated hormonal syndromes. Modified from Falconi et al. 2016.

Name	Biologically active peptide secreted	Incidence (million per year)	Tumor location	Malignant %	Main symptoms/ signs
Insulinoma	Insulin	1–32	Pancreas (<99%)	<10	Hypoglycemic symptoms
ZES*	Gastrin	0.5–21.5	Duodenum (70%) Pancreas (25%) Other (5%)	60–90	Pain, diarrhea, esophageal symptoms
VIPoma	VIP	0.05–0.2	Pancreas (90%) Other (10%)	40–70	Diarrhea, hypo-kalemia, dehydration
Glucagonoma	Glucagon	0.01–0.1	Pancreas (100%)	50–80	
SSoma	Somatostatin	Rare	Pancreas (55%) Duodenum/ jejunum (44%)	>70	Diabetes mellitus cholelithiases diarrhea
GRHoma	GHRH	Unknown	Pancreas (30%) Lung (54%) Jejunum (7%) Other (13%)	>60	Acromegaly
ACTHoma	ACTH	Rare	Pancreas (4–16% all ectopic Cushing`s syndrome)	>95	Cushing`s syndrome
Carcinoid syndrome caused by panNEN	Serotonin Tachykinins	Rare (43 cases)	Pancreas (<1% all carcinoids)	60–88	Flushing, diarrhea, bronchospasm, and cardiac valve fibrosis
Hypercalcemia caused by panNEN	PTHrhP	Rare	Pancreas	84	Hypercalcemia and abdominal pain

* ZES = Zollinger-Ellison syndrome, VIP=Vasoactive intestinal peptide, GHRH = Growth hormone releasing hormone, PTHrhP = Parathyroid hormone-related peptide.

2.2.4.2 Biochemical diagnostics

Several biochemical markers are useful for monitoring panNENs when elevated during primary diagnosis. However, their accuracy in early-stage disease is limited and a normal concentration does not exclude the presence of panNEN. The most widely used marker is serum chromogranin A (S-CgA), with an overall sensitivity of 54–77% and a specificity of 56–92% (Hijioka et al., 2014; Qiao et al., 2014). Located in the secretory dence-core granules of neuroendocrine cells, chromogranin A functions as an acidic glycoprotein. It has been recommended as the most practical serum tumour marker for

sporadic panNEN by the European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) guidelines (Oberg et al., 2017). S-CgA may be elevated in the presence of midgut NENs and NF-panNENs, and almost universally elevated in patients with gastrinoma (Nobels et al., 1997; Taupenot et al., 2003) and in metastatic disease (Modlin et al., 2016; Oberg et al., 2017). Falsely elevated S-CgA concentrations may be observed in the absence of NENs, particularly in patients with renal or hepatic failure, chronic gastritis, inflammatory bowel disease, prostate or thyroid cancer, or those receiving proton pump inhibitors or systemic corticosteroids (Giusti et al., 2004). Elevated levels correlate with advanced disease stage. Despite the low sensitivity of S-CgA, it is an independent predictive indicator in patients with panNEN, correlating with both tumor mass and patient survival (Giusti et al., 2004; Modlin et al., 2016; Pulvirenti et al., 2019; Yao, Pavel, et al., 2011). Therefore, S-CgA may serve as a biomarker in the surveillance of panNENs rather than for diagnosis. S-CgA is also used as an IHC marker of NENs.

Although urinary 5-hydroxyindoleacetic acid (5-HIAA) serves as a valuable diagnostic and monitoring tool for small intestine NENs, but it has less relevance in panNENs. Measurements of circulating 5-HIAA are complex, but serum 5-HIAA levels have demonstrated strong concordance with urinary 5-HIAA content (Adaway et al., 2016). The presence of 5-HIAA is usually related to the carcinoid syndrome (Janson et al., 1997).

PP is a hormone secreted in the periphery of the pancreatic Langerhans islets. Sensitivity in F-panNENs is 54% and in NF-panNENs 57% (Panzuto et al., 2004). The diagnostic accurancy improved markedly when both S-CgA and PP were analysed together, achieving a sensitivity of 95%, compared to 75% with CgA alone ($p=0.02$). Elevated concentrations are often observed in panNEN patients, especially in patients with MEN1, with sensitivity as high as 95% and specificity of 88% (Mutch et al., 1997). However, a recent publication has reported controversial findings regarding PP in MEN1 patients with sensitivities as low as 23% among all panNENs, 33% among panNEN $\geq$ 2 cm in size, and 0% in those with distant metastases (Kostiainen et al., 2025). Further, normal levels do not rule out panNEN. False positive concentrations may occur in situations like excessive diarrhea, excessive use of laxatives, older age, inflammation in the gut, and chronic renal disease.

Neuron-specific enolase (NSE) is a glycolytic enzyme present in neurons and neuroendocrine cells. Serum NSE level is frequently elevated in patients with small-cell lung cancer and in 31–38% of patients with NEN (Baudin et al., 1998; Nobels et al., 1997). Among NEN, high levels are associated with poor differentiation and short progress-free survival (PFS) (Nobels et al., 1997; Yao, Pavel, et al., 2011).

In conclusion, the value of any blood marker for diagnosing panNENs is relatively low, even when used in combination when sensitivity not more than 60% is reached (Qiu et al., 2016).

In the future, multianalyte liquid biopsy may offer an accurate diagnostic tool for panNEN. NETest is a panel of 51 neuroendocrine-related genes of mRNA measured in blood, ranging a score of 0–100%. The score <20% is considered normal, 20-40% suggests stable disease, and >40% indicates progressive disease. NETest offers a high sensitivity of 89–94%, and a specificity of 95–99% in diagnosis of NENs (Oberg et al., 2020). In metastatic cases, the sensitivity exceeds even to 98% (Almeida et al., 2024). Furthermore, NETest has shown superior accuracy compared to CgA in prospective case-control studies (Modlin et al., 2015; Modlin et al., 2021) and correlates with imaging (Malczewska et al., 2019). However, NETest or other multianalyte liquid biopsy markers are not used in clinical practice and is not included to guidelines, due to a lack of validation in prospective studies.

2.2.4.3 Conventional Imaging

An accurate preoperative imaging of panNEN is essential for evaluating the correct disease stage, the most appropriate surgical procedure, and the relationship between primary tumor and peripancreatic vessels.

Computed Tomography (CT) scan is the first-line imaging method in the detection of primary panNEN (Falconi et al., 2016) with a sensitivity of 73% and a specificity of 96%, respectively (Kos-Kudla et al., 2017). CT should include multiphase imaging, with late arterial (30 sec) of pancreatic (40 sec) phase, portal venous phase and delayed phase. During the arterial phase a panNEN lesion shows intense enhancement, whereas adenocarcinomas are typically hypoenhancing. A classic appearance of panNEN on CT is a well-circumscribed, homogeneous, hypervascular lesion with hyperintense tumor enhancement (Figure 3). CT is the most accurate imaging procedure for studying the vascular involvement in the presence of pancreatic malignancies (Foti et al., 2013), and tri-phasic CT is recommended routinely in the preoperative diagnostic workup of panNENs before surgery. However, in the case of a small panNEN, the sensitivity of CT is often inadequate.

Magnetic resonance imaging (MRI) is an accurate imaging modality in detection of primary panNEN tumor (Falconi et al., 2016) due to its excellent soft-tissue contrast. Further, MRI is a well-tolerated scan also among patients with iodinated contrast allergy, and MRI avoids the radiation exposure associated with repeated examinations, such as in patients with inherited syndromes. The typical panNEN finding in MRI is a peripherally hyperenhancing mass on T1 phase (Figure 3). Magnetic resonance cholangiopancreatography (MRCP) is the most effective modality for assessing the relationship between the tumor and pancreatic duct and should be performed preoperatively when enucleation is warranted (Partelli et al., 2017). Among Xiao et al., a duct-road sign, a straight or slightly curved main

pancreatic duct without significant dilatation or compression, in MRI, may be used as a differential diagnosis of a pancreatic mass. Prevalence of a duct-road sign is higher in cases of panNENs than in pancreatic ductal-adenocarcinomas (84% vs. 0%, $p < 0.001$) (Xiao et al., 2019).

Endoscopic ultrasonography (EUS) has an important role in diagnosing and locoregional staging of panNENs. The ability to take tissue samples by means of fine needle aspiration (FNA) or fine needle core biopsy (FNB) is a great advantage of this study. During EUS, panNENs typically appear as well-rounded, hypoechoic lesions with a homogeneous pattern with clear margins. The most typical and important indication to perform EUS is a localisation of F-panNEN before surgery. The Sensitivity of EUS ranges from 57 to 94% (Anderson et al., 2000; Ardengh et al., 2000; Gouya et al., 2003; Zimmer et al., 2000) and according to the latest ENETS Concensus Guidelines, EUS proven to be the most accurate diagnostic technique in panNEN detection (Falconi et al., 2016; Manta et al., 2016) and can describe the distance between the lesion and the main pancreatic duct. The sensitivity of EUS-FNA in diagnosing solid panNENs is better (95%) than in case of cystic panNENs (62.5%, $p < 0.03$)(Dhaliwal et al., 2019).

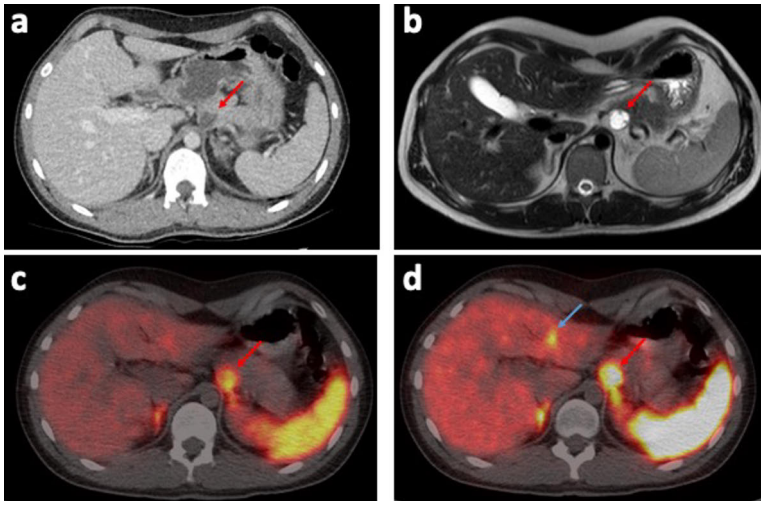


Figure 3. Representation of a MEN1 patient having a panNEN with synchronous liver metastasis. The primary tumor is seen at the junction of the body and tail of the pancreas in a contrast-enhanced CT image (**a**), as well as in a T1 fat-saturated MRI image (**b**), and in the corresponding ^{68}Ga-DOTANOC PET/CT (**c**, **d**). The liver metastasis in left lobe is also illustrated in ^{68}Ga-DOTANOC PET/CT (**d**). Histopathological report revealed a 2.4 mm cystic-solid G2, T2N1 (2/3 lymph nodes) tumour, and further after liver resection a G1, (Ki-67 PI 2%) liver metastasis. *The primary tumor is marked with red arrows and the liver metastasis with blue arrow.

2.2.4.4 Functional Imaging

Principles of PET/CT. PET is widely used for both diagnostic and therapeutic assessment, particularly in various cancer types, as well as in brain and cardiac imaging, and in detecting various inflammatory and infectious processes. PET/CT is a non-invasive, functional imaging modality that utilizes unstable radioactive isotopes to visualize metabolic and biochemical processes, as well as the regional expression of specific proteins or receptors in tissues of living subjects. Radioligand or radioactive tracer is a physiological molecule which has been labelled with a positron-emitting isotope or nuclide such as ^{18}F, ^{68}Ga, and ^{11}C. PET imaging begins with intravenous injection metabolically active radioligand, which then accumulates in a body area of high affinity to this specific molecule. Proton-rich radionuclides that decay via positron emission stabilize the nucleus while giving off a positive charge in the positron emission decay process: after decay of an excess proton, a positively charged positron and a chargeless neutrino are emitted. The emitted positron passes through matter and loses its energy gradually and collides with a nearby electron. The resulting process is called annihilation in which two energetic (511 keV) photons with no mass are emitted in opposite directions (Figure 4). In a PET scanner, detectors are arranged in a ring-shaped pattern. Within the scanner is a patient in whom a positron emission has occurred. Simultaneous detection of two photons in 180 degrees within an electronic time window is the basis of coincidence detection and coincidence imaging, such as PET. The line between two detectors is referred to as a line of response (LOR). The difference in arrival time between the two photons indicates where along the LOR they originated. Over time, enough coincidence events are detected to produce raw data. After several corrections (tissue attenuation, random coincidences, scatter coincidences) a final image is reconstructed.

Most radionuclides used in PET/CT imaging have short half-lives: ^{15}O 124 sec, ^{13}N 10 minutes, ^{68}Ga 68 minutes, and ^{18}F 110 minutes. Radionuclides used are produced artificially in the cyclotron. However, ^{68}Ga is generally obtained from on-site ^{68}Ge/^{68}Ga-generators. Scanning is typically acquired at 10–60 minutes after injection of the PET tracer. As PET imaging detects biochemical processes, it is usually combined with anatomical imaging, computed tomography, or MRI for the localization of functional processes. Standardized uptake value (SUV) is the most common semiquantitative measurement of tracer uptake in tissue and can be calculated when the activity concentration in target tissue is divided by injected activity normalized for the weight of the patient. Many factors affect SUV, including patient weight, injected dose, time between injection and imaging (dose to scan time), motion artifacts, and blood glucose levels in case of [^{18}F]-FDG. SUV_{max} is a maximum standardized uptake value within a region of interest (ROI), traditionally a tumor.

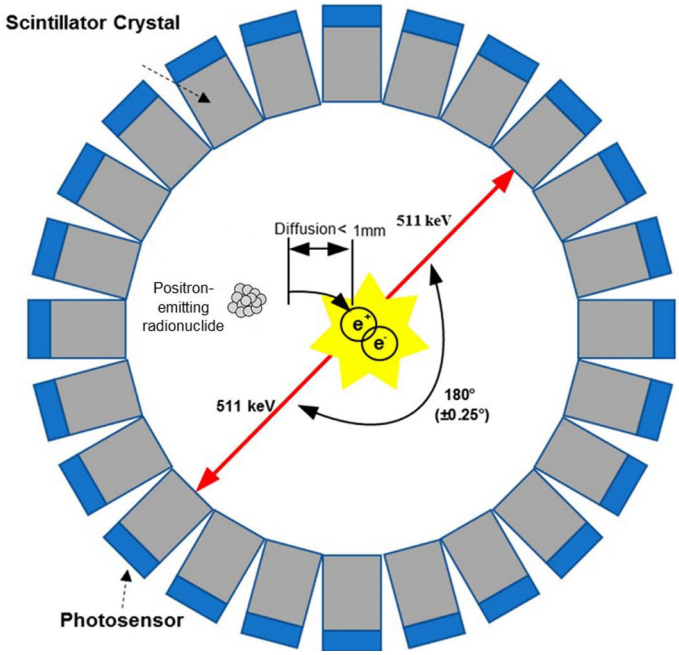


Figure 4. The basic principle of annihilation in a positron emission tomography (PET) scanner. Scintillator crystals, including photosensors, are organized in a shape of a ring, and detect pair of photons resulting from the annihilation of an electron with a positron emitted by the positron-emitting radionuclide. Modified from Jiang et al., 2019.

Somatostatin analog imaging. The physiological actions of somatostatin and its analogs, SSAs, are mediated through five G-protein coupled receptor subtypes, SSTR1-SSTR5 (Maurer & Reubi, 1985). The majority, 80–90% of well-differentiated panNENs, overexpress somatostatin receptors, particularly subtypes 2, 3 and 5 (Diakatou et al., 2015; Papotti et al., 2002; Yerci et al., 2015) and can be visualized by binding of radioactive somatostatin analog. During the last decades, functional imaging with [^{68}Ga]-labelled somatostatin analog ([^{68}Ga]-SSA) PET/CT has replaced the "old-fashioned" somatostatin receptor scintigraphy (SRS) or somatostatin receptor single-photon emission computed tomography (SPECT/CT) with [^{111}In]-pentetreotide. The superior sensitivity of 78–96% and specificity of 79–97% of [^{68}Ga]-SSA PET/CT prefer the use of it in diagnostics of panNENs (Bauckneht et al., 2020; Etchebehere et al., 2014; Naswa et al., 2011; Sharma et al., 2015; Wild et al., 2013), excluding insulinoma due to relatively poor (26%) sensitivity (Sharma et al., 2016). In a meta-analysis including a total of 2105 patients having NEN in the thorax or abdomen, the pooled sensitivity was 93% and specificity 96% (Geijer & Breimer, 2013). In a systematic review and meta-analysis of 1,143 panNEN patients, the pooled sensitivity for detecting the primary tumor was 80% on a per-patient basis and 92% on a per-lesion basis. The high detection

rates for metastatic lesions support the routine use of [^{68}Ga]-SSA PET/CT in the staging of panNENs (Bauckneht et al., 2020). Further, according to several guidelines (Bozkurt et al., 2017; Falconi et al., 2016; Sundin et al., 2017), SSA PET/CT is recommended as the first-line diagnostic procedure for staging and re-staging non-insulinoma panNENs, in the detection of unknown-primary tumor site or early relapse, as well as for patient selection for PRRT or management with "cold" somatostatin analogs. The meta-analysis of 39 studies including 2266 patients, showed that ^{68}[Ga]-SSA PET/CT resulted on a change in clinical treatment in 36% of patients (O. N. Y. Lee et al., 2022). Several different DOTA-peptides, ^{68}[Ga]-DOTA-1-Nal^{3}-octreotide ([^{68}Ga]-DOTANOC), [^{68}Ga]-DOTA-D-Phe^{1}-Tyr^{3}-octreotide ([^{68}Ga]-DOTATOC) and [^{68}Ga]-DOTA-Tyr^{3}-octreotate ([^{68}Ga]-DOTATATE) have been used as a PET/CT tracer for diagnosing of NEN. No clinically relevant differences have been reported among these tracers. The major difference relies on a slightly different affinity to SSTR subtypes: although, all tracers can bind to SSTR2 which is a predominant subtype in NEN, [^{68}Ga]-DOTATOC, and [^{68}Ga]-DOTANOC also binds to SSTR5 and only [^{68}Ga]-DOTANOC presents affinity to SSTR3, too (Antunes et al., 2007). False positive imaging findings are observed in cases of physiological uptake in the uncinate process of the pancreas, accessory spleens/splenules, infectious or inflammatory findings (due to SSTR expression of activated lymphocytes), and non-neuroendocrine tumors, for example, lymphoma, melanoma, breast cell, prostate, or renal cell carcinoma (Bozkurt et al., 2017). False-negative results can occur in lesions under PET/CT spatial resolution, in poorly differentiated lesions, or at sites of physiological biodistribution.

