Neuroendocrine tumours: Understanding the patient experience and improving follow-up

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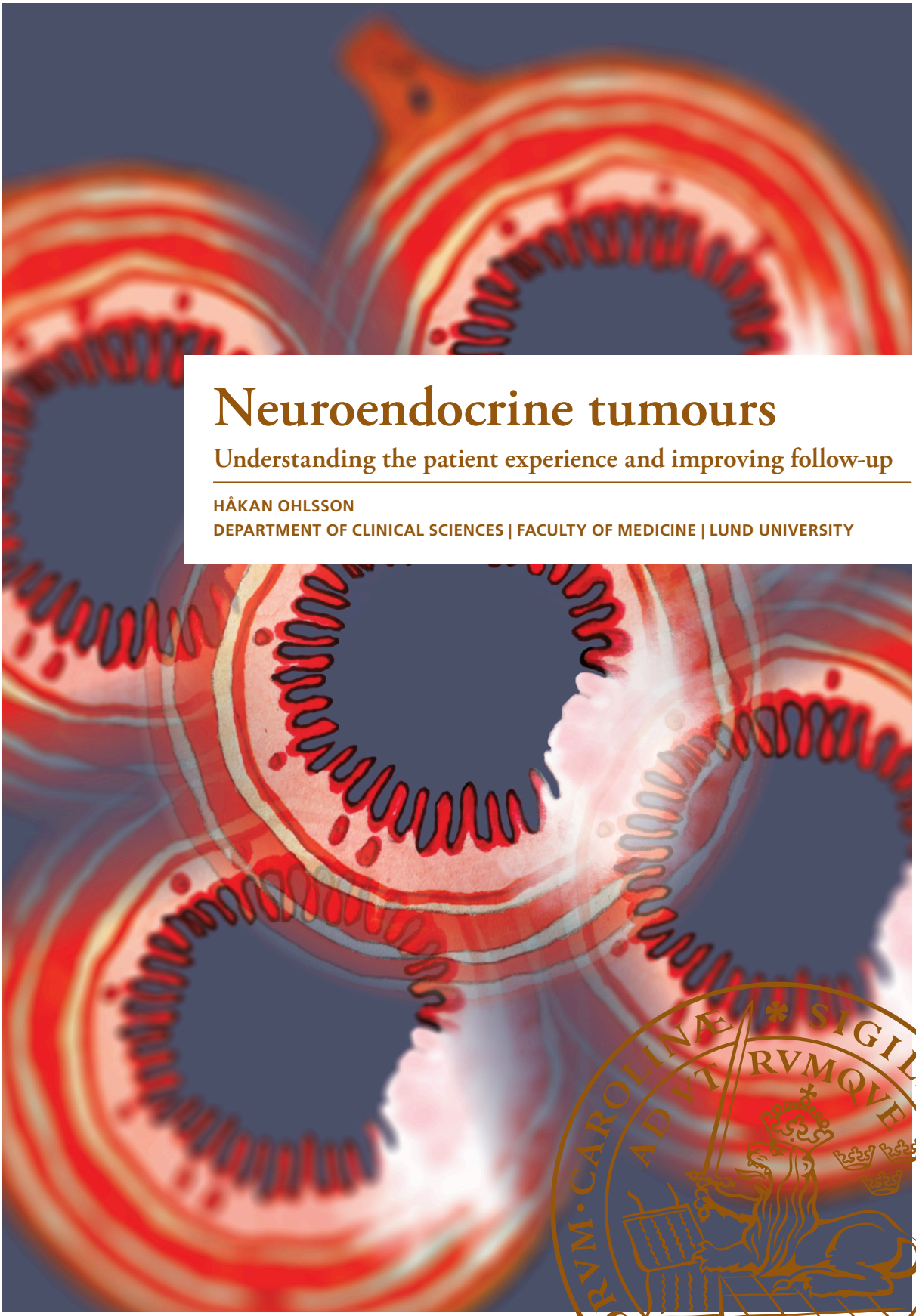

Neuroendocrine tumours

Understanding the patient experience and improving follow-up

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DEPARTMENT OF CLINICAL SCIENCES | FACULTY OF MEDICINE | LUND UNIVERSITY

HÅKAN OHLSSON works as a surgeon at the department of Surgery, Ystad Hospital, Sweden.

With this doctoral thesis we seek to develop current knowledge on the relationship between health-related quality of life, bowel symptoms, total tumour burden and overall survival in patients with neuroendocrine tumours (NET) of the small intestine. Furthermore, this thesis also aims to optimize follow-up for patients with small intestinal NET by scrutinizing the clinical impact of somatostatin receptor imaging in the follow-up setting.

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Håkan Ohlsson

LUND
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Abstract:

Neuroendocrine tumours (NETs) of the small intestine (siNET) are slow-growing malignancies often diagnosed at an advanced stage. Despite their indolent nature, patients frequently experience significant symptoms, including carcinoid syndrome (CS) with diarrhoea, which impact their health-related quality of life (HRQoL). This thesis investigates the determinants of HRQoL in siNET patients, its prognostic value, and the role of somatostatin receptor imaging (SRI) in follow-up.

The research encompasses four studies analyzing clinical and imaging data from a patient cohort at Skåne University Hospital, Lund.

In the first study, specific bowel symptoms such as stool urgency and soiling were identified as key contributors to impaired HRQoL, especially within is social and role functioning domains.