[^{18}F]-FDG. A glucose analog, [^{18}F]-FDG is the most common radiopharmaceutical used in PET imaging, especially for oncological indications. Glucose and also [^{18}F]-FDG are transported to the cell by glucose transport proteins (GLUT1 and GLUT3) and then phosphorylated by hexokinases. Tumor cells with increased metabolic activity, known as the Warburg effect (Vander Heiden et al., 2009), have increased expression of GLUT1 and GLUT3, and increased enzymatic hexokinase activity, leading to higher uptake of [^{18}F]-FDG than in normal tissues (Kawada et al., 2016). Radioligand [^{18}F] has a half-life of 109 min and PET images are acquired one hour after the intravenous injection of [^{18}F]-FDG. Patient has to fast for six hours before the injection, and blood glucose level must not exceed 11.1 mmol/L, although < 10.0 mmol/l is desirable. Generally, [^{18}F]-FDG PET/CT shows low sensitivity for well-differentiated NENs (40% in G1 and 60% in G2), while its role is emerging in the evaluation and management of high-grade (G3) NENs (sensitivity 95% in G3 panNENs) (Calabro et al., 2020). The higher the Ki-67 PI, the more sensitive [^{18}F]-FGD-PET/CT is to detect panNENs (Figure 5). [^{18}F]-FDG can also be used to evaluate the response to PRRT in comparison with SSA PET/CT

(Sansovini et al., 2017; Severi et al., 2013). False-positive imaging findings are observed in cases of infection/inflammation and non-neuroendocrine tumors.

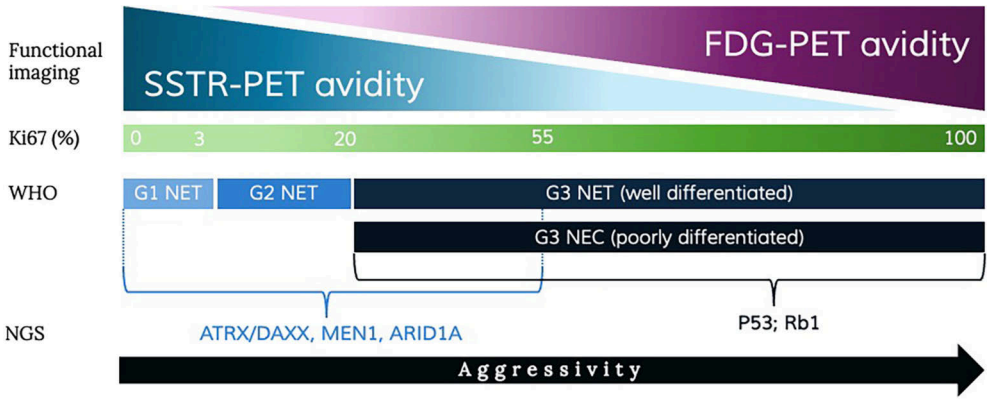


Figure 5. Multimodal evaluation of aggressiveness of pancreatic neuroendocrine neoplasms. FDG, fluorodeoxyglucose; NGS, next generation sequencing; SSTR, somatostatin receptor; WHO, world health organization. Reprinted with permission Acher & Hallet, 2024.

2.2.5 Preoperative diagnostic workup

The management of panNENs is nowadays tailored by a multidisciplinary team including an oncologist, radiologist, nuclear medicine specialist, pathologist, and surgeon with substantial expertise. Various biological factors, such as location, grading, and health history of the patient, should be taken into consideration while assessing the best individual therapy option (Figure 6). Functional panNENs cause symptoms and should be operated on, while small, asymptomatic NF-panNENs are candidates for surveillance. Higher grade and stage are associated with more aggressive behavior, favoring operative treatment over surveillance. However, the prognosis of panNECs is poor, and surgery should be avoided. Further, debulking surgery may be an option for low-grade metastasized panNENs. Curative surgery is a cornerstone of the treatment of panNENs. Other treatment options are varying and complex, including debulking surgery, external beam radiotherapy, peptide receptor radionucleotide therapy, liver-directed therapies (embolization, radiofrequency ablation), systemic treatments, and clinical trials. Patients with high-stage panNEN now have a significantly lower risk of death compared with the early twentieth century (Dasari 2017), primarily due to advances in treatment protocols.

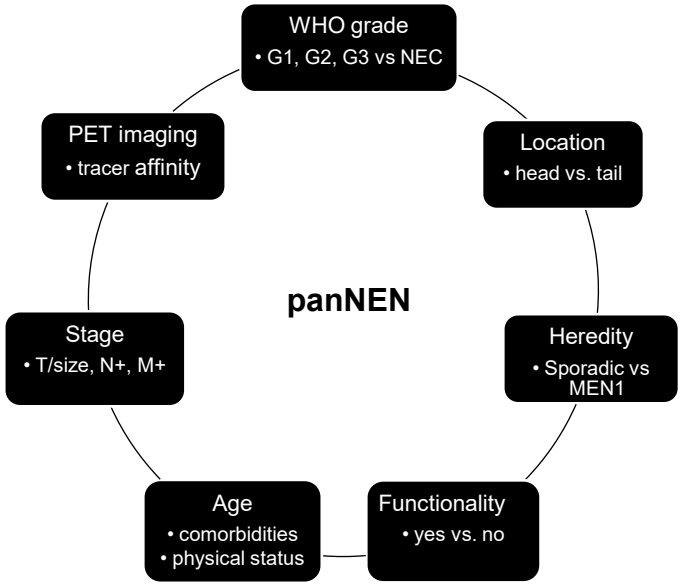


Figure 6. The factors to assess during a diagnostic workup of panNENs before treatment stratification. T; tumor, N+, lymph node metastases; M+, distant metastases.

2.3 Treatment

2.3.1 Surgery

Surgery is a treatment of choice for local or locoregional panNENs (Falconi et al., 2016; Kulke et al., 2010; Partelli et al., 2017) but is not an option in treatment of pancreatic NECs. Surgical management is indicated for NF tumors >2 cm in size (Falconi et al., 2016). Since panNENs usually are local tumors, invasion to the adjacent structures or nearby vessels usually is not a restrictive factor to perform radical surgery. In cases of functional panNEN, surgery is recommended for all operable patients, and clinical symptoms should be controlled prior to intervention (Pavel et al., 2020). Since induction of general anesthesia as well as manipulation of the tumor can provoke life-threatening carcinoid crisis, it is recommended to threat the patient with continuous intravenious octreotide intraoperatively (50ug per hour). If a carcinoid crisis occurs it is essential to avoid adrenergic drugs to treat the hypotension as they may exacerbate the crisis (Kaltsas et al., 2017). In a meta-analysis, mortality of 1.7% and morbidity of 26% after pancreatic surgery were reported (Kokkinakis et al., 2022). Due to the high morbidity and mortality of surgical treatment, the performance status of the patient should be taken into account while planning therapy. The most significant complications include clinically relevant postoperative pancreatic fistula (POPF)(8–13%), haemorrhage (3–7%),

delayed gastric emptying (10–57%), and endocrine and exocrine insufficiency (12–33% in pancreatic resections) (Degisors et al., 2022; Goh et al., 2008; Kim et al., 2025; Moore et al., 2021; Thomas et al., 2022; Wellner et al., 2014; Welsch et al., 2021; Wente et al., 2007).

Surgery may be concidered for metastatic panNENs, as these tumors progress relatively slowly and the liver is often the sole site of the metastases. In cytoreductive surgery, also known as debulking, the aim is to reduce tumor volume in the body. According to several studies, achieving >70% cytoreduction improves PFS and overall survival (OS), as well as reduces clinical symptoms in panNEN patients (Howe et al., 2020; Morgan et al., 2018). However, cytoreduction is not curative, and disease progression is inevitable over time. In a study in which cytoreduction was combined with heated intraperitoneal chemotherapy, worse OS was associated with older age, greater size and number of lesions, a higher Ki-67 PI, and extrahepatic metastases (Gudmundsdottir et al., 2023). Liver transplantation provides a survival benefit compared to liver resection and may be considered in appropriately selected cases (Eshmuminov et al., 2023). Furthermore, resection of primary tumor and synchronous hepatic metastases can be performed safely, simultaneously for selected patients at large tertiary care centers (Addeo et al., 2022; Birnbaum et al., 2015).

In several retrospective studies, a palliative primary tumor resection prolonged the survival of panNEN patients (Huttner et al., 2015; Zhou et al., 2018), and may be considered in selected cases for G1–G2 panNENs, when extra-abdominal disease is ruled out (Partelli et al., 2017). However, the role of palliative primary tumor resection is controversial, due to the lack of prospective, randomized studies (Howe et al., 2020).

2.3.1.1 Resection

Surgical options for approach to panNEN resection depends on tumor size, anatomical location, and proximity to the pancreatic duct. These aspects guide the surgeon in approaching the tumor with pancreaticoduodenectomy (PD), left pancreatectomy with or without splenectomy, or total pancreatectomy. These procedures include regional lymph node dissection. Procedures can be performed using an open, laparoscopic, or robotic approach. Whipple was the first to describe the technique of PD for removing a panNEN located in the pancreatic head (Whipple, 1945). The operation includes resection of the pancreatic head, the distal stomach, the duodenum, the common bile duct, and the gall bladder. Left pancreatectomy is performed for tumors localized at the tail or body of the pancreas.

Laparoscopic technique is one of the most significant surgical development of a present modern medical era. However, laparoscopic pancreatic surgery has some

challenges compared to laparoscopic surgery of some other abdominal organs: location on the retroperitoneum, proximity to great vessels and other critical structures and tissue fragility. Since left pancreatectomy does not require any reconstruction, it is seen as the most suitable resection performed using a minimally invasive approach (Fernandez-Cruz et al., 2008). Laparoscopic left pancreatectomy is safe and associated with even less overall morbidity (less hemorrhage, splenic preservation) and faster recovery compared with an open technique (Hu et al., 2011; Jin et al., 2012; Konukiewitz et al., 2017; Kooby et al., 2008; Venkat et al., 2012; Xie et al., 2012). Despite preconception, similar oncologic resections can be accomplished by mini-invasive surgery in terms of lymph node dissection and resection margins, although larger reports of long-term survival are lacking (Daouadi et al., 2013; Fernandez-Cruz et al., 2007; Jayaraman et al., 2010; Zureikat et al., 2013).

2.3.1.2 Enucleation

Enucleation (EN) is a pancreatic parenchyma-preserving procedure in which only the tumor is removed, without formal pancreatic dissection. A central pancreatectomy is an optional procedure for treatment of benign, central tumors (Paiella et al., 2019), but due to high complication rate it is not commonly used. A frozen section of the tumor may be performed intraoperatively to confirm the benign character of the lesion. EN may be considered in a case of small local panNEN, especially in a case of benign insulinoma (Crippa et al., 2007; Falconi et al., 2016). To perform EN safely, panNEN should be on the anterior surface of the pancreas, with a diameter less than 4 cm and at least 2–3 mm away from the main pancreatic duct. En offers several advantages over standard resections, including reduced operative time and blood loss, preservation of normal pancreatic parenchyma and function, and short hospitalization (Beane et al., 2021). Parenchyma-sparing EN is recommended for patients with MEN1, due to the high likelihood of developing multiple panNENs over their lifetime (Partelli et al., 2017). The oncological safety of pancreatic-sparing operations of NF-panNENs has been confirmed in a large multicentre study of NF-panNENs < 3 cm in diameter (Bolm et al., 2022). In addition, the parenchyma- and lymph node-sparing resection were associated with less blood loss and shorter operative times. Laparoscopic or robotic approach is nowadays commonly used and feasible (Dedieu et al., 2011; Sweet et al., 2007; Tian et al., 2016; J. Xu et al., 2021). Preoperative localization of the tumor using modern imaging studies plays a major role in surgical planning. Intraoperative ultrasound may also be useful in identifying the lesion site and proximity to the main pancreatic duct.

The leading clinical problem of enucleation is ISGPS type B POPF (21%) requiring prolonged (> 3 weeks) percutaneus drainage or angiographic procedure (Bassi et al., 2017; Heeger et al., 2014). POPF can result in serious complications

such as abscess, sepsis, pseudoanerysm, and haemorrhage (Pedrazzoli, 2017). Enucleation of pancreatic tumor locating ≤ 2 mm from the main pancreatic duct is a risk factor for POPF (Brient et al., 2012). A POPF rate as high as 71% was reported when the distance between the tumor and the main pancreatic duct was ≤2 mm, but risk may be reduced by preoperative pancreatic duct stenting (POPF of the stented vs the non-stented group: 37.5% vs 71.4%, p = 0.028) (Q. Xu et al., 2021).

2.3.2 Endoscopic Ultrasound-guided Radiofrequency Ablation

Pancreatic surgery is associated with substantial morbidity and even mortality particularly in older patients with pre-existing comorbidities. Radiofrequency ablation (RFA) is a technique that induces tumor mass thermal necrosis of tumors tissue and has been used for years to treat the solid malignancies, both percutaneously and intraoperatively. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) is a novel, minimally invasive therapy for small (<3 cm) F-panNENs (especially insulinomas) and NF-panNENs and has been described to have high efficacy and low adverse events (Armellini et al., 2023; Oleinikov et al., 2019). During procedure, a RFA needle with high-frequency altering current is inserted into the target tissue under EUS guidance. Maintaining a distance of at least 2 cm away from the pancreatic and bile ducts is crucial to avoid damage to these structures (Figure 7). EUS-RFA is capable of reaching tumors at all regions within the pancreas. This is of particular importance in tumors of the pancreatic head where PD is surgical resection of choice. In a systematic review, including 61 patients and 73 tumors from 12 studies, the overall effectiveness of EUS-RFA was 96% (range 75–100%) on a mean follow-up period of 11 months (range 1–34 months) (Imperatore et al., 2020). Larger tumor size was associated with treatment failure (21.8 ±4.71 mm in the non-response group vs. 15.07 ±7.34 mm in the response group), with a cut-off value of 18 mm, whereas tumor location was not predictive of response to EUS-RFA. EUS-RFA seems to be a safe treatment option. In study of pancreatic insulinomas, EUS-RFA was found safer than surgical resection and seemed also effective (Crino, Napoleon, et al., 2023). In a recent systematic review and meta-analysis, the pooled overall adverse event rates were 17.8% (95% CI 9.1–26.4%) for F-panNENs and 24.6% (95% CI 7.4–41.8%) for NF-panNENs (Armellini et al., 2023). Overall mild adverse events were observed in 21/142 (14.7%) patients; moderate/severe adverse events on only one patient (0.7%). The recent ENETS guidelines update recommends surgery as a first-line treatment for insulinomas but indicates that EUS-RFA may be considered for insulinomas <2 cm in patients deemed unfit for surgery (Hofland et al., 2023). The lack of large, prospective studies with adequate follow-up limits the widespread use of this promising interventional

technique. There is an international, randomized multicenter study in progress, which may provide further approval for EUS-RFA in patients with panNEN, especially insulinoma (Crino, Partelli, et al., 2023).

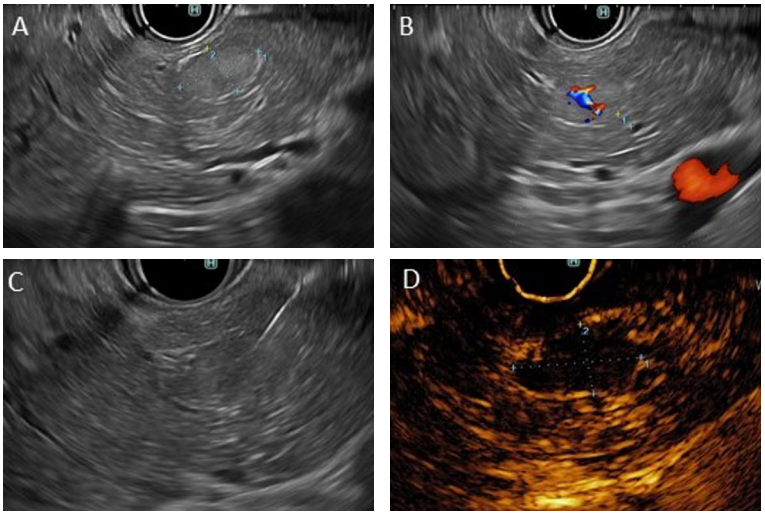


Figure 7. Radiofrequency ablation (RFA) of an insulinoma measuring 13 x 8 mm using endoscopic ultrasonography (Hitachi) (**A**). Doppler imaging demonstrated hypervascularity with a distance of 2.8 mm from the main pancreatic duct (**B**). The RFA needle inside the tumor (**C**). Following ablation, the tumor tissue appeared avascular when visualized using the SonoVue® contrast agent (**D**). Images on courtesy of Hannes Kortekangas, Abdominal Centre, Turku University Hospital, 2021.

2.3.3 Medical Therapy

2.3.3.1 Somatostatin Analogs

Somatostatin is a cyclic peptide hormone that occurs naturally in two isoforms, composed of 14 and 28 amino acids, respectively (Reichlin, 1983). It is broadly distributed across various human tissues, including the central nervous system, pancreas, and gastrointestinal tract. It is recognized as a universal endocrine inhibitor due to its suppressive effect on paracrine, exocrine, and endocrine tissues. Somatostatin has an extremely short half-life of approximately 3 min. The development of long-acting somatostatin analogs, such as octreotide and lanreotide, has enabled their pharmacological application in disease management (Bauer et al., 1982).

Somatostatin analogs (SSAs) have significantly influenced the treatment of NENs and are most typically used in cases of inoperable, advanced disease. They were initially developed to control symptoms of carcinoid syndrome by inhibiting

the release of neuropeptides (Kvols et al., 1986). Afterwards, the antisecretory effect was proved in many series (O'Toole et al., 2000). They also control hormonal symptoms caused by F-panNENs.

There is strong evidence to support that somatostatin analogs have antiproliferative effect and can inhibit the growth of NENs (Ducreux et al., 2000; Strosberg & Kvols, 2010). Effects to better survival has been shown by two randomized, double-blind, placebo-controlled studies: in a PROMID study (n=85), octreotide LAR significantly lengthened time-to-tumor progression (14.3 months within octreotide group and 6.0 months in placebo group) in patients with metastatic well-differentiated midgut NENs, and in the CLARINET study, lanreotide prolonged PFS in patients with G1 and selected G2 NENs (hazard ratio for progression of death 0.47, 95% CI 0.30–0.73) (Caplin et al., 2014; Rinke et al., 2009). However, the medical therapy of panNEN can be seen as palliative treatment. In several studies, objective antitumoral responses tends to appear quite modest (4-7%), while ability to perform disease stabilization is better (55–81%)(Ducreux et al., 2000; Wymenga et al., 1999).