The second study examined the association between somatostatin receptor-expressing tumour volume (SRETV) and HRQoL in metastatic NET, revealing no correlation between QLQ-C30 Summary Score and SRETV and a weak correlation between SRETV and symptoms of the carcinoid syndrome.

The third study assessed the clinical utility of routine somatostatin receptor PET-CT in follow-up of metastatic siNET and found that a significant proportion (86%) of imaging did not lead to major changes in treatment, suggesting a need for more tailored surveillance protocols. The study also identified six risk factors with independent association on risk for major change in treatment.

The fourth study explored the predictive value of HRQoL on overall survival, demonstrating that lower HRQoL scores were independently associated with worse prognosis after adjustment for clinical confounders, supporting its role as a potential marker of progressive disease.

This thesis emphasizes the importance of HRQoL assessment in routine clinical care and suggest avenues for optimizing patient management, including refined follow-up strategies and targeted symptom control of socially stigmatizing bowel symptoms.

Key words: Neuroendocrine tumour, Health-related quality of life, Carcinoid syndrome, Bowel symptoms, Somatostatin receptor imaging, Prognosis

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“3,6 Roentgen. Not great. Not terrible”

-Anatoly Dyatlov, 1986

Table of Contents

Abstract

Neuroendocrine tumours (NETs) of the small intestine (siNET) are slow-growing malignancies often diagnosed at an advanced stage. Despite their indolent nature, patients frequently experience significant symptoms, including carcinoid syndrome (CS) with diarrhoea, which impact their health-related quality of life (HRQoL). This thesis investigates the determinants of HRQoL in siNET patients, its prognostic value, and the role of somatostatin receptor imaging (SRI) in follow-up.

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This thesis emphasizes the importance of HRQoL assessment in routine clinical care and suggest avenues for optimizing patient management, including refined follow-up strategies and targeted symptom control of socially stigmatizing bowel symptoms.

Thesis at a glance

Paper	Aims	Patients	Methods	Findings
I	Identify which bowel symptoms most affecting HRQoL in siNET and compare HRQoL to the general population.	119 siNET patients	HRQoL assessed via QLQ-C30 and bowel symptoms using MSKCC-BFI. Linear regression with adjustment for clinical variables used to investigate relationship between specific bowel symptoms and function scales.	Low social function and high prevalence of bowel symptoms compared to general population. Urgency, soiling, and food sensitivity had the most impact on HRQoL, especially within role and social domains.
II	Assess correlation between SRETV and HRQoL.	71 metastatic GEP-NET patients.	Linear regression between QLQ-C30 Summary Score and total tumour volume defined as either SRETV or TLSRE	No correlation between total tumour volume and overall HRQoL. Weak correlation between tumour volume and symptoms of carcinoid syndrome.
III	Evaluate how often SSTR PET-CT scans lead to major treatment changes in siNET follow-up and determine risk factors predicting major change.	164 siNET patients with ≥2 SSTR PET-CT scans 2013-2021. 570 scans (observations) included.	Retrospective review of medical records. Mixed models logistic regression between clinical factors and major change. Receiver operating curve for risk model to assess predictive accuracy and NPV.	Major change in treatment occurred after 14% of scans. Female sex, high age, normal S-CgA, normal urine 5-HIAA, no progressive disease on last scan and no extrahepatic metastasis on last scan all independently associated with no major risk. A risk model using these factors might guide reduced use of SSTR PET-CT.
IV	Determine if HRQoL is associated with survival in patients with advanced siNET.	85 patients with advanced siNET.	Cox regression between QLQ-C30 Summary Score and OS adjusting for clinical and sociodemographic factors. Model evaluation using Harrell's C and AIC.	Low HRQoL scores predicted worse survival and adds predictive accuracy on clinical parameters. Regular measurement of HRQoL for siNET patients might be useful.

Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
5-HT	Serotonin
68Ga	Gallium-68
177Lu	Lutetium-177
CgA	Chromogranin A
CNS	Central Nervous System
CS	Carcinoid Syndrome
CT	Computerized Tomography
DOTA	Tetraazacyclododecane tetraacetic acid
DOTATATE	DOTA coupled to Tyr3-Octreotate
DOTATOC	DOTA coupled to Tyr3-Octreotide
EECs	Enteroendocrine Cells
ENETS	European Neuroendocrine Tumour Society
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
GEP-NET	Gastroenteropancreatic Neuroendocrine Tumour
GI	Gastrointestinal
GI.NET21	Quality of Life Questionnaire for Gastrointestinal Neuroendocrine Tumours
HRQoL	Health-Related Quality of Life
IBS	Irritable Bowel Syndrome
IQR	Interquartile Range
MBq	Megabecquerel
MiNEN	Mixed Neuroendocrine–Non-Neuroendocrine Neoplasm
MSKCC-BFI	Memorial Sloan Kettering Cancer Center Bowel Function Instrument
MRI	Magnetic Resonance Imaging
NANETS	North American Neuroendocrine Tumour Society
NE-cells	Neuroendocrine Cells
NEC	Neuroendocrine Carcinoma
NET	Neuroendocrine Tumour
OS	Overall Survival
PET-CT	Positron Emission Tomography–Computed Tomography
PFS	Progression-Free Survival
PRO	Patient Reported Outcome
PRRT	Peptide Receptor Radionuclide Therapy