Conventional SSAs, octreotide and lanreotide, bind to SSTR2. Pasireotide (SOM230), the most recently developed SSA, binds with high affinity to four of five SSTR subtypes. Compared with octreotide, pasireotide exhibits 40, 30, and five times more binding to SSTR5, SSTR1, and SSTR3, but demonstrates 2.5 times less affinity to SSTR2 (Bruns et al., 2002; Hofland et al., 2005). Despite the promising preclinical data (Mohamed et al., 2014; Quinn et al., 2012) and studies supporting its antisecretory (Kvols et al., 2012) and antiproliferative effect (Wolin et al., 2013), pasireotide has not been able to provide highly superior SSA effect for treatment of NENs (Ferolla et al., 2017; Kulke et al., 2017). In addition to the common side effects of SSAs, such as abdominal pain, nausea, and diarrhea, an increased incidence of hyperglycemia has been reported with pasireotide use (Wolin et al., 2013). However, pasireotide may be beneficial in NETs exhibiting a specific SSTR profile, as well as in selected cases of insulinoma.

2.3.3.2 Chemotherapy

The use of chemotherapy in management of panNENs has decreased after development of other systemic therapies such as SSAs, everolimus and sunitinib. There is no placebo-controlled data supporting the benefit of chemotherapy over supportive care in NENs. There are a few randomized studies comparing the effect of different chemotherapy agents but no significant difference in PFS (Engstrom et al., 1984; Meyer et al., 2014; Moertel & Hanley, 1979; Moertel et al., 1980) and minimal effect on OS (advantage for combining streptozocin and doxorubicin compared with streptozocin and 5-FU)(Moertel et al., 1992; Sun et al., 2005) has been reported.

Variable and unspecific grading in history and trials made with highly heterogenic population of different NENs makes research results highly uncertain. However, chemotherapy is the first-line treatment of choice in high-grade NENs, especially in pancreatic NECs. Platinum-based doublets (cisplatin or carboplatin combined to e.g. etoposide, docetaxel or gemcitabine) are the standard of care for NECs, but also streptozocin, temozolomide, capecitabine and some combinations has been used. A orally administered first-line combination of capesitabine and temozolomide (CAPTEM), demonstrated a response rate of 70% in panNEN patients and median PFS of 18 months (Strosberg et al., 2011). Some studies have reported that higher Ki-67 (cutoffs 60% and 55%, respectively) might predict for increased response rates to platinum and etoposide chemotherapy drugs (H. K. Kim et al., 2017; Sorbye et al., 2013). A large retrospective study on G3 GEP-NENs, the Nordic NEC trial, reported a low response rate of platinum-based chemotherapy in patients with Ki-67 PI <55 % compared to patients with Ki-67 PI exceeding 55 % (42%, $p < 0.01$), but regardless of that, the overall prognosis of patients with lower Ki-67 was better (Sorbye et al., 2013). Further, Rb loss and KRAS mutation may serve as predictors for platinum-based chemotherapy. O6-methylguanine-DNA methyltranferase (MGMT), an enzyme involved in DNA repair, may serve as a predictive marker for response to temozolomide-based chemotherapy in panNENs (Perren et al., 2017). However, a subsequent trial of 143 patients with advanced panNENs showed no correlation between MGMT methylation and treatment response (Hijioka et al., 2017).

In treatment of panNEN, to differentiate G3 panNETs from panNECs by means of immunohistochemistry (p53, Rb and Ki-67) is mandatory to make the right decision for treatment. According to ENETs guidelines, the efficacy of chemotherapy in G3 NEN is presently uncertain (Garcia-Carbonero et al., 2016). However, due to poor prognosis (median survival of 24 months) of localized G3 GEP-NENs (Walter et al., 2017), adjuvant treatment after surgery with a platinum/etoposide regimen is recommended (Strosberg et al., 2010).

2.3.3.3 Other Medical Therapy

SSAs revolutionized the management of panNENs at the time. During recent decades, novel targeted drugs, everolimus and sunitinib, have been introduced in the treatment of panNENs. Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR), a key component of tumorigenesis, and is registered in treatment for advanced panNEN. RADIANT3 study, a placebo controlled, randomized phase III trial, demonstrated the median PFS of 11.0 months with everolimus compared with 4.6 months in placebo group among patients with advanced, well or moderately differentiated panNENs (HR for progression or death 0.35; 95% CI: 0.27 – 0.45, $p < 0.001$) (Yao, Shah, et al., 2011).

Sunitinib is an oral multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, KIT (CD117) and RET (Rearranged during Transfection). It is used for well-differentiated panNEN patients with progressive, unresectable, metastatic, and locally advanced disease based on a randomized, placebo-controlled trial, with median PFS was 11.4 months in the research group and 5.5 in the placebo group (HR for progression of death, 0.42 95% CI: 0.26–0.66, $p < 0.001$) (Zhou et al., 2010).

Interferon, IFN-a2b is registered in Europe for the treatment of NENs associated with carcinoid syndrome. It may also be used for F-panNENs to treat symptoms related to hypersecretion of hormones and neuropeptides. Generally, it can be used as an add-on therapy to SSA in a case of refractory carcinoid syndrome or if SSAs are not preferred due to an unsuitable SSTR profile or are not tolerated (Pavel et al., 2017). However, the limited availability of interferon currently restricts its clinical use.

New tyrosine kinase inhibitor represents a novel treatment option for progressive panNENs. In 2025, the FDA approved cabozantinib for advanced panNETs. The CABINET trial demonstrated a median PFS increase of 13.8 months with cabozantinib, compared to 4.4 months with placebo in patients who have previously been treated with PRRT or targeted therapy or both (Chan et al., 2025).

2.3.4 Peptide Receptor Radionuclide Therapy

The high-level expression of SSTRs on the cell surface of NENs provides potential not only for functional imaging but also for tumor-targeted therapy with traditional pharmacological SSAs, as well as radioisotope-labeled SSAs. Peptide receptor radionuclide therapy (PRRT) is indicated in the treatment of patients with inoperable or metastasized, well-differentiated G1 and G2 NENs and during progression of disease during SSA treatment. Two peptides, ^{90}Yttrium(Y)-DOTA^{0}-TYR^{3}-octreotide ([^{90}Y]-DOTATOC) and [^{177}Lutetium(Lu)]-DOTATATE are currently in clinical use, with preference given to the latter due to its lower renal toxicity. High response rates, PFS of 16–36 months and OS of 22–55 months, have been reported by several retrospective studies (Bodei et al., 2011; Bushnell et al., 2010; Cwikla et al., 2010; Ezziddin et al., 2014; Kwekkeboom et al., 2008; Valkema et al., 2006). The first prospective, phase III randomized NETTER-1 trial in 230 patients with progressive inoperable metastatic midgut NENs, showed superior median PFS of 28.4 months after PRRT with ^{177}Lu-DOTATATE plus supportive SSA compared to high-dose SSA (60mg octreotide LAR every 4 weeks), with a median PFS of 8.4 months (HR 0.21; 95% CI, 0.14-0.33, $p < 0.0001$) (Strosberg et al., 2017). However, ^{177}Lu-DOTATATE did not significantly improve final median OS when compared to high-dose octreotide (Strosberg et al., 2021). High patient performance, high uptake on

pre-treatment SSA-imaging, and low hepatic tumor burden (<25%) predicts favourable treatment outcome (Ezziddin et al., 2014; O. N. Y. Lee et al., 2022). Usually, two to five cycles are provided every 6–12 weeks and, in most cases, treatment can be repeated. According to ENETS guidelines, PRRT may be used as a second-line therapy for G1–G2 NF-panNENs with a positive SSA-PET/CT after failure of SSA, everolimus and/or cytotoxic chemotherapy (Pavel et al., 2016). In a recent NETTER-2 study, [^{177}Lu]-DOTATATE plus octreotide 30mg LAR showed a significant PFS benefit compared to high-dose octreotide 60 mg LAR among well-differentiated, high-grade (G2–G3) GEP-NENs (Singh et al., 2024). In the NEOLUPANET study of 31 panNEN patients, [^{177}Lu]-DOTATATE neoadjuvant treatment before curative surgery was safe but the additional benefit of neoadjuvant PRRT is under research (Partelli, Landoni, et al., 2024).

2.3.5 Surveillance

Although all panNENs possess malignant potential, active surveillance has emerged as a viable management option in selected cases. Recent studies suggest that patients with NF-panNEN ≤2 cm without local invasion or distant metastases do not benefit from surgery (Ye et al., 2022), and active surveillance of small incidental NF-panNENs represents a potential alternative to resection (Ricci et al., 2022). Several retrospective studies with a follow-up under 5 years have demonstrated that active surveillance did not increase the disease-related mortality when compared to initial surgical resection (Barenboim et al., 2020; Gaujoux et al., 2013; Lee et al., 2012; Sadot et al., 2016). However, in one study, patients who underwent surgery showed significantly better 10-year survival compared with those under surveillance (82.6% vs 53.7%, $p < 0.001$). Notably, the survival benefit was no longer significant for tumors <1.5 cm ($p = 0.317$ or higher for smaller lesions) (Zhang et al., 2016). The ENETS guidelines recommend observation for lesions no larger than 2 cm. In a retrospective study of 3261 patients with panNENs ≤2 cm from the Surveillance Epidemiology and End Results (SEER) registry, regional invasion was observed in 10% and distant metastases in 9% of patients, and surgery was associated with improved survival regardless of disease stage (Mei et al., 2023). Some prospective studies have confirmed the safety of watchful waiting of small, <2 cm NF-panNENs (Heidsma et al., 2021; Partelli, Massironi, et al., 2022), but additional data with follow-up extending beyond 10 years are necessary to fully confirm the safety of the surveillance treatment strategy.

Postoperative surveillance is also necessary. The North American Neuroendocrine Cancer Tumor Society (NANETS) recommends cross-sectional imaging every 3–6 months following resection, and then every 6–12 months in the subsequent years (Kulke et al., 2010). ENETS recommends surveillance—including

measurement of biochemical markers and conventional imaging—every 3–9 months for patients with operated G1 and G2 tumors (Falconi et al., 2016). Several studies have been conducted to reduce healthcare costs and minimize patients' exposure to radiation. Zaidi et al. recommend surveillance intervals of 12, 6 and 3 months for patients at low, intermediate, and high risk of recurrence, respectively (Zaidi et al., 2019). In their cohort of 1 006 patients with panNENs, the factors associated with poor prognosis and higher risk scores included symptomatic tumors (jaundice, pain, bleeding), tumor size ≥ 2 cm, Ki67 PI > 3%, and lymph node involvement. Another group reported that G2 grade (compared with G1), lymph node metastases, and perineural invasion were the most important factors for recurrence scoring system (Genc et al., 2018).

2.4 Prognosis of panNEN patients

Assessment of prognosis and prediction of tumor aggressiveness is the main goal of diagnostic workup and serves as the foundation for subsequent treatment strategy. PanNENs carry the most unfavorable prognosis compared to other primary sites of NEN, but a significant rise in survival rates has been observed over time (Dasari et al., 2017). However, both potential overtreatment and undertreatment have also been recognized (Partelli, Battistella, et al., 2024). Therefore, it is essential individually to assess the aggressiveness of the tumor before making treatment decisions.

2.4.1 Histopathology

Differentation. All panNENs have malignant potential. However, there are several features to predict the aggressive nature of panNENs. Firstly, panNETs and PDNECs have very different prognoses and are currently agreed to be two entirely independent categories, with different origins and biology (Yachida et al., 2012). PanNENs are usually slow-growing with a heterogeneous potential to send metastases, but are often curable and progress slowly. Instead, PDNECS are very aggressive malignancies, with even worse prognosis than ductal adenocarcinomas, with a median survival of only 11 months (Basturk et al., 2014). Patients with small-cell(SC)-NEC have worse survival than those with large-cell(LC)-NECs (9 vs. 12 months, $p = 0.025$) (Venizelos et al., 2021).

TNM-stage. In addition to WHO grading, the ENETS and 8th edition of the AJCC staging systems are the most important tools for predicting prognosis of panNENs (Deng et al., 2018; Rindi et al., 2012). However, these have systems have prognostic limitations, and some modifications have been proposed. Modified ENETs system provided better prognostication by diverse resultant survival curves than ENETs and 7th edition of AJCC. However, the recent 8th edition of AJCC staging system also

provides good prognostic stratification for panNENs (Li et al., 2018) and appears to be more suitable for staging these tumors than the ENETS, mENETS, or 7th edition of AJCC (Wang et al., 2022) among G1 and G2 panNEN patients. The 5-year survival rates based on AJCC stage are: stage I, 93.0%; stage II, 92%; stage III, 85.2% and stage IV, 54%, respectively (Chauhan et al., 2024). Lately, the 9th edition of AJCC has not served any changes in the T, N, or M categories of panNENs.

Grade. The WHO grade is likely the most well-known prognostic factor in patients with GEP-NENs: the higher the grade, the shorter the survival time (Nunez-Valdovinos et al., 2018). The five-year survival rates for G1, G2, and G3 GEP-NENs are 75%, 62%, and 7%, respectively (Cives & Strosberg, 2018). However, the cutoff values used to define the grades remain controversial and are the subject of ongoing debate. Ki-67 PI threshold of 5% has been proposed to distinguish G1 from G2 (Rindi et al., 2012; Scarpa et al., 2010). In a systematic meta-analysis of 4651 GEP-NEN patients, no difference in five-year survival was observed between the group with a Ki-67 cut-off value of <3% for G1 tumors and the group with a cutoff of ≤2%, an modification introduced in the 2017 update of the WHO classification criteria for panNENs (Scoazec et al., 2017; Tao et al., 2023). Moreover, Wang et al. developed a "TNMG" staging that incorporates both 8th edition of TNM staging and WHO grading, demonstrating greater accuracy predicting prognosis than either TNM stage or WHO grade alone (Wang et al., 2021). Moreover, TGM stating in which N stage was replaced by grade/differentiation was predictive for PanNENs OS (Yang et al., 2016).

Size of the tumor. More than 20% of panNENs are less than 2 cm in size (Kuo & Salem, 2013). These smaller tumors are associated with a less aggressive clinical behaviour compared to larger lesions (Bettini et al., 2011). The size of tumor is the most important prognostic factor of the T category in TNM-staging. Larger tumor size is a linear indicator of poorer survival outcomes (Perinel et al., 2022). The ENETS guidelines recommends surgical management for NF-panNENs >2 cm in size. Surveillance strategy is widely accepted but still controversial in cases of panNENs smaller than 2 cm in diameter (Sallinen et al., 2017). In this systematic review and meta-analysis, tumor growth was observed in 22% in sporadic panNEN cases and 52% in MEN1-associated patients, while distant metastases developed in 0% of sporadic and 9 % of MEN1 panNEN patients. Various tumor cutoff values have been proposed for predicting clinical outcomes, including thresholds of 2.5 cm, 1 cm, and 1,7 cm, (Partelli, Battistella, et al., 2024; Perinel et al., 2022; Regenet et al., 2016). Guidelines recommend that for tumors smaller than 2 cm, surveillance may be a reasonable management strategy, as the likelihood of metastases is low. In one of the first prospective surveillance studies of small panNENs, Ganjoux et al. monitored 46 patients with serial imaging, and after follow-up of 34 months, 17% of patients underwent resection (Gaujoux et al., 2013). However, none of the patients developed nodal or distant metastasis, and no difference in survival outcome was noted between the surgery group and the non-operative group.

Further, in the prospective ASPEN trial involving 500 patients with NF-panNEN ≤2 cm in size (94 in the surgical group and 406 in the surveillance group), the authors suggested that surveillance appeared safe, since only four patients (1%) experienced tumor growth, three (<1%) developed dilation of the main pancreatic duct, and none developed distant metastases during a median follow-up of 25 months (Partelli, Massironi, et al., 2022). Prospective, nationwide PANDORA study reported similar findings, with a progression rate of 11%—defined as tumor growth exceeding 0.5 cm per year—of which only one patient (1.3%) developed metastases detected during surgery (Heidsma et al., 2021). On the contrary, operated patients had significant survival benefit, both overall survival (OS) and recurrence-free survival (RFS), compared to patients treated with observation in a study of 3261 panNENs ≤ 2 cm in size ($p < 0.0001$) (Mei et al., 2023). The widely accepted 2 cm cutoff to identify aggressive disease has also been questioned by a study reporting better five-year survival in the surgical group compared to the observational group among patients with 1–2 cm panNENs (Chivukula et al., 2020). However, the latter two studies are retrospective registry-based analyses with inherent selection bias and did not exclude patients with aggressive features, such as a Ki-67 PI >20%, main duct dilation, or symptoms—factors typically considered in clinical management of panNEN patients.

In contrast, three other studies reported metastasis rates of 8%, 17% and 17% for patients with small panNENs (Haynes et al., 2011; Lombardi et al., 2015; Sallinen et al., 2018). In the analysis of the SEER database, distant metastasis rate of small tumors was 9% (Sonbol et al., 2022). In a study of Assi et al., the five-year survival rate of 1–2cm panNEN patients was 92% in the operated group (n = 890) and 70% in the surveillance group (n = 124) (Assi et al., 2020). The optimal cutoff remains a subject of debate as different studies vary in their associations between tumor size and survival outcomes. Assessment of tumor aggressiveness should incorporate not only tumor size but also additional indicators of aggressive behaviour.

Lymph nodes. In addition to grade, lymph node metastases and distant metastases are the most important factors predicting prognosis of panNENs (Curran et al., 2015; Partelli et al., 2013). Both, the ENETS staging system and the 8th edition of AJCC staging categorize panNENs into two stages according to N status: N0: no metastases or N1: one or more metastatic lymph nodes. The 7th edition of AJCC staging was updated to correspond with the ENETS system for NENs and has higher predictive ability in well-differentiated panNENs than the three-category system used in case of panNECs and pancreatic carcinomas (Rindi et al., 2012; Rindi et al., 2006). However, several novel reports are revealing that three-category staging (0/1–3/>4 lymph node metastases (LNM) or 0/1–2/≥3 LNM) could serve better discriminatory capacity than the two-category system to predict survival of panNENs (Gao et al., 2021; Luo, Jin, et al., 2017; Partelli et al., 2018; Zhang et al., 2021). Furthermore, sufficient regional lymphadenectomy of at least eight lymph

nodes improves prognostic accuracy (Zhang et al., 2021). Nodal staging schemes that take both the number of LNM and the number of examined lymph nodes into consideration have been developed (lymph node ratio, LNR, and log odds of positive lymph nodes, LODDS). LNR was an independent prognostic factor for survival, but the currently used PLN staging was more reliable than LNR or LODDS (Gaitanidis et al., 2018; Gao et al., 2021). Prognostic significance of lymph node status is more significant among T1–2 patients than among T3–T4 patients (Xu et al., 2018).

Distant metastasis. The most typical metastatic sites of GEP-NENs are liver, lungs, and bone (Zheng et al., 2019). The extent of liver metastasis (unilobar vs. bilobar) and the presence of extra-abdominal metastasis are significant prognostic factors independent of tumor grade; patients with unilobar metastases show better survival than those with extra-abdominal disease (Panzuto et al., 2014). However, the metastatic target organ is considered only in the 8th edition of the AJCC staging system. Survival of panNEN patients with liver metastases has improved over the past three decades, partly due to the introduction of multimodal therapies; however, unresected primary tumors remain linked to worse outcomes (Frilling et al., 2024).