QLQ-C30	Quality of Life Questionnaire Core 30
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
S-CgA	Serum Chromogranin A
siNET	Small Intestinal Neuroendocrine Tumour
SRI	Somatostatin Receptor Imaging
SRETV	Somatostatin Receptor Expressing Tumour Volume
SSA	Somatostatin Analog
SSTR	Somatostatin Receptor
SSTR PET-CT	Somatostatin Receptor Positron Emission Tomography–Computed Tomography
SUV	Standard Uptake Value
TLSRE	Total Lesion Somatostatin Receptor Expression
ULN	Upper Limit of Normal
VOI	Volume of Interest
WHO	World Health Organization

QLQ-C30 Subscales

PF2	Physical Functioning
RF2	Role Functioning
EF	Emotional Functioning
CF	Cognitive Functioning
SF	Social Functioning
FA	Fatigue
PA	Pain
NV	Nausea and Vomiting
DY	Dyspnoea
AP	Appetite Loss
SL	Insomnia
CO	Constipation
DI	Diarrhoea
FI	Financial Impact
QL2	Global Quality of Life

GI.NET21-Specific Subscales

SF21	Social Functioning (GI.NET21-specific)
ED	Endocrine Dysfunction (e.g., flushing)
GI	Gastrointestinal Symptoms
TR	Treatment-Related Symptoms
DRW	Disease-Related Worries
MBP	Muscle and Bone Pain
SX	Sexual Functioning
INF	Information from Health Care Providers
BI	Body Image
WL	Weight Loss
WG	Weight Gain

Original papers

This thesis is based on the following original papers, referred to in the text by their roman numerals (I-IV):

I. Ohlsson H, Wahlberg G, Malmström M, Gustafsson R, Sundlöv A, Nordenström E, Almquist M. Impact of Specific Bowel Symptoms on Quality of Life in Patients with Midgut Neuroendocrine Tumours. World J Surg. 2021 Sep;45(9):2793-2803. doi: 10.1007/s00268-021-06146-9.

II. Ohlsson H, Gålne A, Trägårdh E, Malmström M, Sundlöv A, Almquist M. Relationship between somatostatin receptor expressing tumour volume and health-related quality of life in patients with metastatic GEP-NET. J Neuroendocrinol. 2022 Jun;34(6):e13139. doi: 10.1111/jne.13139.

III. Ohlsson H, Spaak E, Gålne A, Sundlöv A, Almquist M. Optimal follow-up with somatostatin receptor PET/CT imaging in patients with small intestinal neuroendocrine tumours. J Neuroendocrinol. 2024 Aug;36(8):e13396. doi: 10.1111/jne.13396.

IV. Ohlsson H, Nilsson M, Sundlöv A, Malmström M, Almquist M. Quality of life as a predictor for survival in patients with small intestinal neuroendocrine tumours. (Submitted to Journal of Neuroendocrinology)

Introduction

Neuroendocrine tumours of the small intestine (siNET) are uncommon malignancies that frequently present with metastatic disease. Nevertheless, due to the low proliferative propensity of the NET-cells, survival is often quite favourable. One unique feature of siNET is the ability to secrete serotonin which in a metastatic setting can cause the carcinoid syndrome (CS). Together with flushing of the skin, one of the more bothersome qualities of CS are debilitating bowel symptoms including abdominal pain, loose stools, urgency, and frequent bowel movements. Meanwhile, patients with siNET have lower health-related quality of life than the general population. While a relationship with diarrhoea and low HRQoL has been showed before, the specific bowel symptoms that most bother siNET-patients is not known. Adding to this, the biological and clinical factors for understanding the low QoL of siNET-patients is poorly understood. While studies have shown improvement in HRQoL after NET-directed therapy, it is still unclear whether this is explained by decreased tumour burden or control of symptoms.

Disease-related worry significantly contributes to low HRQoL in NET patients, who undergo lifelong surveillance through urine and blood tests, along with imaging with somatostatin receptor positron emission tomography and computerized tomography (SSTR PET-CT). While SSTR PET-CT has demonstrated its utility in the diagnostic and staging setting, it is unclear whether it also provides useful information during follow-up.

For many cancer forms – low HRQoL is a predictor of worse prognosis. But is it the symptoms themselves that indicate more aggressive disease or is it the depressive symptoms of low HRQoL that depletes the energy reserves of the patient? Whether the causal pathways behind this can be clarified and if this relationship exists for patients with small intestinal NET has not been studied before.

As patients with siNET now survive longer than before, HRQoL has become under increased interest. Therefore, with this thesis, we strive to illuminate the factors behind low HRQoL in patients with siNET and possibly also provide avenues for HRQoL-improvement, improved follow-up and better patient expectation management in the future.

Background

Brief history

Siegfried Obendorfer, working as a pathologist at the university of Munich, was in 1907 the first to describe a tumour in the small intestine behaving like a benign tumour but displaying carcinoma-like features microscopically[1] . He coined it karzinoide (carcinoma-like) and the term carcinoid has up until recently been used to represent this disease. During the last decade, this term has been replaced by neuroendocrine tumours (NET).

Originally, gastro-entero-pancreatic NETs (GEP-NET) were classified based on their embryological origin:

- Foregut NET: Gastric, duodenal, and pancreatic origin.
- Midgut NET: Small intestinal, appendiceal, or right/transverse colon origin.
- Hindgut NET: Left colon or rectal origin.