Infiltrative growth pattern to pancreatic parenchyma is associated with a poorer OS compared to a non-infiltrative growth (Chatterjee et al., 2020). Infiltration pattern predicts survival also among small <2 cm tumors (Taskin et al., 2022). A study by Shiavo Lena et al. reported that invasion to adjacent organ and/or major vessels was the most powerful and more reliable predictor of recurrence than grade at multivariate analysis (Schiavo Lena et al., 2023). The prognostic significance of vascular invasion and lymphatic invasion has been reported by another study (Mizumoto et al., 2017). Currently, invasion of the pancreatic parenchyma and invasion into the great veins are not included in the AJCC or ENETS staging protocols. Furthermore, bile duct involvement is identified as a high-risk factor, further supporting the need for surgical intervention (Nanno et al., 2017).

Necrosis is a sign of more rapid growing and is actually one of the diagnostic characteristics of PCNECs. Necrosis has been reported as a marker for poor prognosis in panNENs (Demir et al., 2011; Han et al., 2014). However, the lack of a novel study cohort with reliable exclusion of PDNECs makes it difficult to assess the true impact of necrosis on the prognosis of PanNETs.

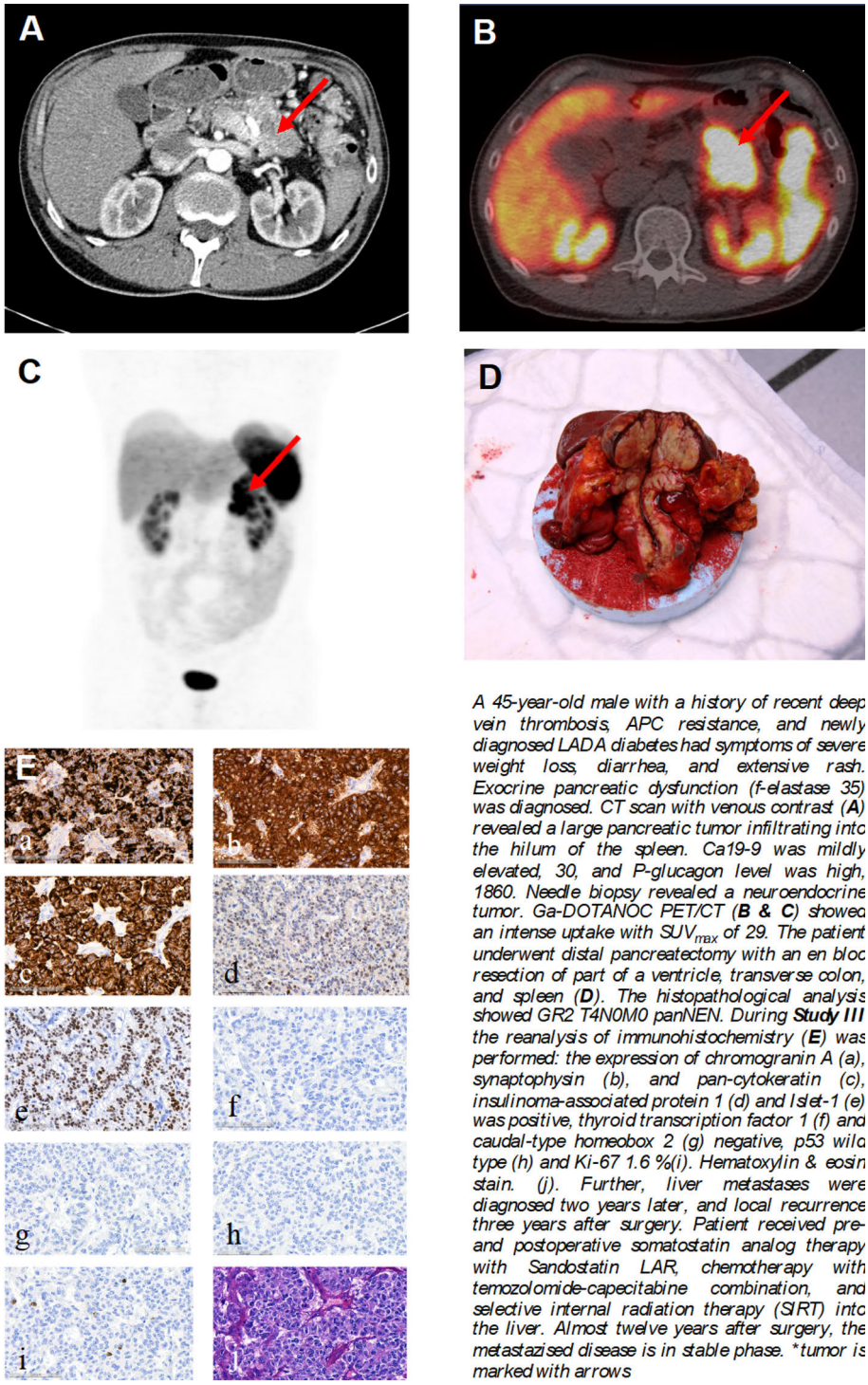
Functionality: Insulinomas have a better prognosis than NF-panNENs and other functional panNENs. However, there are controversial reports of the prognosis of other functional tumors vs. NF-panNENs (Gao et al., 2019; Mei et al., 2023). Glucagonomas typically are slow-growing tumors diagnosed in an advanced stage with a mean survival of 3–7 years (Chastain, 2001). A patient case with glucagonoma in Study III is presented in Figure 8.

Nomograms and risk models. Several study groups have developed scoring systems and nomograms to predict post-operative outcomes for panNEN patients.

For instance, Bilimoria et al. established a prognostic score based on age, grade, distant metastases, tumor functionality, and type of resection in a study of 3851 resected panNENs (Bilimoria et al., 2008). Zaidi et al. validated a recurrence risk score to guide surveillance of 1 006 surgically treated panNEN patients (Zaidi et al., 2019). Another study group developed a nomogram incorporating tumor diameter, number of positive lymph nodes, Ki-67 PI, and vascular and perineural invasion data from 632 G1/G2 panNEN patients (Pulvirenti et al., 2021). In study of 211 NF-panNENs, Genc et al. found that tumor grade 2, node-positive disease, and perineural invasion predicted recurrence (Genc et al., 2018). However, these risk scores and nomograms can be challenging to use in clinical practice. Furthermore, none of these have been incorporated into current treatment guidelines. A systematic review suggests that the absence of prospective studies may be the reason for this exclusion, and recommends the development of an online prediction model calculator to assess the postoperative prognosis of NF-panNEN patients (Chen et al., 2023).

IHC biomarkers and gene mutations. Novel histopathological implementations may help determine whether continued surveillance or surgical management is appropriate with patients with small (<2 cm) asymptomatic panNENs. Several studies have demonstrated that loss of genomic DAXX/ATRX and the presence of alternative lengthening of telomeres (ALT) are associated with poor survival and distant metastases on follow-up of operated patients (Hackeng et al., 2022; J. Y. Kim et al., 2017; Neyaz et al., 2023; Singhi et al., 2017). DAXX/ATRX status can be assessed by immunohistochemistry, while activation of ALT can be determined using specific FISH analysis, which reveals long and heterogeneous telomeres with characteristic subnuclear formations. These results have been confirmed in the preoperative setting, by EUS-FNA, in studies accomplished by paired preoperative and postoperative samples (Singh et al., 2021; VandenBussche et al., 2017). Hackeng et al. also showed that loss of ATRX/DAXX and presence of ALT were not present in other GEP-NENs than panNENs, which represents the finding that these genetic alterations may be the key to panNEN pathogenesis (Hackeng et al., 2022). In the future, it is possible to incorporate this sort of prognostic preoperative tissue analysis into the clinical evaluation of panNEN patients. The landmark studies considering diagnosis and treatment panNENs are illustrated in Table 4.

Immunohistochemistry may serve as a tool to evaluate therapy responses (Hijioka et al., 2017). For instance, MGMT (O6-methylguanin-DNA methyltransferase) expression may serve as a predictive marker of a response to temozolomide-based chemotherapy in panNEN (Perren et al., 2017). Several studies show that MGMT-deficient patients have higher response rates on alkylating-agent chemotherapy (temozolomide) and longer PFS compared to MGMT-proficient NET patients (Kunz et al., 2023; Walter et al., 2025).



*A 45-year-old male with a history of recent deep vein thrombosis, APC resistance, and newly diagnosed LADA diabetes had symptoms of severe weight loss, diarrhea, and extensive rash. Exocrine pancreatic dysfunction (f-elastase 35) was diagnosed. CT scan with venous contrast (**A**) revealed a large pancreatic tumor infiltrating into the hilum of the spleen. Ca19-9 was mildly elevated, 30, and P-glucagon level was high, 1860. Needle biopsy revealed a neuroendocrine tumor. Ga-DOTANOC PET/CT (**B & C**) showed an intense uptake with SUV_{max} of 29. The patient underwent distal pancreatectomy with an en bloc resection of part of a ventricle, transverse colon, and spleen (**D**). The histopathological analysis showed GR2 T4N0M0 panNEN. During **Study III** the reanalysis of immunohistochemistry (**E**) was performed: the expression of chromogranin A (a), synaptophysin (b), and pan-cytokeratin (c), insulinoma-associated protein 1 (d) and Islet-1 (e) was positive, thyroid transcription factor 1 (f) and caudal-type homeobox 2 (g) negative, p53 wild type (h) and Ki-67 1.6 %(i). Hematoxylin & eosin stain. (j). Further, liver metastases were diagnosed two years later, and local recurrence three years after surgery. Patient received pre- and postoperative somatostatin analog therapy with Sandostatin LAR, chemotherapy with temozolomide-capecitabine combination, and selective internal radiation therapy (SIRT) into the liver. Almost twelve years after surgery, the metastazised disease is in stable phase. *tumor is marked with arrows*

Figure 8. A case report of a patient in Study III with glucagonoma.

Table 4. Landmark clinical studies (Binderup et al., 2010; Caplin et al., 2014; Chan et al., 2017; Dasari et al., 2017; Hackeng et al., 2022; Heidsma et al., 2021; Partelli, Battistella, et al., 2024; Partelli, Massironi, et al., 2022; Rinke et al., 2009; Strosberg et al., 2021; Zhang et al., 2021).

Study	Primary Result
Rinke, *J Clin Oncol*, 2009	The PROMID study demonstrated the antiproliferative action of SSA, octreotide LAR, in metastatic, well-differentiated, midgut NENs: octreotide LAR lengthened time to progression compared with placebo (14.3 vs. 6 months, p<0.001)
Binderup, *Clin Cancer Res*, 2010	In a prospective study of 98 NEN patients, positive [^{18}F]-FDG PET/CT was associated with a higher risk of death (HR 10.3, 95% CI 1.3–78.9) compared with negative [^{18}F]-FDG PET/CT. In multivariate analysis, [^{18}F]-FDG PET/CT was the only factor predicting survival, exceeding the prognostic value of WHO grade and liver metastases.
Caplin, *N Engl J Med*, 2014	The CLARINET trial proved the antiproliferative action of SSA, lanreotide in advanced, nonfunctional GEP-NENs with Ki67 <10%: lanreotide was associated with prolonged PFS compared with placebo (median not reached vs median 18 months, p<0.001).
Dasari, *JAMA Oncol*, 2017	Epidemiological study of 64,971 NEN patients from the SEER database: A 6.4-fold age-adjusted increase in incidence from 1.1 to 7.0 per 100,000 during 1973 to 2012 was observed across all sites, stages, and grades of NENs. The significant improvement in OS rates for panNENs from 2000–2004 to 2009–2012 was observed (HR, 0.56; 95% CI, 0.44-0.70).
Chan, *Theranostics*, 2017	NETPET grading system with five different groups classified depending on uptake and intensity of [^{18}F]-FDG and [^{68}Ga]Ga-SSA imaging correlated with OS of the 62 metastasized NEN patients
Strosberg, ***N ENGL J MED***, 2017	The NETTER-1 study demonstrated that PRRT treatment with Lutetium was associated with better than octretide in patients with advanced, progressive, somatostatin-receptor-positive midgut NENs
Zhang, *Ann Surg*, 2021	Number of positive nodes is prognostic while panNENs, supporting the use of three categy system (N0-2) in N staging in the future. Sufficient amount (> 8) of lymph nodes evaluated improves the prognostic accurancy.
Hackeng, *Pancreas*, 2021	ATRX/DAXX-negativity and ALT-positivity were associated with worse survival (among NF-panNENs than wild-type NF-panNENS (5-year RFS: 40% vs 85%, p<0.001 and 42% vs 86%, p<0.001). Moreover, ATRX/DAXX loss and ALT-positivity were associated with better survival among panNENs < 2cm in size
Heidsma, ***BJS***, 2021	Prospective, nationwide, multicenter PANDORA study suggested that watchful waiting is both safe and feasible for asymptomatic NF-panNENs. ≤ 2 cm in size (n=76). During median follow-up of 17 months eight patients (11%) showed tumor progression of which one developed metastases and none died due to panNEN. Surveillance strategy successfully prevented surgery in over 90% of patients.
Partelli, ***BJS***, 2022	Prospective, multicenter ASPEN trial suggested that surveillance is safe for NF-panNENs ≤ 2 cm in size (94 in the surgical group and 406 in the surveillance group). In surveillance group, only 4 patients (1%) experienced tumor growth, three (<1%) developed dilation of the main pancreatic duct, and none developed distant metastases during a median follow-up of 25 months.
Partelli, *BJS Open*, 2024	Radiological tumor size <2.5 cm, surgery performed before 2015, and tumor location in the pancreatic tail/body were independent predictors of potential overtreatment, which occurs in one-third of patients receiving surgical treatment. Radiological tumor size <2.5 cm was the only determinant of potential undertreatment occurring in 6 % of patients.

* NEN, neuroendocrine neoplasm; SSA, somatostatin analog; PFS, progression-free survival; SEER, Surveillance, Epidemiology, and End Results; ATRX/DAXX, alpha-thalassemia/mental retardation X-linked/death domain-associated protein; ALT, alternative lengthening of telo.

2.4.2 Imaging

2.4.2.1 Conventional Imaging

Presence of calcifications in the primary tumor on CT scan (which occurs in 16%) correlates positively with the grade and the presence of both lymph node metastasis and synchronous liver metastases in well-differentiated panNENs (Poultsides et al., 2012). Further, the presence of iso- or hypo-attenuating regions in the tumor on the arterial phase of CT is associated with regional lymph node metastases (univariate analysis $p = 0.005$, multivariate analysis $p = 0.032$) (Mizumoto et al., 2017). Dilation of the common bile duct or pancreatic duct predicts aggressiveness of panNENs, also among small NF-panNENs (Sallinen et al., 2018; Shen et al., 2024). In a study of 183 surgically treated panNETs, a poorly defined radiological tumor border in CT scan was an independent prognostic factor predicting both OS and RFS (both $p < 0.001$) (Ahn et al., 2024). Further, distinct MRI features of "nonbright lesion" on T2-weighted MRI images were associated with worse PFS of panNEN patients (Canellas, Lo, et al., 2018).

Stage - Lymph node metastases. The accuracy of preoperative imaging modalities in detecting nodal involvement in NF-panNENs is limited. Sensitivity of any imaging (including CT, MRI, EUS, [^{68}Ga]-SSA-PET, and Octreoscan) to detect LNM preoperatively varies between 6–26 %, and specificity between 95–100%. (Partelli, Muffatti, et al., 2022; Zhang et al., 2023). Although preoperative detection of LNM is challenging, certain imaging features may predict its presence. Sun et al. reported that non-enhancement pattern and main duct dilatation predicted node-positive disease of panNENs at multivariate analysis (Sun et al., 2019).

Stage - Distant metastases. Multiphase contrast-enhanced CT is used as a first-line modality for staging panNENs. CT offers high spatial resolution and is accurate in pulmonary metastases (sensitivity 100%, specificity 82%) (Albanus et al., 2015). However, the accuracy of CT to detect small liver metastases and bone metastases is poor. In the diagnosis of bone metastases, a sensitivity of 47–80% and a specificity of 49–98% have been reported (Albanus et al., 2015; Ambrosini et al., 2010). MRI is particularly invaluable for detecting liver metastases, with a sensitivity of 78–100% and a specificity of 89–100% of a diffusion-weighted MRI (d'Assignies et al., 2013; De Robertis et al., 2016; Giesel et al., 2012). In a recent study of 30 well-differentiated NEN patients, gadoxetic acid-enhanced MRI detected more liver metastases than [^{68}Ga]-DOTATATE PET/CT (Drucker Iarovich et al., 2024). For bone metastases, MRI shows high accuracy, on a regional basis, but a whole-body MRI is not routinely used in panNEN staging.

Radiomics is a field of research that investigates and reports the occurrence of quantitative metrics, so-called radiomic metrics, in medical imaging. Several studies report that texture analysis and radiomic features in CT or MRI may be used for

predicting the tumor grade (Canellas, Burk, et al., 2018; Choi et al., 2018; Ohki et al., 2021). In future these kinds of nomograms and radiomics-based grading could be incorporated with machine learning to produce automated, high-level data from individual scans.

2.4.2.2 Functional Imaging

[^{68}Ga]-*SSA PET/CT* is regarded as the gold standard for diagnosing panNENs. Evidence suggests that higher [^{68}Ga]-SSA uptake is associated with lower grade and improved survival in GEP-NEN patients, although cutoff values vary between studies (Ambrosini et al., 2015; Campana et al., 2010; Kayani et al., 2008; Panagiotidis et al., 2017; Partelli et al., 2014; Sharma et al., 2014). In advanced disease, the tumor burden assessed by [^{68}Ga]-SSA-PET/CT is a strong predictor of survival. In a prospective study of 184 NEN patients, total tumor volume (TTV) measured on [^{68}Ga]-DOTATATE PET/CT correlated inversely with PFS and DSS, a relationship that persisted in the panNEN subgroup analysis (Tirosh et al., 2018). Further, TTV is superior compared to SUV_{max} of a single predominant lesion in prognosis assessment of metastatic disease (Toriihara et al., 2019). In a retrospective study of 84 metastatic well-differetiated NENs, the total [^{68}Ga]-DOTATAC-avid tumor volume remained the only independent predictor of time-to-progression (outperforming grade and stage) in multivariate analysis (Thuillier et al., 2022). However, it seems that [^{68}Ga]-SSA PET/CT is prognostic only if [^{18}F]-FDG is negative (Chan et al., 2023). Despite well-established prognostic implications in metastatic panNENs, studies evaluating the predictive value of [^{68}Ga]-SSA PET/CT in localized panNENs remain limited. In two recent studies, patients underwent dual-tracer imaging before surgery for panNENs. No correlation was found between [^{68}Ga]-DOTATOC uptake (SUV_{max} and/or SUV_{mean}) and WHO grade. Survival analysis was not performed due to short follow-up period (Mapelli et al., 2021; Paiella et al., 2022).