However, in recent decades, there has been a shift towards classifying NETs by their anatomical origin, such as small-intestine or pancreatic NET. Small intestinal NET (siNET) originate from neuroendocrine cells (NE-cells) found in the krypts of Lieberkühn throughout the GI-tract[2]. During normal intestinal physiology, the NE-cells constitute a part of the neuroendocrine system.

The neuroendocrine system of the small intestine

In 1938, it was proposed that NE-cells form part of a diffuse hormonal system, called the neuroendocrine system, which communicates with both the nervous system and nearby cells[3]. Unlike other epithelial cells of the GI-tract, NE-cells are characterised by expressing markers of the central nervous system (CNS), such as synaptophysin and Chromogranin A (CgA).

The NE-cells of the small intestine are known as enteroendocrine cells (EECs) and are found scattered among the enterocytes of the epithelium. Their exact role is not entirely understood but it is thought that they act as the sensory system of the intestinal tract by detecting ingested nutrients or metabolites from gut microbiota[4]. EECs convey this information to adjacent cells through paracrine actions, to the

nervous system via connections called neuropods, and into the bloodstream through secreted hormones. See figure 1 for an illustration. Additionally, in response to danger, EECs can enhance the barrier function of the epithelium and to act as intermediaries between epithelial cells and immune cells or other parts of the intestinal system. EECs are characterized by being able to secrete hormones, most notably serotonin (5-HT)[5]. Serotonin can, depending on which side of the blood-brain barrier it is located, act either as a hormone or a neurotransmitter. For the aim of this thesis, we will focus on the hormonal effects. Although serotonin is involved in various intestinal activities including nausea, vomiting, and secretion, it has not been shown to be responsible for any specific function[6] .

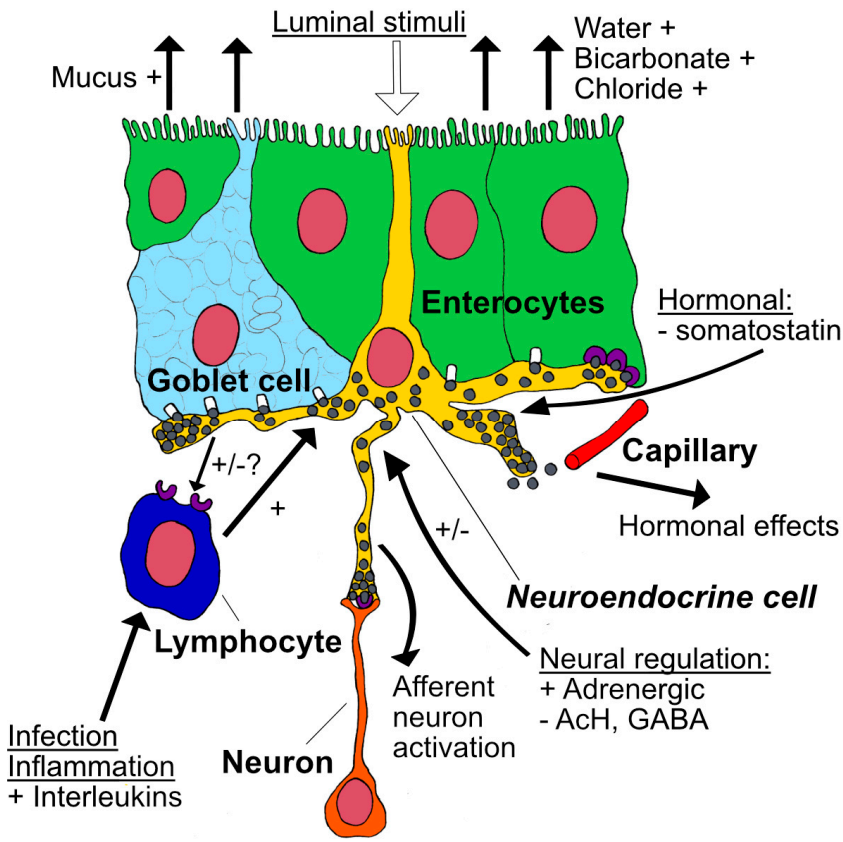

Figure 1. Schematic illustration of interactions between the neuroendocrine cell and the small intestinal milieu.

Regarding intestinal peristalsis, serotonin appears to both increase and decrease contraction of smooth muscle cells and activate both excitatory and inhibitory enteric motor neurons. The effect of serotonin on intestinal peristalsis therefore seems to be highly dependent on the experimental conditions and to the subtype of receptor expressed on the surrounding cells. For example, when exposed to bile-salt or cholera-toxin, increased serotonin release leads to increased enterocyte fluid secretion[7]. In irritable bowel syndrome (IBS), it has been hypothesized that dysregulation of the brain-gut axis through altered serotonin secretion is involved in both the diarrhoea- and constipation form of the syndrome[8].

Classification of NET

In accordance with the WHO Classification[9] of Neuroendocrine neoplasms (NENs), NENs are subclassified into a well-differentiated type (NET) or neuroendocrine cancer (NEC). While NET grows in an indolent manner, NEC behaves biologically more like an adenocarcinoma and is characterized by an aggressive course with more rapid progression and poorer survival. For NET, two proliferation indices are used:

- Immunohistochemical staining for the protein Ki-67 (indicating that the cell is undergoing mitosis). Based on the percentage of cells that express this protein, a Ki67-index is reported.
- Mitotic rate, expressed as the number of mitoses per 2 mm², determined by counting 50 fields of 0.2 mm² each, covering a total area of 10 mm²

The final grade is based on whichever of the two proliferation indices places the neoplasm in the higher-grade category. See table 1 for details. Higher grade indicates more aggressive disease[10] with grade 2 GEP-NET having a hazard ratio for death of 1.8 compared to grade 1 NET[11].