Functional imaging is mandatory in the diagnosis of panNENs, but the ability of [^{68}Ga]-SSA PET/CT to detect LNM is poor, despite high specificity in detecting primary tumor (Paiella et al., 2022; Partelli, Muffatti, et al., 2022; Zhang et al., 2023). A potential explanation for this might be the poor resolution due to the small size of LNMs. However, PET/CT has overcome conventional imaging in staging of NENs (Schraml et al., 2013). Compared to CT, the use of [^{68}Ga]-SSA PET/CT leads to increased detection of extra-hepatic metastases, especially node and bone metastases (Albanus et al., 2015). High accuracy for detecting liver metastases has also been reported, with a sensitivity of 97% and a specificity of 98%, using MRI as the reference standard (Grawe et al., 2023). Furthermore, the clinical value of [^{68}Ga]-SSA PET/CT is evident, as it altered disease stage or management in 55% of patients

(Ambrosini et al., 2010). Similarly, [^{68}Ga]-SSA PET/CT affected treatment decisions in 47 % of MEN1 patients (Kostiainen et al., 2023).

[^{18}F]-FDG PET/CT is considered useful in G3 panNETs and NECs, in cases where [^{68}Ga]-SSA-negative lesions are identified on conventional imaging in panNEN patients, and during restaging when grade progression of previously low-grade, well-differentiated disease is suspected (Ambrosini et al., 2021). Originally indolent, well-differentiated NENs may exhibit dedifferentiation, characterized by the loss of the ability to express SSTRs, accompanied by increased glucose metabolism and [^{18}F]-FDG avidity. EANM and ENETS guidelines recommend the use of [^{18}F]-FDG for the localization of NECs and high-grade NENs with aggressive behaviour, for prognostic stratification, and eventually for clarification of equivocal findings on conventional imaging (Bozkurt et al., 2017; Sundin et al., 2017). The ENETS guideline suggests considering [^{18}F]-FDG PET/CT to assess tumor burden and prognosis in cases of rapid tumor progression in earlier diagnosed G1–G2 panNENs (Falconi et al., 2016).

In general, the role of [^{18}F]-FDG PET/CT in low-grade well-differentiated panNENs has been controversial. However, there is a lot of data in favor of more active use of [^{18}F]-FDG PET/CT in diagnostic work-up of G1–G2 panNENs, and [^{18}F]-FDG PET/CT may be used in selected cases to detect those at higher risk for unfavourable disease course. Several studies have demonstrated the positive correlation between Ki-67 PI and [^{18}F]-FDG uptake and poorer overall survival for [^{18}F]-FDG-avid well-differentiated NENs (Binderup et al., 2010; Bucau et al., 2018; Garin et al., 2009; Johnbeck et al., 2016). In a prospective study of 166 GEP-NEN patients, a positive [^{18}F]-FDG PET/CT scan was the only identifier of high risk for death (HR: 3.6; 95% CI, 2.2–5.9; $p < 0.001$) in G1 and G2 patients (Binderup et al., 2021). A meta-analysis of 23 studies revealed that patients with high [^{18}F]-FDG uptake showed a 2.8-fold increased risk of disease recurrence and a 3.5-fold increase in the risk of death compared with those with a low [^{18}F]-FDG uptake (Han et al., 2021). Furthermore, in a recent study by Magi et al., PFS of G1 GEP-NENs (n = 55) was longer in patients with negative [^{18}F]-FDG PET/CT compared to positive [^{18}F]-FDG PET/CT ($p = 0.04$), and the significance was particularly evident in the pancreatic group (n = 24, $p = 0.008$) (Magi et al., 2022). Some studies has disagreed with the prognostic value of [^{18}F]-FDG PET/CT (Panagiotidis et al., 2017; Sharma et al., 2014). However, both studies involved relatively small patient cohorts (n = 104 and n = 37, respectively).

Patient cohorts with solely panNENs used to assess the prognostic value of [^{18}F]-FDG-PET/CT are relatively rare. In the multivariate analysis of a prospective study of 60 advanced panNENs (G1/G2/grade missing: 15/32/13), [^{18}F]-FDG finding was found to be the only independent prognostic factor for PFS ($p = 0.013$) (Sansovini et al., 2017). This finding is consistent with a study that reported significantly longer

median OS in the [^{18}F]-FDG-negative subgroup compared with the [^{18}F]-FDG-positive subgroup of panNEN patients (199/495 NEN patients) (median OS 114 vs. 53 months, $p < 0.001$) (J. Zhang et al., 2020). Sato et al. reported that [^{18}F]-FDG positivity was the only factor in multivariate analysis to correlate with shorter RFS in panNEN patients (Sato et al., 2020). The latest ENETS guidelines indicate that [^{18}F]-FDG PET/CT may be valuable for prognostification and therapy planning (Kos-Kudla et al., 2023).

Further, [^{18}F]-FDG-avid tumors had worse response to PRRT therapy and poorer prognosis compared to [^{18}F]-FDG-negative tumors (Thapa et al., 2016). However, [^{18}F]-FDG-positive patients receiving PRRT had longer survival than patients not receiving PRRT (4.4 vs 1.4 years, $p = 0.001$), whereas no difference was detected for [^{18}F]-FDG-negative patients (Binderup et al., 2021). Several study groups have established prognostic scoring systems in which the score calculated using dual tracer imaging has proven to be prognostic for GEP-NEN tumors (Chan et al., 2017; Hayes et al., 2022; Karfis et al., 2020; H. Lee et al., 2022). Studies considering the prognostic value of [^{68}Ga]-SSA PET/CT and/or [^{18}F]-FDG-PET/CT in panNENs are presented in Table 5.

Table 5. Studies evaluating the prognostic value of [^{68}Ga]-SSA, [^{18}F]-FDG, and dual-tracer PET/CT in the assessment of panNENs in addition to Study I (Ambrosini et al., 2015; Cingarlini et al., 2017; Gao et al., 2023; Magi et al., 2022; Mapelli et al., 2021; Matsumoto et al., 2019; Paiella et al., 2022; Partelli et al., 2014; Sansovini et al., 2017; Sato et al., 2020; Tomimaru et al., 2015).

	n	Design	Follow-up (median)	Tracers	Conclusion
Ambrosini et al. 2015	43	Retrospective	20 months	[^{68}Ga]-DOTANOC	Ki-67 PI, [^{68}Ga]-DOTANOC SUV_{max} (cutoff 37.8) and type of therapy associated with PFS
Tomimaru et al. 2015	36	Prospective	2.5 years	[^{18}F]-FDG	[^{18}F]-FDG SUVmax correlated to grade and [^{18}F]-FDG SUVmax ≥2,5 correlated to worse DFS
Sansovini et al. 2017	55	Prospective	59 months	[^{18}F]-FDG	32/55 (58%) patients had [^{18}F]-FDG-avid lesion before PRRT. [^{18}F]-FDG positive patients had significantly poorer median PFS than [^{18}F]-FDG-negative patients (21.1 vs. 68.7 months)
Matsumoto et al. 2019	24	Retrospective surgical cohort	12 months	[^{18}F]-FDG	The SUV_{max} ≥2.0 group had poorer DFS and OS than the tracer negative group
Sato et al. 2020	72, (56 NF-panNENs)	Retrospective	65.6 months	[^{18}F]-FDG	[^{18}F]-FDG-avidity was associated to metastatic behavour and shorter RFS among NF-panNENs
Magi et al. 2022	24*	Retrospective	nr	[^{18}F]-FDG	[^{18}F]-FDG-avidity was associated to longer PFS in G1 panNENs
Gao et al. 2023	46	Retrospective	nr	[^{68}Ga]-DOTATATE and [^{18}F]-FDG	Higher uptake of [^{18}F]-FDG correlated to higher grade
Partelli et al. 2014	49	Retrospective	nr	[^{68}Ga]-DOTANOC and [^{18}F]-FDG	No influence for treatment, despite in case of panNEN with Ki-67 >10
Cingarlini et al. 2017	35	Retrospective	nr	[^{68}Ga]-DOTATOC and [^{18}F]-FDG	[^{18}F]-FDG PET/CT has high PPV in the identification of G2 panNENs over G1
Paiella et al. 2022	124	Retrospective, surgical cohort	nr	[^{68}Ga]-DOTATOC ja [^{18}F]-FDG	Cutoff [^{18}F]-FDG uptake of >4.2 had sensitivity of 49% and specificity of 73% for differentiating G1 tumor from G2
Mapelli et al. 2021	84	Retrospective	22.8 months#	[^{68}Ga]-DOTATOC ja [^{18}F]-FDG	[^{68}Ga]-DOTATOC uptake measures were higher in T3/T4 panNENs than in T1/T2 tumors. Further, intense [^{68}Ga]-FDG uptake measures were associated with T-stage and also predicted angioinvasion.

* Total of 55 gastro-entero-pancreatic NENs, #mean follow-up time. Abbreviations: nr, not reported; PFS, progression-free survival
PPV, post predictive value; PRRT, peptide receptor radionuclide therapy.

3 Aims

This thesis was designed to investigate the prediction of the aggressiveness of panNENs using PET/CT and IHC biomarkers. The specific aims of the present study were:

I To evaluate in a prospective cohort, whether the malignant potential of NF-panNENs could be predicted with dual-tracer PET/CT imaging using ^{68}[Ga]-DOTANOC and ^{18}[F]-FDG

II To correlate IHC expressions of somatostatin receptor 1–5 with receptor density assessed with ^{68}[Ga]-DOTANOC PET/CT, and to evaluate if the SSTR expression profile is associated with aggressiveness of the tumor

III To retrospectively evaluate prognostic factors in surgically managed panNEN patients over a 30-year period and to perform a modern IHC re-analysis

4 Materials and Methods

4.1 Study subjects

Table 6. Population and setting of the studies.

Study	I	II	III
Population	NF-panNEN	NF-PanNEN	PanNEN
Design	prospective	prospective	retrospective
Number of patients	31	21	373
Number of tumors or lesions	53	35	375
PET tracers	[^{68}Ga]-DOTANOC and [^{18}F]-FDG	[^{68}Ga]-DOTANOC and [^{18}F]-FDG	-
IHC stainings	-	SSTR1–5, Ki-67	SYP, Chrom A, INSM1, pan-CK, TTF-1, p53, CDX2, ISL1, Ki-67

* NF, Nonfunctional; panNEN, Pancreatic neuroendocrine neoplasm; [^{68}Ga]-DOTANOC, ^{68}[Ga]-DOTA -1-Nal3-octreotide; [^{18}F]-FDG, ^{68}[F]-fluoro-2-deoxyglucose; SSTR, Somatostatin receptor; SYP, Synaptophysin; Chrom A, chromogranin A; INSM1, Insulinoma-associated protein 1; pan-CK, Pan-cytokeratin; TTF-1, Thyroid transcription factor 1; CDX2, Caudal-type homeobox 2; ISL1, Islet-1.

4.1.1 Study I

P-NETPET-study was a prospective, two-center, clinical trial at Turku and Helsinki University Hospitals. Patients were recruited by surgeons and endocrinologists. Total of 35 patients suspected of having NF-panNEN after primary CT were prospectively imaged using [^{18}Ga]-DOTANOC PET/CT and [^{18}F]-FDG PET/CT from January 2016 to January 2018. None of the patients had specific symptoms indicating a functional panNEN. Population of the study is described in Table 6. Four patients were excluded, and a total of 31 patients were enrolled in the P-NETPET cohort. Twenty-two patients underwent histopathological confirmation, and nine patients with a positive [^{68}Ga]-DOTANOC PET/CT were followed up (33.5±6.2 months). On PET/CT imaging, these study patients had a total of 53 lesions, of which 40 were confirmed by

histopathological sample. All patients provided a written informed consent. In Studies I and II, all tumors were assigned to two groups: a non-aggressive group and an aggressive group based on grade and stage of the disease (Table 7).

Table 7. Division of panNEN tumors into two groups according to aggressiveness in Studies I and II. Modified with permission of copyright holder from Study II.

Non-Aggressive tumors	Aggressive tumors
G1 tumors without any metastases	G2 tumors
	G3 tumors
	Any tumor with lymph node metastases
	Any tumor with distant metastases

4.1.2 Study II

As a part of the P-NETPET study, IHC analysis of all five SSTRs was performed. Among the 22 patients included in the P-NETPET study, the diagnosis was confirmed histologically. Twenty patients underwent surgery, while two patients had endoscopic ultrasound-guided core needle biopsy (EUS-FNA). However, one patient had insufficient tissue amount from the EUS-FNB for further IHC analysis. In total, 21 patients were included in Study II. These patients had 35 histologically confirmed tumors, of which 28 lesions were detectable upon PET/CT imaging.

4.1.3 Study III

Patients who underwent surgical operations for panNEN from January 1990 through December 2020 were included to the biobank search from six Finnish hospital-based biobanks: the Helsinki Biobank, the Auria Biobank, the Finnish Clinical Biobank Tampere, the Northern Finland Biopank Borealis, the Biobank of Eastern Finland and the Central Finland Biobank. In addition, regional surgical registries were utilized for the cohort formation. Previous CT or MRI one year before surgery was preferential. Patients with previous or simultaneous pancreatic adenocarcinoma were excluded. In total, 300 patients (302 samples) with sufficient size tissue sample available for reanalysis were considered to the IHC analysis and formed the FinPanNET TMA cohort. In addition, 73 operated patients without IHC analysis were included. Totally, 373 patients (375 tumors) were included into the study forming the FinPanNET clinical cohort (Table 8). All the cases were staged according to the 8th edition of the AJCC TNM classification (*AJCC Cancer Staging Manual*, 2017).

Table 8. Baseline characteristics in Study III: FinPanNET Clinical cohort (n=373 patients, 375 tumors and FinPanNET TMA cohort (n=300 patients, 302 tumors).

		FinPanNET clinical cohort	n	FinPanNET TMA cohort	n
Age (years)*		58 (45.9–66.7)	373	57.7 (46–66.8)	300
Sex ratio (F:M)		163/210	373	131/169	300
Follow-up time (years)*		8.75 (5.4–12.7)	371	9.2 (5.4–13.3)	300
Genetic fenotype	Sporadic disease	322 (86.3)	373	254 (84.7)	300
	Hereditary syndrome	51 (13.7)		46 (15.3)	
Functionality	Insulinoma	85 (22.7)	375	63 (20.7)	300
	Gastrinoma	8 (0.3)		6 (2)	
	Glucagonoma	2 (0.1)		2 (0.7)	
	VIPoma	3 (0.1)		2 (0.7)	
	ACTHoma	6 (0.2)		4 (1.4)	
	Other Functioning	2 (0.1)		2 (1.0)	
	Nonfunctional	269 (71.7)		221 (73.7)	
Type of surgery	Pancreatoduodenectomy	77 (20.6)	374	58 (19.4)	299
	Left pancreatectomy	211 (56.4)		169 (56.5)	
	Enucleation	67 (17.9)		57 (19.1)	
	Other	19 (5.1)		15 (5.0)	
Venous resection		13 (3.6)	366	11 (3.8)	291
Tumor size (cm)*		2.2 (1.5–4.0)	361	2.2 (1.5–4.0)	289
Grade	G1	261 (70)	373	217 (72.1)	301
	G2	103 (27.6)		81 (26.9)	
	G3	9 (2.4)		3 (1.0)	
N-stage	N0	278 (77.4)	359	225 (78.4)	287
	N1	81 (22.6)		62 (21.6)	
M-stage	M0	314 (87.2)	360	246 (86.0)	286
	M1	46 (12.8)		40 (14.0)	

* Values in parentheses are percentages unless indicated otherwise; *median (I.Q.R)

Abbreviations: MEN1, multiple endocrine neoplasia type 1; ASA, American Society of Anesthesiologists classification; CCI, Charlson Comorbidity Index; NEN, neuroendocrine neoplasia; CEA, carcinoembryonic antigen; Ca19-9, carbohydrate antigen 19-9; CgA, circulating chromogranin A; ULN, upper limit of normal; S-5HIAA, serum 5 hydroxyindoleacetic acid; S-PP, serum pancreatic polypeptide.

4.2 Methods

4.2.1 Dual tracer PET/CT (Study I and II)

In study I and II, PET/CT imaging were performed at Turku PET Centre using the Discovery STE or VCT scanner (General Electric Medical Systems, Milwaukee, WI, USA) and at the Nuclear Medicine Department in Helsinki University Hospital using Siemens Biograph mCT (Siemens Healthineers, Erlangen, Germany) or the Gemini PET-CT scanner. One [^{68}Ga]-DOTANOC PET/CT and one [^{18}F]-FDG PET/CT scans were done at a private institute at the Docrates Cancer Center in Helsinki using the Siemens Biograph 6 scanner (Siemens Medical Solutions, Malvern, PA, USA). Further, one patient in Study I underwent [^{18}F]-FDG PET/MRI with Inquinuity TF PET/MRI scanner (Phillips Medical System, Cleveland, OH) at Turku PET Center.

Patients underwent a whole-body PET/CT scan from the level of the skull base to the mid-thigh beginning about one hour after the injection of [^{68}Ga]-DOTANOC or [^{18}F]-FDG. Patients fasted for 6 h before the study. Before [^{18}F]-FDG PET/CT, blood glucose level was measured for patients with diabetes or previous history of glucocorticoid usage (range 4.6–8.3 mmol/l). A low-dose PET/CT was followed by a whole-body diagnostic CT scan after automated injection of contrast agent, either with [^{68}Ga]-DOTANOC or [^{18}F]-FDG PET/CT. Attenuation correction was performed using a low-dose ultrafast CT protocol (80 mAs, 140 kV, 0.3 mSv per field of view). Images were reconstructed full width at half maximum and fully 3-dimensional maximum-likelihood ordered-subset expectation maximization (OSEM). Data was corrected for dead time, decay, and photon attenuation and was reconstructed to a 128 x 128 matrix.

The diagnostic accuracy of the PET/CT studies was assessed by comparing the PET-images and the histopathological reports. When histological confirmation was not available (nine cases in Study I), the consensus was based on the sum of the laboratory tests and imaging procedures. A positive [^{68}Ga]-DOTANOC was considered true positive if further imaging and laboratory findings supported the presence of panNEN. A negative [^{18}F]-FDG was considered true negative if no progression or other signs of aggressive behavior were observed during surveillance.

The SUV_{max}–values were determined for every tumor or abnormal anatomical region on both [^{68}Ga]-DOTANOC and [^{18}F]-FDG PET/CT. For the PET/CT-studies areas with a focal activity greater than background that could not be identified as physiological activity were considered to indicate tumor tissue. Krenning score was evaluated for every lesion based on [^{68}Ga]-DOTANOC-PET/CT by comparing SUV_{max} of the tumor to the reference organs such as liver and spleen. Score 1 indicates a lesion uptake lower than normal liver, score 2: lesion uptake equal to normal liver uptake, score 3: lesion uptake higher than normal liver and score 4:

lesion uptake higher than spleen or kidneys (Krenning et al., 1999). Further, the NETPET-score (grades P1–5) was defined by using the dual tracer imaging. Grade P1 indicated purely somatostatin analogue avid lesion without [^{18}F]-FDG-uptake and P5 indicated the presence of a significant [^{18}F]-FDG-positive and SSA-negative disease. In grade P2 lesion SSA-avidity was greater than [^{18}F]-FDG-avidity, in P4 [^{18}F]-FDG-avidity greater than SSA-avidity. Further, in P3 the uptake of two tracers was equal with threshold of SSA SUV_{max}=15 and [^{18}F]-FDG SUV_{max} =7 (Chan et al., 2017). The ADW 4.4 workstation was used on PET/CT image analysis.

4.2.2 Immunohistochemical analysis (Study II and III)

Study I. Only patients and tumors with a histopathological confirmation were included in the correlation analysis. Ki-67 labeling indexes were studied in the whole series of tumors using the MIB-I antibody (Dako, Agilent Pathology Solutions, Santa Clara, CA) and an automated staining instrument (BenchMark Ultra, Ventana Medical Systems, Inc., Tucson, AZ). All stainings were prepared in the clinical pathology laboratory (HUSLAB, Helsinki University Hospital) under standardized conditions. Stained slides were digitized using a Panoramic scanner (3DHISTECH, Budapest, Hungary), and Ki-67 values were calculated from hot spot areas comprising at least 2000 cells. A publicly available application, Immunoratio, suitable for panNENs, was used for quantitative image analysis (Remes et al., 2012).

Study II. Fresh, 3.5 μm thick, whole slide tissue sections were deparaffinized, processed using heat-induced antigen retrieval, and then incubated with primary antibodies SSTR1–5 and Ki-67. Immunoreactions were detected using either a polymer-based ultraView or OptiView Universal DAB Detection Kit (Ventana Medical Systems, Inc., Tucson, AZ, USA) or EnVision Detection System (Dako, Agilent Pathology Solutions, Santa Clara, CA, USA). Automated (Benchmark ULTRA, Ventana Medical System, Inc., Tucson, AZ, USA) or semi-automated (AutoStainer, Lab Vision Corp., Fremont, CA, USA) staining instruments were used. Appropriate positive controls (pancreas, small intestine) were used for each antibody.

Immunoreactivity for SSTR2 was classified solely by membranous staining with a scoring system introduced by Elston et al. (Elston et al., 2015) and Körner et al. (Korner et al., 2012). Briefly, samples were scored as: negative (0) for no membranous staining, weak (1) for partial membranous positivity for <10% of the tumor cells, and moderate (2) partial membranous positivity for ≥10% of the tumor cells. A strong (3) score was assigned when circumferential membranous positivity was observed on tumor cells, and an intense (4) score when >95% of the tumor cells presented a strong, circumferential staining pattern. Additionally, cytoplasmic immunoreactivity in SSTR1 and SSTR3-5 staining was evaluated using the

following scoring: negative (0), weak intensity (1), moderate intensity (2), and strong intensity (3). The definition of the overall score of stainings as positive or negative is described in Figure 9. The proliferation index based on the Ki-67 immunoreactivity in the nuclei was determined as previously described.

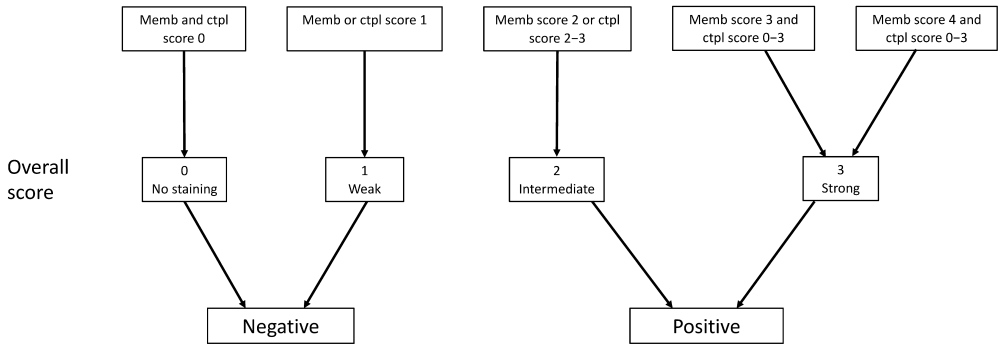


Figure 9. Classification of SSRT overall score as positive or negative based on membranous and cytoplasmic score in the Study II. Abbreviations: Memb, membranous; Ctpl, cytoplasmic. Reproduced with the permission of the copyright holder.

Study III Local pathologist screened and approved patients and finally selected the samples used in the FinPanNET TMA cohort. Formalin-fixed, paraffin-embedded tissue samples (FFPE) were selected for further tissue microarray block (TMA) construction in a local biobank using a TMA Grand Master (3DHISTECH, Budapest, Hungary) or Galileo TMA CK4500 (Isenet, Milan, Italy) microarrayer. After a histological review, fresh hematoxylin-eosin (H&E) stained slides were prepared from the original FFPE tissue samples and digitized with a slide scanner. Digitized slides were uploaded into CaseViewer (3DHISTECH) or NDP.view2 (Hamamatsu Photonics, Hamamatsu City, Japan) software, where the areas for the TMAs were annotated. To ensure representative sampling, the biobanks used 1 mm punchers and took two cores from the middle of the tumour, two cores from the tumour border and one core from the tumour adjacent tissue if applicable considering the tumour size.

After this, the TMAs were sent to the HUS Diagnostic Centre, Department of Pathology (Helsinki, Finland) for further immunohistochemical analysis. Fresh 3.5 µm thick TMA sections were deparaffinized and treated with heat-induced and protease-based antigen retrieval before incubating with primary antibodies. Antibody binding was visualized using a polymer-based OptiView or ultraView Universal DAB Detection Kit (Ventana Medical Systems, Inc., Tucson, AZ, US). An automated BenchMark ULTRA (Ventana) staining instrument was used, and all slides were counterstained with Mayer's haematoxylin (Dako, Agilent Pathology Solutions, Santa Clara, CA, US). Appropriate positive controls were used for each antibody.

SYP, Chrom A, insulinoma-associated protein 1 (INSM1), and pan-cytokeratin (pan-CK) stainings were used to confirm neuroendocrine differentiation and epithelial origin. Those were considered positive if at least 90 % of the tumor cells showed at least moderate intensity. Thyroid transcription factor 1 (TTF-1), caudal-type homeobox 2 (CDX2), and Islet-1 (ISL1) were used to indicate the site of a primary tumor (lung, small intestine, pancreas, respectively). They were considered positive if >10 % of the nuclei of the tumor cells showed positivity. p53 was used in the differentiation from neuroendocrine carcinoma and was considered positive if aberrant nuclear staining was present.

The PI, as measured with Ki-67 immunohistochemistry, was analysed with a deep-learning based Aiforia algorithm (Aiforia Technologies, Helsinki, Finland) (Remes et al., 2012). The highest Ki-67 PI of four parallel TMA spots per tumor was used for further statistical analysis.

4.2.3 Statistical analysis

Variables following normal distribution were reported as means and standard deviations (SD), variables not following normal distribution as medians and interquartile ranges (IQR), and categorical variables as frequencies and proportions. The Shapiro-Wilk test in Study I and the Kolmogorov–Smirnov test in Study II were utilized to test deviations from the normal distribution. Due to a lack of normally distributed data, Spearman's rank correlation was used to test the relationship between Ki-67 PI and SUV_{max} in Study I, and Ki-67 PI and SSTR expression in Study II. The Mann–Whitney U or the Kruskal–Wallis tests were used to evaluate differences between the groups in continuous variables. Fisher's exact test was utilized for binary variables, the linear-by-linear association test for ordinal variables, and the Jonckheere–Terpstra test between continuous and ordinal variables. In Study III, categorical variables were compared using the chi-square or Fisher's exact tests, and continuous variables were compared using Student's t-test or Mann–Whitney U-test, when appropriate. Further, in Study III, survival probability was estimated according to the Kaplan-Meier method. Log-rank test and Cox proportional hazard regression model were used for univariable survival analysis, respectively. 95% confidence intervals were presented. All tests were two-sided. The optimal prognostic value for tumor size in Study III was calculated from the ROC curve using the Youden index. All tests were two-sided, and the level of statistical significance was set at 0.05. Data analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA) in Study I and Study II and SPSS, version 27.0 (IBM SPSS Statistics, version 27.0 for Mac; SPSS, Inc., Chicago, IL, USA) in Study III.

5 Results

The main findings from this thesis are summarized in Table 9.

Table 9. Main findings from studies I-III.

Study	Results	
I	[^{18}F]-FDG uptake correlated positively with Ki-67 PI. Further, [^{18}F]-FDG-PET/CT had PPV of 78% in detection of potentially aggressive tumor (G2, G3, LN+, M+) and NPV of 69%.	There was no negative correlation between [^{68}Ga]-DOTANOC uptake and the Ki-67 PI. However, both Krenning score and NETPET score correlated with Ki-67 PI.
II	SSTR2 was the only SSTR subtype to correlate with [^{68}Ga]-DOTANOC PET/CT (positive vs. negative), confirming that SSTR2 has the highest impact on [^{68}Ga]-DOTANOC PET signaling.	Expression of SSRT5 was higher in tumors with low Ki-67 PI indicating better prognosis in NF-PanNEN patients
III	A tumor diameter greater than 2.4 cm predicts poor prognosis for both functional and nonfunctional panNET patients.	Other poor prognostic factors include: increasing age, high grade, high Ki-67 PI, advanced TNM-stage, functional tumors other than insulinoma, tumors requiring pancreatoduodenectomy and operations performed prior to 2010.

* PI, proliferation index; PPV, positive predictive value; NPV negative predictive value; LN+, lymph node metastasis; M+, distant metastases; PI, proliferation index; SSTR, somatostatin receptor.

5.1 Positive [^{18}F]-FDG PET/CT predicts poor prognosis among nonfunctional panNEN patients (Study I)

[^{68}Ga]-DOTANOC-PET/CT was positive in 30 patients and thus the sensitivity of the [^{68}Ga]-DOTANOC-PET/CT detecting NF-panNETs was 97% and specificity 100%. The only [^{68}Ga]-DOTANOC-negative tumor was [^{18}F]-FDG-positive G1 tumor with multiple (11/13) lymph node metastases.

Overall survival of patients was 97% and disease specific survival 100% during the follow-up time (median 31.0, IQR 2.2 months). One patient died due to long-term surgical complication and disease-specific mortality was 0 %. Hence, the

aggressiveness of tumors was evaluated by using the grade and stage of the disease (Table 7). There was no correlation between [^{68}Ga]-DOTANOC uptake intensity and the Ki-67 PI of the tumor (Spearmans's ρ 0.271, p = 0.190). However, when comparison was made to physiological organ activity by using Krenning score or combining [^{68}Ga]-SSA imaging to [^{18}F]-FDG-imaging in NETPET-score, there was a significant correlation betwnn both Krenning score and Ki-67 PI (p = 0.013) and between NETPET score and Ki-67 (p = 0.036). Distribution of the lesion according to Krenning and NETPET scores are presented in Table 10.

Table 10. Krenning and NETPET score of the lesions (n=43) in Study I. Reproduced with the permission of the copyright holder.

Krenning score	n (%)	NETPET score	n (%)
1	1 (2)	P1	32 (75)
2	4 (9)	P2	8 (19)
3	24 (56)	P3	1 (2)
4	14 (33)	P4	1 (2)
		P5	1 (2)

* Out of 53 lesions, 43 were analysed. A single patient with 13 tumors (two microadenomas, one [^{68}Ga]-DOTANOC-avid lymph node, and seven [^{68}Ga]-DOTANOC-negative false negative lesions in surgical specimen) was excluded from this analysis.

[^{18}F]-FDG PET/CT was positive for 11 (35%) of 31 patients and the SUV_{max} ranged from 3.0 to 18.6 (median 4.5, IQR 3.4–8.7). Total, 64% (7/11) of [^{18}F]-FDG-avid tumors were identified as potentially aggressive tumors characterized by grades 2 and 3, lymph node involvement or distant metastases. Two [^{18}F]-FDG-avid tumors were classified as indolent, being G1 T3N0M0 tumors, despite exhibiting very large diameters (≥9 cm). Two patients lacked histological confirmation, and one patient, with a G2 tumor by EUS-FNB, was assessed as too frail for surgery. They were followed up closely. [^{18}F]-FDG PET/CT was positive in 19 % (3/16) of G1 tumors, 63% (5/8) of G2 tumors and 100% (1/1) in G3 tumors. A significant positive correlation was observed between [^{18}F]-FDG-uptake and the tumor Ki-67 expression (Spearmans's ρ 0.458, p = 0.021) (Figure 10).

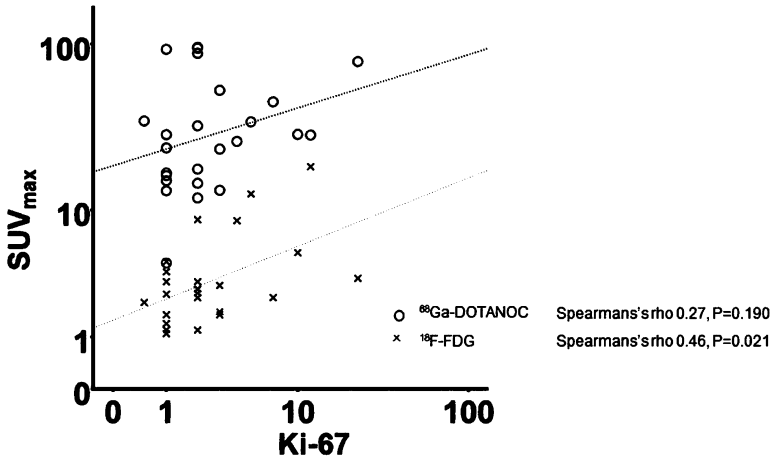


Figure 10. Logarithm variation of the relationship between the tumor Ki-67 and uptake of [^{68}Ga]-DOTANOC (black circles) and [^{18}F]-FDG (grey circles) for every tumor in the Study I. Modified with permission of the copyright holder.

Lesion analysis: In lesion-based analysis on [^{68}Ga]-DOTANOC PET/CT, 52 primary lesions on 31 patients were analysed: 45 lesions were true positive (TP) and eight false negative (FN) lesions. The lesion-based sensitivity of [^{68}Ga]-DOTANOC PET/CT was 85% and specificity 100%. Further, in lesion-based analysis on [^{18}F]-FDG PET/CT, 52 lesions were analysed. In total, 7/52 lesions (13%) were TP lesions with aggressive behavior, and 32/52 (62%) were true negative (TN) lesions with non-aggressive behavior (Table 7). Nevertheless, 8% of lesions (4/52) were [^{18}F]-FDG-avid but presented with non-aggressive histopathology and were assessed as false-positive (FP) lesions. Moreover, 17% (9/52) of lesions were [^{18}F]-FDG-negative but had an aggressive histopathology and were assessed as FN lesions. A positive predictive value (PPV) of [^{18}F]-FDG PET/CT to detect a potentially aggressive tumor was 78%, and the negative predictive value (NPV) 69%.

Six patients had lymph node metastases. Two of these (33%) had an [^{18}F]-FDG-positive tumor, and four had [^{18}F]-FDG-negative (67%) tumor. Thus, 18% (2/11) of [^{18}F]-FDG-positive patients had lymph node metastases (LNMs) vs. 20% (4/20) of [^{18}F]-FDG-negative patients had LNMs. In five patients (83%), preoperative [^{68}Ga]-DOTANOC-PET/CT did not reveal LNMs. One patient had several LNMs, but [^{68}Ga]-DOTANOC PET/CT showed only one metastatic lesion. Hence, detection of lymph node involvement was poor in both [^{68}Ga]-DOTANOC and [^{18}F]-FDG PET/CT.

5.2 Somatostatin receptor subtype 2 expression correlated with [^{68}Ga]-DOTANOC PET/CT imaging (Study II)

Overall, expression of SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5 were detected during immunohistochemical analysis in 74%, 91%, 80%, 14%, and 77 % of NF-panNENs, respectively (Figure 11).

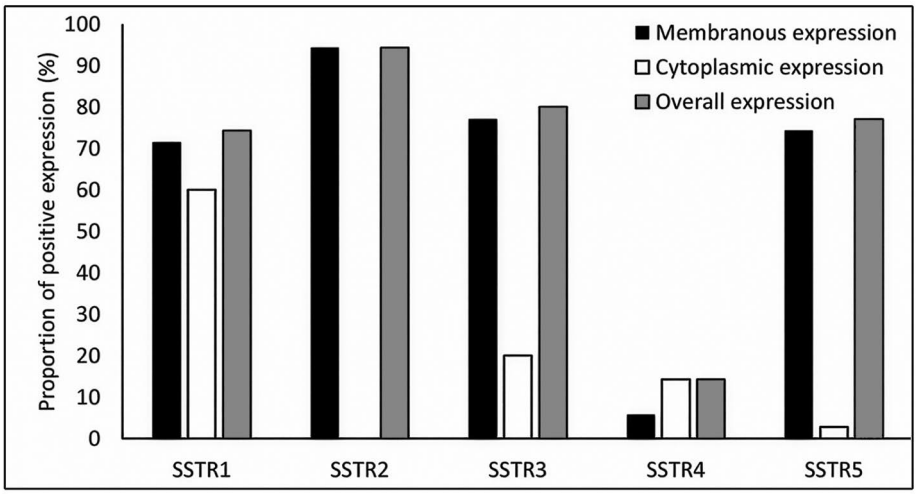


Figure 11. Frequency (%) of SSTR1-5 expressions in the tumors in Study II. SSTR2 staining was completely membranous. Reproduced with the permission of the copyright holder.

There was a positive correlation between SSTR2 expression and positive/negative [^{68}Ga]-DOTANOC PET/CT (Spearmans's ρ -0.382, p = 0.043), but no association between expression of other SSTRs (SSTR1 and SSTR3-5) and [^{68}Ga]-DOTANOC imaging. When SSTR2 expression was scored either positive or negative, all the [^{68}Ga]-DOTANOC-positive tumors (n=22/23) expressed SSTR2 while the only [^{68}Ga]-DOTANOC-negative tumor did not express SSTR2 in the cell membrane (Spearmans's ρ -1.000, p = 0.043). However, there was no association between expression of any SSTR (SSTR1–5) and uptake intensity (SUV_{max}) of [^{68}Ga]-DOTANOC. The Krenning score and the NETPET score of tumors correlated with SSTR2 but not with SSTR1 or SSTR3–5 immunohistochemical expression.

5.3 Somatostatin receptor subtype 5 expression correlated with Ki-67 proliferation index of panNEN (Study II)

In study II, a negative correlation between SSTR5 IHC expression and Ki-67 PI was found (Spearmans's ρ -0.053, CI -0.654–0.039, p = 0.038), and persisted when tumors were classified into WHO grades 1, 2 and 3 according to Ki-67 PI (Figure 12). For SSTR5 positive tumor the mean Ki-67 PI was 2.44 (CI 1.00–3.00) and 6.38 (CI 2.25–8.75) for SSTR5 negative tumors. Further, SSTR5 membranous expression correlated negatively with [^{18}F]-FDG uptake intensity of the tumor. Interestingly, there was no association between SSTR1-SSTR4 expression and Ki-67 PI or tumor grade.