Table 1. 2019 WHO classification of Neuroendocrine Neoplasms of the gastrointestinal system. NET (Neuroendocrine tumour), NEC (Neuroendocrine carcinoma), MiNEN (Mixed neuroendocrine–non-neuroendocrine neoplasm) are categorized as follows: *Mitotic rates are expressed as the number of mitoses per 2 mm². *The Ki-67 proliferation index is calculated by counting at least 500 cells in the regions with the highest labeling intensity ("hot spots"). **Poorly differentiated NECs are inherently considered high-grade and are not formally graded.

Terminology	Differentiation	Grade	Mitotic rate*	Ki-67 index*
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2–20	3–20%
NET, G3		High	>20	>20%
NEC, small-cell type	Poorly differentiated	High**	>20	>20%
NEC, large-cell type			>20	>20%
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

Anatomical origin and functional status

In addition, as GEP-NET that originate from different anatomic sites behave biologically different and can secrete different hormones, the primary site must also be established. For example, metastatic pancreas NET (pNET) have worse prognosis than metastatic siNET with median OS of 20 and 58 months, respectively. Furthermore, NETs are subclassified into whether they secrete hormones (functioning NET) or not (non-functioning). Compared to more poorly differentiated tumours, those with lower grades are more likely to express somatostatin receptors (SSTR) and to secrete hormones.

Stage

Next to grade and origin, stage is an important factor in the initial assessment of NET. For this, the TNM system of the European Neuroendocrine Tumour Society (ENETS) is used[12,13], see table 2. The staging system is based on the depth of tumour invasion, presence of regional node metastasis and presence of distant metastasis.

Table 2. ENETS staging of small intestine NET

T – primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour invades mucosa or submucosa and size ≤1 cm
T2	Tumour invades muscularis propria or size >1 cm
T3	Tumour invades subserosa
T4	Tumour invades peritoneum/other organs
For any T add (m) for multiple tumours	
N – regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M – distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1[a]	Distant metastasis

Epidemiology and prognosis

Neuroendocrine tumours are the most common malignancy of the small intestine[15] and has become more common during the last decades with an annual, age-adjusted incidence increasing from 1.09 in 1973 to 6.98 per 100.000 persons by 2012. For GEP-NET the incidence is now 3.56 per 100.000 persons of which 1.05 of 100.000 are siNET[11]. This is reflected by a rise in 20-year limited-duration prevalence (the proportion of patients alive on a certain day and diagnosed within 20 years prior to that date), of 48 of 100.000 persons in 2012. The increased incidence can partly be explained by better diagnostics such as increased use of endoscopic procedures and cross-sectional imaging leading to earlier detection of localized NET and an ageing population (with NET being more common in the later decades in life). The rise in limited-duration prevalence is caused by both higher incidence and the markedly improved survival which has occurred during the last decades. Interestingly, the incidence of metastatic NET has decreased while regional NET has remained stable[16]. Women are diagnosed somewhat less common than men and have a slightly better prognosis[17].

For siNET, compared to other malignant neoplasms, the overall survival is quite favourable, see figure 2. Unsurprisingly, advanced stage is related to shorter overall survival[18]. According to a recent meta-analysis, 5-year overall survival (OS) is 67% for siNET (grade 1 and 2) with distant metastasis[19]. For localized and regional siNET, median OS is 13 and 12 years, respectively[11].

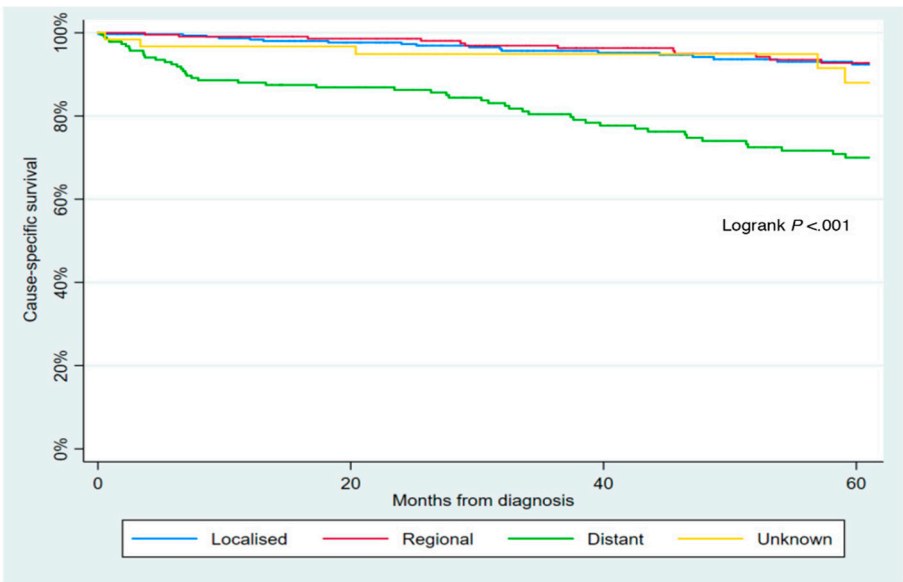

Figure 2. Five-year cause-specific survival for patients with small intestinal NET.
Patients grouped by stage. Reprinted from[16] © ,with permission from Elsevier.