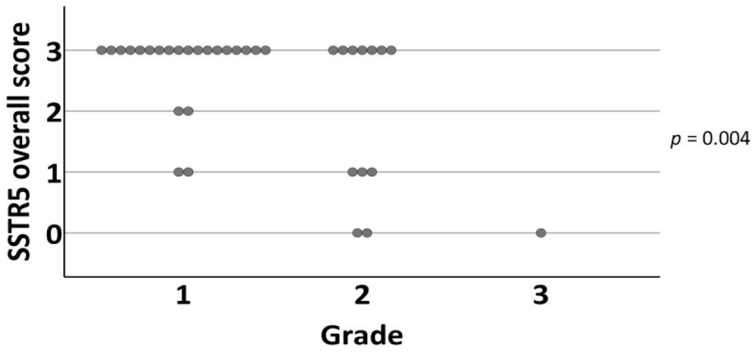


Figure 12. Distribution of tumors overall SSTR5 expression (0=negative, 1=weak expression, 2=moderate expression, 3=strong expression) according to WHO grade (1–3) of the tumor in Study II. Reproduced with permission of the copyright holder.

The non-aggressive tumors (Table 7) (n = 19) had higher SSTR5 and SSTR1 expression than aggressive ones (n = 16). The association between SSTR1 and SSTR5 expressions and tumor aggressiveness is presented in Figure 13.

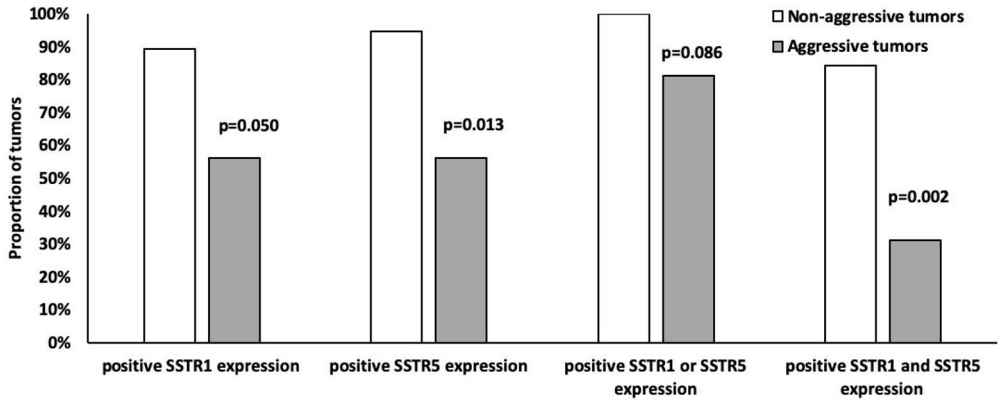


Figure 13. Frequency of SSTR1 and SSTR5 (%) positivity (overall score 2-4) among indolent (n = 19) and aggressive (n = 16) tumors in Study II. Printed with permission from the copyright holder.

In Study II six patients had twenty-nine lymph node metastases in total (mean 4.8, SD 3.4 lymph nodes). None of these six primary tumors expressed cytoplasmic SSTR3, but in lymph node metastases the cytoplasmic expression of SSTR3 was significantly higher than in primary tumors (median increase by two scores, IQR 1.5–2.0, $p = 0.031$, results within patients were averaged, paired Wilcoxon rank test).

5.4 Characterization of the national, multicentre FinPanNET clinical cohort of panNENs (Study III)

Patient characteristics of the FinPanNET clinical cohort are presented in Table 8. The median follow-up time was 8.8 years (IQR 5.4–12.7). Median time from diagnosis to operation was 1.7 months (IQR 0.72–3.72 months). In total 137 patients underwent surgery in period 1990–2009, compared to total 236 patients in period 2010–2020.

Survival analysis. In total, 52 patients (14%) died from disease. During entire follow-up period, the disease specific survival (DSS) of the cohort was 86%. DSS of panNEN patients was 98% after one year, 97% after two years, 92% after five years, and 84 % after ten years. At univariable analysis older age, higher WHO grade ($p<0.001$), higher Ki-67 index ($p < 0.001$), higher T-stage ($p < 0.001$), LNM ($p < 0.001$) and distant metastases ($p < 0.001$), tumors requiring pancreatoduodenectomy and larger diameter of the tumor ($p < 0.001$) were significantly associated with shorter DSS (Figure 14). A tumor`s diameter smaller than 2.4 cm was associated with both longer survival and fewer recurrences. Further, functionality of the tumor was related to DSS of the panNEN patients: 5-year DSS of the NF-panNENs was

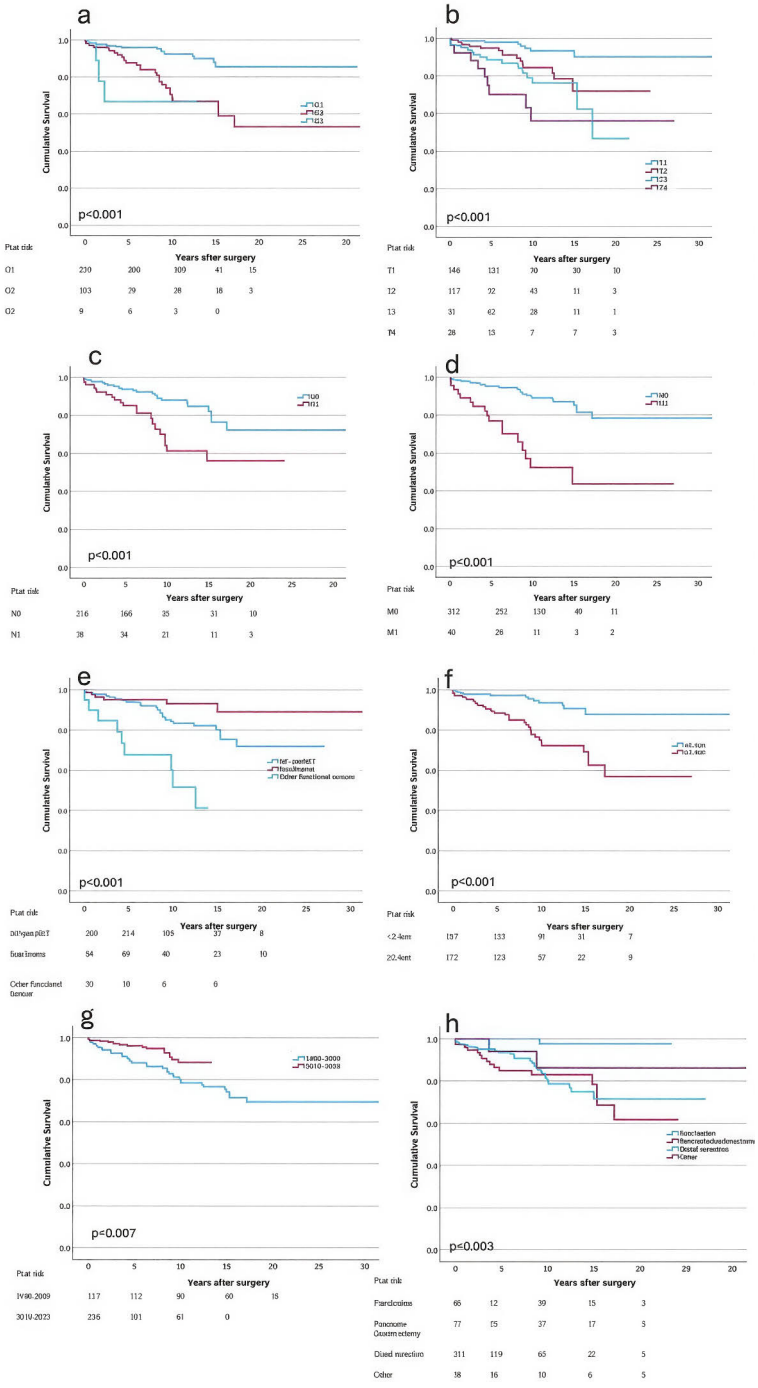


Figure 14. Disease-specific survival for the patients in Study III according to the WHO grade (**a**), T category (**b**), lymph node status (**c**), distant metastasis status (**d**), functionality (**e**) size of the tumor (**f**), time interval when surgery was performed (**g**) and surgical procedure (**h**). Modified with permission of the copyright holder from Study III.

94%, insulinomas 95%, and other functional tumors 68% ($p < 0.001$). Patients operated in the year 2009 or before had poorer DSS than patients operated in 2010 and after ($p = 0.007$).

Recurrence analysis. In a subgroup analysis of NF-panNENs, recurrence occurred in 51/269 localized NF-panNEN patients (13.7%), of which 19/269 (7%) died of disease. The disease-related survival of NF-panNENs was 86%. In addition to the prognostic factors detected in the whole FinPanNET clinical cohort, the occurrence of symptoms was significantly associated with recurrence of NF-panNENs: after five years of surgery, the symptomatic patients relapsed more often (35%) than incidentalomas (9%) ($p < 0.001$). However, in the survival analysis there was no significant correlation.

IHC analysis. The FinPanNET TMA cohort included 300 patients and 302 tumor samples. The expressions of IHC markers are presented in Figure 15. WHO grade changed in one third (90/272, 33%) of the cases after the re-analysis of Ki-67 PI: 12 G1 tumors were re-analysed as G2, 64 G2 tumors as G1, and 11 G3 tumors as G2. In addition, three G3 tumors were re-categorized as G1 tumors. Finally, after re-evaluation, Ki67 PI was <3 % in 217 (72%) cases, 3–20 % in 81 (27%) cases, and >20% in three (1%) cases.

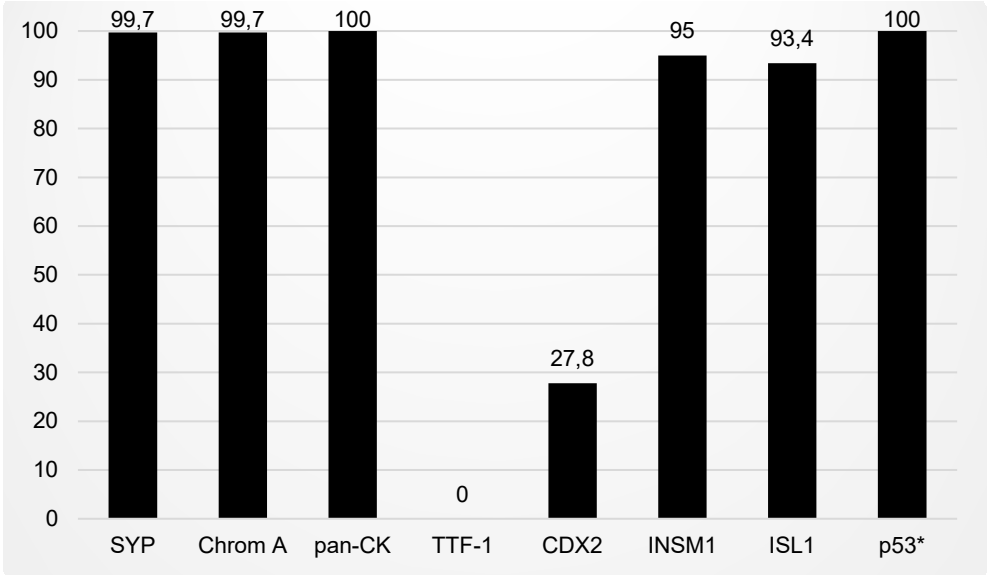


Figure 15. Expression of immunohistochemical biomarkers in Study III. *For p53, a wild type" staining was considered a positive finding. Modified with permission of the copyright holder.

6 Discussion

Prediction of the aggressiveness of panNEN is the main goal of diagnostic workup and a further basis for treatment strategy. Compared to other primary sites of NEN, panNENs carry the most unfavourable prognosis. However, a significant rise in survival rates has been observed over time (Dasari et al., 2017). PanNENs probably include at least two types of entities: aggressive, advanced panNENs with poor prognosis, and, on the other hand, incidentalomas with slow progression identified mostly during the last two decades due to modern cross-sectional imaging. Traditionally, surgery has been stated as the only curative treatment for panNENs, but the option for surveillance has been introduced in ENETS guidelines (Partelli et al., 2017). However, the knowledge of surveillance is controversial. Further, in a recent study of 384 NF-panNEN patients, over a third of the patients still experienced potential overtreatment (Partelli, Battistella, et al., 2024). This thesis aimed to produce new knowledge of the prediction of the aggressiveness of panNENs using PET/CT and immunohistochemistry.

6.1 Prognostic value of PET/CT

The main aim of **Study I** was to investigate in a prospective setting whether the dual-tracer PET/CT could predict the aggressive nature of NF-panNEN patients. The primary endpoint was the uptake and interpretation (positive or negative) of [^{68}Ga]-DOTANOC- and [^{18}F]-FDG PET/CT in comparison with the grade and stage of the tumor. According to previous retrospective studies (Kayani et al., 2008), we hypothesized that the higher the uptake of [^{68}Ga]-DOTANOC, the lower the Ki-67 PI. Finally, we found no such correlation, despite the high sensitivity of [^{68}Ga]-DOTANOC in the primary diagnosis of panNEN (patient-based sensitivity 97% and lesion-based sensitivity 85%). However, when physiological organ activity was included, there was a correlation between Krenning score (Krenning et al., 1999) and Ki-67 PI of the tumor, as well as between NETPET-score (Chan et al., 2017) and Ki-67 PI. Various studies support the positive correlation between [^{68}Ga]-SSA PET/CT and better prognosis (Ambrosini et al., 2015; Tirosh et al., 2018), but contradictory findings have also been reported (Chan et al., 2017). Notably, most of the previous studies were conducted among metastatic, high-grade diseases from various primary

sites. In concordance with our results, two recent studies accomplished for localized panNENs preoperatively revealed no correlation between [^{68}Ga]-SSA uptake and WHO grade (Mapelli et al., 2021; Paiella et al., 2022).

In **Study I**, 34% of the patients had [^{18}F]-FDG-avid tumors. The sensitivity of [^{18}F]-FDG PET/CT to detect well-differentiated panNEN was comparable to retrospective series in which the sensitivity of [^{18}F]-FDG PET/CT ranged between 51% and 66% (Kayani et al., 2008; Paiella et al., 2022; Rinzivillo et al., 2018). In our study, [^{18}F]-FDG uptake significantly correlated with Ki-67 PI. While tumors were categorized into [^{18}F]-FDG-positive and [^{18}F]-FDG-negative, the correlation with WHO grade remained statistically significant. This finding suggests that [^{18}F]-FDG PET/CT is a useful tool for predicting tumor grade and prognosis of patients with NF-panNEN. The association between [^{18}F]-FDG-avidity and OS has been confirmed in a prospective series by Garin et al. (Garin et al., 2009). In concordance with this, in a small (n=24) retrospective subseries of G1 panNEN patients, [^{18}F]-FDG-positive patients had shorter PFS compared [^{18}F]-FDG-negative patients. Further, [^{18}F]-FDG PET/CT finding was the only factor to predict progression (Magi et al., 2022). This specific analysis was made for only G1 tumors, demonstrating that the prognostic value of [^{18}F]-FDG extends to low-grade, well-differentiated tumors and is applied particularly to NENs originating from the pancreas. Further, two studies have suggested that [^{18}F]-FGD PET/CT is even better than WHO grade to predict the prognosis of panNEN patients (Binderup et al., 2010; Johnbeck et al., 2016). In **Study I,** [^{18}F]-FDG/PET CT showed a PPV of 78% in identifying potentially aggressive tumors (G2, G3, node-positive disease, and/or distant metastasis), while a negative predictive value was 69%. In concordance with this, another study reported a PPV of 90.5% of [^{18}F]-FDG PET/CT in detecting G2 out of G1 panNENs (Cingarlini et al., 2017). Furthermore, another study group reported a sensitivity of 91% and specificity of 86% to distinguish progressive disease from stable disease correctly (Rinzivillo et al., 2018).

Biopsy is strongly recommended as part of the diagnostic workup for panNENs. Dual-tracer imaging, incorporating [^{18}F]-FDG PET/CT, may be particularly useful in cases where obtaining a representative biopsy is not possible, such as in patients with multiple tumors associated with MEN1 syndrome. Moreover, while EUS with biopsy can yield valuable data about tumor biology and local disease status, it does not provide information on disease staging, as PET/CT does. [^{18}F]-FDG or dual-tracer PET imaging is also recommended in cases where there is suspicion of transformation from a low-grade to a higher-grade tumor.

Current guidelines do not recommend [^{18}F]-FDG PET/CT routinely in diagnostic work-up of panNENs. However, in **Study I,** the combined sensitivity of dual tracer imaging in the diagnosis of panNEN was 100%, a result replicated in other literature, being as high as over 99% (Paiella et al., 2022; Partelli et al., 2014). Our results of

Study I suggest that dual tracer PET/CT prior to treatment decisions could provide valuable information to identify and evaluate aggressiveness of the tumors.

In our study, neither [^{68}Ga]-DOTANOC nor [^{18}F]-FDG PET/CT could find the lymph node positive disease, a result in concordance with two retrospective analyses (n=83/124) where panNEN patients were preoperatively imaged with dual-tracer PET/CT (Mapelli et al., 2021; Paiella et al., 2022). Nodal status is one of the most critical factors for predicting the prognosis of panNENs (Niessen et al., 2022), particularly in tumors smaller than 4cm (Z. Zhang et al., 2020). The ability of any imaging studies to detect node-positive disease remains limited. A potential conclusion is that combining functional imaging with prognostic IHC markers may improve prognostic assessment.

In Study I, only two patients had synchronous distant metastases during primary diagnosis, and [^{68}Ga]-DOTANOC PET/CT detected both. No recurrence was detected during follow-up. One progression (enlargement and more intense [^{18}F]-FDG uptake of an observed tumor) was detected without any changes in treatment during follow-up. This result is in concordance with the studies confirming the high sensitivity of [^{68}Ga]-SSA PET/CT in detecting distant metastasis of panNENs (Bauckneht et al., 2020; Cuthbertson et al., 2021; Sadowski et al., 2016)

6.2 Correlation of SSTR immunohistochemical (IHC) analysis to PET/CT and the value of SSTR IHC expression to prognosis

In **Study II,** SSTR subtype 2 expression correlated with [^{68}Ga]-DOTANOC PET/CT: one patient was [^{68}Ga]-DOTANOC-negative and lacked SSTR2 expression. Moreover, the rest of the patients (22/23) had a [^{68}Ga]-DOTANOC-positive tumor and expressed SSTR2. However, we found no correlation between SSTR2 expression (or any other SSTR subtype) and [^{68}Ga]-DOTANOC uptake, in discordance with some previous retrospective studies (Kaemmerer et al., 2011; Miederer et al., 2009; Olsen et al., 2016). Further, we included all 35 lesions to gather a cohort as large as possible, unlike Kaemmerer and colleagues (Kaemmerer et al., 2011), who excluded lesions smaller than 15 mm to eliminate the partial volume effect. In **Study II**, the median tumor size was 2 cm, and the smallest tumor detected was 5 mm in size.