Imaging

In order to achieve accurate diagnosis and staging, imaging of NET is essential. Being readily available and achieving high morphological resolution, the first-line method for this is computerized tomography (CT). Meanwhile, CT has its limitations, mainly in detection of small NET-metastases in lymph nodes, small liver metastases, bone and peritoneum[20]. Although not suitable for evaluation of larger areas of the body; for select areas such as the brain, liver and pancreas, contrast-enhanced magnetic resonance imaging (MRI) is preferred[21].

Somatostatin receptor PET-CT

Somatostatin receptor positron emission tomography computerized tomography (SSTR PET-CT) exploits the fact that well-differentiated NET cells express SSTR on its surface. By intravenous injection of a somatostatin analogue (DOTA-TOC or DOTA-TATE) bound to a positron-emitting isotope (e.g. ^{68}Gallium), increased uptake in the body indicating NET can be imaged using positron emission tomography (PET). While several variants of this technique are available, at our institution, ^{68}Ga-DOTA-TATE was used for somatostatin receptor imaging until 2019. For regulatory reasons following the approval of Somakit TOC by the European Medicines Agency in 2019[22], there was a shift in production to the equally accurate ^{68}Ga-DOTA-TOC at Skåne University Hospital.

Although the resolution of PET-imaging can restrict detection of very small lesions, the diagnostic accuracy is high with sensitivity and specificity at 91%[23]. In the staging setting, SSTR PET-CT has repeatedly been shown to have a strong impact on clinical decision making[24–29]. The main drawbacks of SSTR PET-CT are low availability, radiation exposure and significantly higher cost with ^{68}Ga-DOTA-TATE PET/CT being priced at 24453 SEK compared to 2490 SEK for CT[30]. Consequently, SSTR PET-CT is recommended by guidelines for staging, restaging and determination of SSTR-status[31,32].

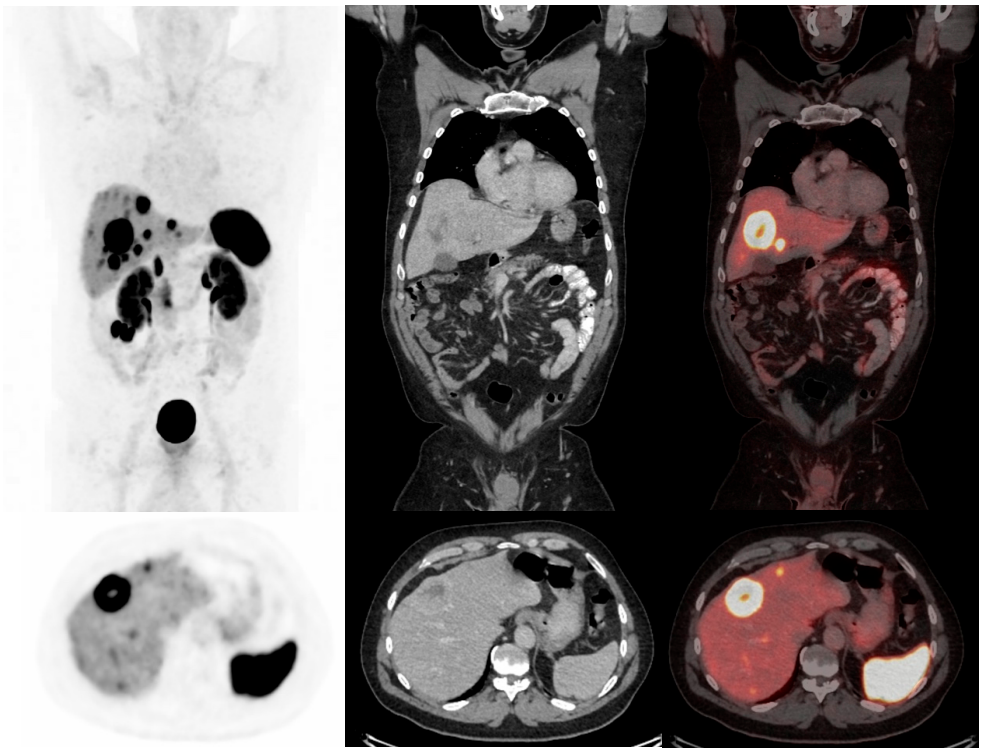

Figure 3. Example of images from somatostatin receptor PET-CT on a patient with NET.
Top row shows coronal projections and bottom row shows axial projections. The left images show uptake intensity of SSTR on PET, the middle are CT images without PET and the images on the right shows combined PET-CT. Reprinted with permission from A Gålne.

Since the introduction of SSTR PET-CT, there has been an interest to assess the parameters of SSTR PET-CT with the outcome of NET patients[33,34]. A method has recently been described for measuring somatostatin receptor expressing tumour volume (SRETV), and an estimation of total lesion somatostatin receptor expression (TLSRE) on ^{68}Ga-DOTA-TATE PET/CT[35]. Of these, a strong association was demonstrated between total SRETV and PFS[36].

Clinical picture and the carcinoid syndrome

The slow-growing nature of SiNET can lead to an insidious clinical presentation with few symptoms until advanced stage is noticed. Consequently, 39% and 38% of cases present with regional or metastasized disease, respectively[37]. Moreover, siNET often present with multifocal tumours (30% of cases)[38] and frequently also infiltrate the surrounding mesentery. This infiltration causes a desmoplastic reaction

and fibrosis which can lead to both small bowel obstruction (SBO) or intestinal ischemia.

For regional and localized disease, the serotonin from functioning NETs are metabolized in the liver. However, when metastases in or beyond the liver has developed, serotonin can enter the systemic circulation and cause wheezing, flushing of the skin and diarrhoea. The high levels of serotonin can also cause right-sided heart disease through tricuspid valve fibrosis. First described by the Malmö-based doctors Thorson, Biörck and Waldenström in 1954, these symptoms, together with metastatic functioning siNET, constitutes the carcinoid syndrome (CS) [39]. At diagnosis, 20% of patients with NET have the carcinoid syndrome and 40% of those that present with metastatic disease[40].

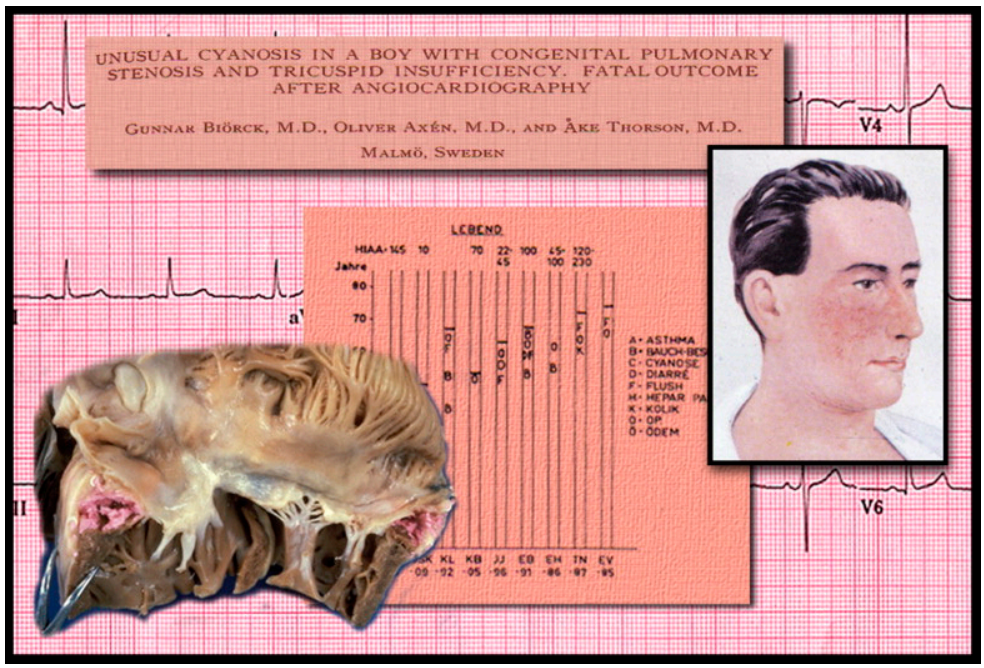

Figure 4. The clinical manifestations of carcinoid diseas.
First described in 1952 by Biörck and colleagues (frontispiece, top center), when they characterized a constellation of symptoms (bottom center) including flushing (top right), diarrhoea, edema, wheezing, and right-sided heart failure, the latter of which results from the deposition of fibrotic subendocardial plaques (bottom left; fibrotic plaques stained pink) and is commonly referred to as "carcinoid heart disease." This syndrome is associated with abnormally high levels of the serotonin metabolite 5-HIAA (center). Reprinted from Modlin et al[41] © 2004, with permission from Elsevier

Bowel symptoms

Although serotonin has a wide range of effects in the small intestinal epithelial milieu, the diarrhoea of the carcinoid syndrome is thought to be caused both by gastrointestinal motor dysfunction and increased secretion. One prominent study from the pre-SSA era in 1993 showed a 50% decreased transit-time through the small intestine and six times faster transit in the colon in patients with siNET and CS, compared to healthy subjects. Postprandial colonic tone is also markedly increased in subjects with CS[42] and jejunal perfusion studies showed net-secretion instead of net-absorption in the small intestine of NET patients with CS[43]. While CS is the main cause for bowel symptoms in patients with NET, other causes are also possible. These include [44,45]:

- Bile acid malabsorption after small bowel resection and/or right hemicolectomy
- Small intestinal bacterial overgrowth after the above surgical procedures.
- Pancreatic insufficiency from somatostatin analogue treatment
- Intestinal ischemia due to mesenteric tumour spread.

The diarrhoea in patients with NET is often a major concern for patients. One study using qualitative methodology by conducting exit interviews following a clinical trial on siNET-patients with CS indicated that diarrhoea was a multi-facetted concept. The multiple facets included loose stool, urgent bowel movements, frequent bowel movement, being unable to go to the toilet fast enough, having another bowel movement immediately after another, and soiling[46]. Based on this, we suggest that bowel symptoms may be a better umbrella term for these symptoms, rather than, in this context, the poorly defined term “diarrhoea”.