In **Study II,** the IHC expression of SSTR5 (both membranous and overall) correlated negatively with Ki-67 PI (p = 0.034), indicating SSTR subtype 5 as a marker for better prognosis for NF-panNENs. On average, SSTR5-expressing tumors had a Ki-67 PI of 2.4 (95% CI: 1.0–3.0) vs. tumors not expressing SSTR5 had a Ki-67 PI of 6.4 (95% CI: 2.3–8.8). Further, the correlation remained statistically significant when Ki-67 PI was divided into WHO grades. Additionally,

the membranous expression of SSTR5 correlated negatively with [^{18}F]-FDG SUV_{max}. This finding is in concordance with **Study I**, which showed that [^{18}F]-FDG-avidity is an indicator of poor prognosis of NF-panNENs. To the best of our knowledge, this is the first prospective study to reveal the prognostic significance of SSTR5, in concordance with previous retrospective analysis of 199 surgically treated panNENs (Song et al., 2016). Biological behaviour of SSTR5 are partly unknown, but it functions as inhibiting insulin secretion (Strowski et al., 2003), and combined with SSTR2 it upregulates apoptosis and restrains carcinogenesis (Cordelier et al., 1997; Kimura et al., 1999). Previous literature has shown that expression of SSTR2 could predict a better prognosis for NEN patients (Brunner et al., 2017; Mehta et al., 2015; Song et al., 2016). However, neither we nor a study by Kaemmerer et al. found such an association (Kaemmerer et al., 2015).

In **Study II** tumors were classified into two categories based on their level of aggressiveness (Table 7). Non-aggressive tumors (G1, no lymph node or distant metastases) had higher SSTR1 and SSTR5 expressions than aggressive ones. Further, most of the indolent tumors (84%) expressed both SSTR1 and SSTR5, while only 31% of aggressive tumors expressed both of these receptors.

A single difference was observed when comparing SSTR expression between primary tumors and LNM samples: cytoplasmic SSTR3 was more frequently expressed in LNM than in primary tumors. In a study of pulmonary carcinoid tumors, SSTR3 expression was associated with poor survival and increased risk for lymph node metastases (Righi et al., 2010; Vesterinen et al., 2019). Further, of all NEN sites, panNENs have the worst outcome. Interestingly, panNENs also have higher SSTR3 expression than NENs originating from other primary sites (Kaemmerer et al., 2011; Zamora et al., 2010). According to previous studies and our results, SSTR3 might have a specific role in the dedifferentiation of single panNEN to a more aggressive type of disease. Further studies concerning this issue are warranted.

In Study II, SSTR2 was the most frequently expressed receptor subtype in NF-panNENs, detected in 91% of tumors (Figure 11). The reduced clinical efficacy of pasireotide compared with other SSAs may be explaned by its lower binding affinity for SSTR2, despite its higher affinity for SSTR1, SSTR3, and SSTR5.

Currently, histological assessment of SSTR expression is not routinely performed in panNEN patients. In the future, incorporating SSTR profiling into the diagnostic workup may offer valuable insights. Mapping SSTR subtype expression in circulating tumor cells through liquid biopsy could provide prognostic information at the individual patient level and significantly influence treatment decisions. However, limited sensitivity restricts the use of liquid biopsy in routine practice (Almeida et al., 2024).

6.3 Prognostic value of tumor size

In the nationwide FinPanNET study (**Study III)**, a tumor diameter cutoff of less than 2.4 cm was associated with lower recurrence rates and improved survival. Tumors smaller than 2.4 cm had significantly better five-year RFS (96% vs. 71%, $p < 0.001$) and DSS (97% vs. 89%, $p < 0.001$) compared with larger tumors. However, in **Study I** the tumor diameter did not correlate with tumor Ki-67 PI. In **Study I**, there were relatively many large tumors in a small cohort, which may have resulted in the fact that statistical significance was not reached. Several studies have proved the prospective value of the tumor size, but the optimal cutoff is controversial. Guidelines recommend that tumors larger than 2 cm should be referred to surgery, but both higher and lower cutoff values have been proposed. In concordance with our results, a retrospective study of 384 operated NF-panNENs reported that patients with tumors larger than 2.6 cm benefited from surgery (Partelli, Battistella, et al., 2024). However, smaller cutoff values (ranging from 1.5 to 1.7 cm) have also been proposed for identifying more aggressive disease (Regenet et al., 2016; Zhang et al., 2016).

In **Study III**, larger tumor diameter correlated positively with the presence of node metastases, with a cutoff of 2.4 cm most accurately detecting node-positive vs. node-negative disease. LNM were detected in 6% of patients with a tumor <2 cm, and in 31% (70/225) of patients with a tumor ≥2 cm in diameter. Lopez-Aguiar et al. reported 9% node-positivity rate in resected panNEN smaller than 2 cm. Further, in a meta-analysis of 13 374 resected panNEN patients, 11.5% of small ≤2 cm tumors (functional and nonfunctional) had LNM, while in the case of small ≤2 cm NF-panNENs the LNM rate was 10.3%.

6.4 Other clinical factors to predict prognosis

In **Study III,** the functionality of the tumor was associated with recurrence and survival of the patients: five-year RFS of insulinomas was 95%, NF-panNENs 82% and other functional 69%. In our study, there were eight gastrinomas, six ACTHomas, three VIPomas, and two glucagonomas. Gastrinomas have a high risk for lymph node metastases, as high as 80%, and 10-year survival is poor, 57% (Weber et al., 1995). Further, the National Comprehensive Cancer Network guidelines recommend regional lymphadenectomy in patients with F-panNEN other than insulinoma (Shah et al., 2021). The better survival of F-panNENs compared to NF-panNENs has been proved in several studies (Kasumova et al., 2017; Luo et al., 2023; Yang et al., 2017). However, the functionality of panNEN was not associated with survival in some studies (Chen et al., 2020; Mei et al., 2023). Chen et. al concluded that poor outcomes of NF-panNENs are associated with more advanced

disease stage compared to F-panNENs, which are diagnosed earlier due to hormonal symptoms.

The median age of the patients in **Study III** was 58 years. Older patients (≥58 years) were associated with a poorer prognosis than younger patients, and consistent results have been reported earlier (Cherenfant et al., 2013; Han et al., 2014; Tan et al., 2020). Younger patients most likely seek management more actively than older patients. Further, surgeries performed before 2010 were associated with worse survival and more recurrences compared to surgeries performed afterwards. This was most likely reflecting significant advancements in panNENs diagnostics and surgical techniques over the study period. Our study is in concordance with several other studies that demonstrate increased survival rates and longer PFS in recent decades (Halfdanarson et al., 2008; Niksic et al., 2022; White et al., 2022). Especially survival in distant-stage disease has improved, most certainly due to improvements in therapies such as PRRT, targeted therapies (everolimus and sunitinib), and liver-directed therapies (Dasari et al., 2025).

We aimed to confirm the neuroendocrine origin of these tumours through immunohistochemical re-evaluation. The diagnosis of NEN relies on confirming the neuroendocrine differentiation in the context of appropriate morphology, achieved through modern immunohistochemical analysis using several antibodies. Notably, Trikalinos et al. showed that 27% of G1 neoplasms were reclassified as G2, 13% of G2 tumours as G1, and one out of 11 (9%) G3 neoplasms as G2 upon re-analysis of 176 panNEN cases from the SEER database (Trikalinos et al., 2020). Furthermore, Marasco et al. reported a Ki-67 change in 59% of patients and grading modification in 24% of patients in a re-analysis of 101 gastroenteropancreatic NEN patients (Marasco et al., 2023). These discrepancies may be attributed to the heterogeneous classification historically used. Next-generation immunohistochemical analysis, including linear-restricted transcription factors (such as CDX2, Islet 1, and SATB2) and proteins correlating with molecular genetic events (e.g., p53 and Rb), is essential in order to precisely characterise these tumours. Furthermore, in this study, two pseudopapillary tumours and one acinar cell tumour were excluded through immunohistochemical re-analysis, initially diagnosed as panNENs by local institutions. This highlights the complexity of histopathological diagnosis and underscores the necessity of experienced immunohistochemical analysis for accurate diagnosis.

In **Study III,** incidentally found, non-symptomatic NF-panNENs had better outcomes (fewer recurrences and better survival) than symptomatic NF-panNENs, a result supported by other studies (Birnbaum et al., 2014; Cheema et al., 2012; Ricci et al., 2022). However, the incidental diagnosis was not significantly prognostic in the FinPanNET clinical cohort, most likely due to a better prognosis of symptomatic insulinomas. As many as 23% of the patients in the FinPanNET clinical cohort had

insulinoma. In addition, other functional tumors (n=19) had worst prognosis compared to insulinomas and NF-panNENs.

6.5 Strengths and limitations

6.5.1 Strengths

The most important strength of **Study I and II** is a prospective setting of rare disease such as panNEN. **Study I** was the first ever published study evaluating dual tracer PET/CT prospectivily with [^{68}Ga]-DOTANOC and [^{18}F]-FDG. Most PET/CT scans were executed in the national PET Centre, Turku PET Centre. Furthermore, at the time of publication, **Study II** was the first prospective study about the relationship between SSTRs and [^{68}Ga]-SSA PET/CT and the only one conducted for panNEN patients, respectively. All the patients in **Study II and III** had histopathological confirmation. In **Study I, II and III** all samples were re-evaluated by immunohistochemical Ki-67 staining with an automated image analysis.

The major strengths of **Study III** included a large patient cohort, a long median follow-up of over eight years, histopathological re-evaluation and confirmation of neuroendocrine differentiation, and data obtained directly from individual patient records rather than from registries.

6.5.2 Limitations

First, the population studied in the P-NETPET study (**Studies I and II**) was relatively small, with a total of 31 patients, due to the rarity of panNENs. The power of the study may have been increased by a larger study cohort, but it is unlikely that it would have changed the study's conclusion. Secondly, in **Study I**, the lack of histopathological confirmation of patients managed by surveillance restricted the analysis. Every attempt was made to gather a tissue sample from the tumors, but in some cases and in multiple tumors, it was not possible or ethically approvable because of invasive nature of EUS. However, the correlation between the PET/CT imaging and Ki-67 PI was made only among patients with histopathological confirmation.

Further, the mean follow-up time in **Study I** was 31.3 months and **Study II,** 30.2 months. Due to the relatively short follow-up period, WHO grade, as well as nodal and metastastatic status, were used as markers of tumor aggressiveness and served as the primary endpoints. Different PET/CT scanners were used to acquire images obtained at different centers, making direct SUV_{max} comparison unsure. Possibly, partly due to this, we found no correlation between uptake (SUVmax) of [^{68}Ga]-

DOTANOC and SSTR1–5 density but the correlation between [^{68}Ga]-DOTANOC imaging (positive vs. negative) and SSTR2 expression was found.

Study III included only patients who underwent surgical treatment, excluding indolent, small panNENs managed with active surveillance, as well as patients with advanced-stage panNENs for whom surgery is not beneficial. Further, IHC re-analysis was conducted using four parallel TMA spots per tumor, suggesting that intratumoral heterogeneity may have influenced the results of the analysis. Survival analysis was conducted using univariable rather than multivariable methods, in order to provide a clear and straightforward overview of associations.

6.6 Future prospects

Several promising PET-tracers have been investigated. Novel [^{18}F]-labelled SSA SiTATE (formerly known [^{18}F]-SIFA*lin*-TATE) appears as an interesting and potential tracer for PET-imaging in NENs (Niedermoser et al., 2015). Clinical in-human data of [^{18}F]-SiTATE is still limited but recent studies indicate high image quality and high tumor uptake levels (Ilhan et al., 2020; Ilhan et al., 2019). ^{18}F is a cyclotron-produced radionuclide with a longer halflife (110 min) and lower positron energy (with a maximum of 635 keV) than ^{68}Ga (Sahnoun et al., 2020). ^{68}Ga is primarily obtained from costly and limited available on-site ^{68}Ge/^{68}Ga-generators, while ^{18}F is the most general isotope in PET-imaging, and widely produced and available. Despite the higher uptake of [^{18}F]-SiTATE into the healthy liver and spleen, this radiotracer displayed higher tumor uptake, tumor-to-spleen ratios, and tumor-to-liver ratios compared to [^{68}Ga]-DOTATOC (Ilhan et al., 2020).

Further, the sensitivity of [^{68}Ga]-SSA PET-imaging to detect insulinomas is limited to 33–85% (Prasad et al., 2016; Reubi & Waser, 2003). Insulinomas express high levels of glucagon-like peptide 1 receptor (GLP-1R) on their cell surface. A GLP-1R analog, [^{68}Ga]-labelled exendin-4, [^{68}Ga]-DOTA-exendin-4 has shown superior accurancy (93–94%), compared to [^{68}Ga]-SSA-PET/CT (65%), SPECT/CT (68%), CT/MRI (40–84%) and EUS (83%) in two prospective studies (Antwi et al., 2018; Boss et al., 2024). Turku University Hospital was one of the five centers participating in a prospective study of 69 patients, which demonstrated the superior sensitivity of [^{68}Ga]-DOTA-exendin-4 PET/CT in the diagnosis of insulinomas (Boss et al., 2024).

Traditionally, surgery has been the only potential curative treatment for panNENs. However, as the incidental detection of small panNENs has become more common, active surveillance has emerged as a potential management option for these tumors. Further, the use of RFA in the treatment of panNENs has been the target of interest, recently. The RFA is used in several malignant conditions, for instance in renal carcinoma, as potential option for surgery. Despite the reports of usability of

RFA in panNENs, the RFA has not established its status in management of panNENs. In the future, a valuable study would be a multicenter clinical trial prospectively randomizing patients with small panNENs into three arms: surgical intervention, RFA, and active surveillance, with a sufficiently long follow-up period.

Traditionally, the IHC marker CDX2 has been identified in adenocarcinomas of intestinal origin and is used as an indicator of the intestinal differentiation in NENs (Moskaluk et al., 2003; Werling et al., 2003). **In Study III**, CDX2 expression among panNEN patients was, as high as 28% (84/302). Few publications have reported CDX2 staining in panNEN (Depoilly et al., 2022; Moser et al., 2024). Our future aim is to evaluate the correlation between prognosis and the CDX2 profile of panNENs.

Several study groups have produced nomograms and scoring systems to predict the aggressiveness of panNENs, but the usability of complicated systems in clinical practice is poor. Several fields in medical diagnostics are currently being equipped with artificial intelligence (AI). For instance, some AI applications in digital IHC analysis have already been proven to be non-inferior to manual histopathological evaluation. The usage (and developing protocols) of AI is also under intense investigation in the field of conventional and functional imaging (Yan et al., 2024). Notably, TTV detected in [^{68}Ga]-SSA PET/CT is associated to PFS and DSS (Tirosh et al., 2018). Further, by means of AI, it could be possible to create a multiparametric biomarker that combines data from clinical patient characteristics, tumor histopathology, and functional imaging. By means of this biomarker, the assessment of prognosis could be more precise and help clinicians personalize the management of panNEN patients.

7 Conclusions

The conclusions of this study were as follows:

I Dual tracer PET/CT was useful in preoperative assessment of panNEN patients: the positive [^{18}F]-FDG PET/CT predicted a higher grade of the tumor, and the [^{68}Ga]-DOTANOC had also prognostic value since a higher Krenning score predicted a lower tumor grade. However, PET/CT failed to assess the lymph node involvement of NF-panNENs.

II Somatostatin receptor subtype 2 was proven to have the highest impact on [^{68}Ga]-DOTANOC PET/CT signaling on panNENs since SSTR2 was the only receptor subtype of which expression correlated with [^{68}Ga]-DOTANOC PET/CT. Further, the non-aggressive tumors (G1, no lymph node or distant metastases) expressed SSTR1 and SSTR5 more often than the aggressive ones.

III A panNEN diameter larger than 2.4 cm was associated with worse outcomes. Moreover, factors such as older age, elevated WHO grade, higher Ki-67 PI, advanced TNM stage, functionality of the tumor (other than insulinoma), the necessity for pancreatoduodenectomy, and surgeries performed prior to 2010—as compared to those performed in the subsequent two decades—were associated with poorer prognosis.

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List of Figures and Tables

Figures

Figure 1. Regional anatomy of pancreas including vascular relationships 14
Figure 2. Representative figures of hematoxylin & eosin staining and Ki-67 staining of well-differentiated neuroendocrine tumor and poorly differentiated neuroendocrine carcinoma....17
Figure 3. Representation of a MEN1 patient having a panNEN with synchronous liver metastasis 25
Figure 4. The basic principle of annihilation in a positron emission tomography (PET) scanner....27
Figure 5. Multimodal evaluation of aggressiveness of pancreatic neuroendocrine neoplasms 29
Figure 6. The factors to assess during a diagnostic workup of panNENs before treatment stratification 30
Figure 7. Radiofrequency ablation of an insulinoma measuring 13 x 8 mm using endoscopic ultrasonography 34
Figure 8. A case report of a patient in Study III with glucagonoma....44
Figure 9. Classification of SSRT overall score as positive or negative based on membranous and cytoplasmic score in the Study II 57
Figure 10. Logarithm variation of the relationship between the tumor Ki-67 and uptake of [^{68}Ga]-DOTANOC (black circles) and [^{18}F]-FDG (grey circles) for every tumor in the Study I 61
Figure 11. Frequency (%) of SSTR1-5 expressions in the tumors in Study II 62
Figure 12. Distribution of tumors overall SSTR5 expression according to WHO grade (1–3) of the tumor in Study II....63
Figure 13. Frequency of SSTR1 and SSTR5 (%) positivity (overall score 2-4) among indolent and aggressive tumors in Study II....64
Figure 14. Disease-specific survival for the patients in Study III according to the WHO grade, T category, lymph node status, distant metastasis status, functionality size of the tumor, time interval when surgery was performed and surgical procedure 65

Figure 15. Expression of immunohistochemical biomarkers in Study III 66

Tables

Table 1. The 2022 WHO classification and grading for neuroendocrine neoplasms of the gastrointestinal and hepatopancreatobiliary tract. 19
Table 2. AJCC 8th edition staging definitions, modified ENETS (mENETS) staging definitions, and ENETS staging definitions, and for PanNENs. 20
Table 3. The most common panNEN-associated hormonal syndromes. 22
Table 4. Landmark clinical studies. 45
Table 5. Studies evaluating the prognostic value of [^{68}Ga]-SSA, [^{18}F]-FDG, and dual-tracer PET/CT in the assessment of panNENs in addition to Study I. 50
Table 6. Population and setting of the studies. 52
Table 7. Division of panNEN tumors into two groups according to aggressiveness in Studies I and II. 53
Table 8. Baseline characteristics in Study III: FinPanNET Clinical cohort (n=373 patients, 375 tumors and FinPanNET TMA cohort (n=300 patients, 302 tumors). 54
Table 9. Main findings from studies I-III. 59
Table 10. Krenning and NETPET score of the lesions (n=43) in Study I. 60

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