Medical therapy

The increased survival rate of later years for metastasized NET is not only explained by the slow-growing nature of NET but also by improved therapeutics, most notably somatostatin analogues (SSA). SSA resemble the naturally occurring hormone somatostatin which acts to inhibit hormone excretion, cell growth and smooth muscle contraction. Consequently, SSA is effective in controlling the symptoms of the carcinoid syndrome[47,48] with improvement in flushing and diarrhoea in up to 80% of patients[35,36] . In addition, SSA controls tumour growth with improvement of time to tumour progression[49] and increased progression-free survival compared to placebo[50]. SSA is first-line therapy for low-grade GEP-NET and is taken as long-acting subcutaneous injections every 4 weeks (but can be increased to every 2 weeks if symptom control is not achieved). For patients with SSA-refractory CS diarrhoea,

treatment with telotristat ethyl (an inhibitor of the synthesis of serotonin) can be added[51,52].

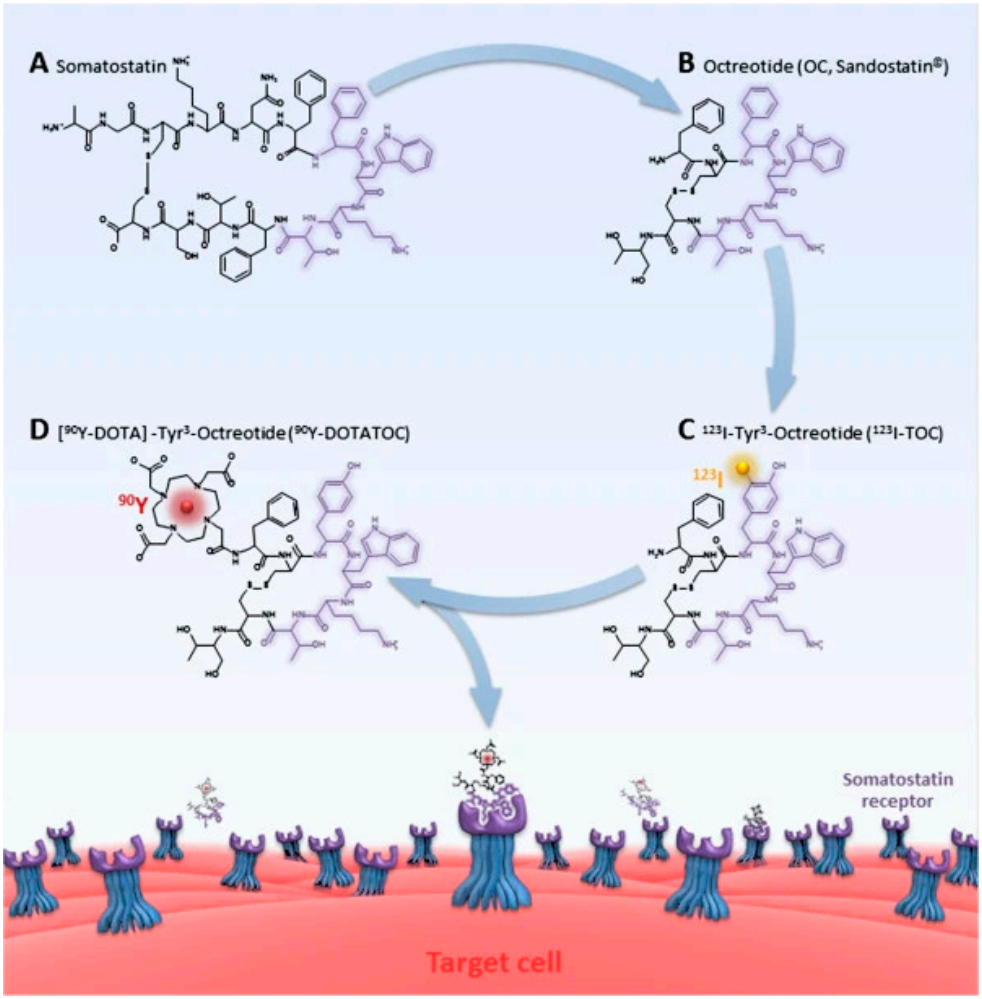

Figure 5. Schematic overview of somatostatin analogue alterations for different purposes.
The natural somatostatin receptor ligand, the 14 amino acid peptide somatostatin (A), was tied to the biologically more stable 8 amino acid peptide Octreotide (OC, B), which is used for the treatment of symptomatic neuroendocrine tumours. Introduction of a tyrosine into the 3rd position of the Octreotide sequence resulted in Tyr^3-Octreotide (TOC, C), which allows for iodination of the tyrosine residue with the γ-emitter ^{123}I and subsequent somatostatin receptor targeted imaging. For the use in somatostatin receptor targeted radiotherapy TOC was coupled with the chelator DOTA, which led to the octapeptide DOTA-TOC (D). © Reprinted under Creative Commons from Marincek et al.

For patients with metastatic progressive siNET despite SSA-treatment, peptide receptor radionuclide therapy (PPRT), is indicated. Similar to SSTR PET-CT, PRRT exploits the SSTR-expression of NET by injection of a beta-emitting isotope, ^{177}Lu-DOTATATE, coupled to SSA. While PRRT has shown improved progression-free survival (PFS) and prolonged time to deterioration of symptoms and quality of life[53], statistically significant improved OS has still not been shown[54].

Surgical treatment

For resectable stage T1-4, N0-1 M0 siNET, surgery of all primary tumours and systematic lymphadenectomy with macroscopic radical intent is recommended by guidelines[10,55,56]. For patients with stage IV disease, a tailored approach is necessary, considering the extent of liver metastasis, tumour grade, performance status, comorbidities and risk for surgical complications[57]. This being said, resection of the primary tumour is often indicated in order to control local symptoms such as small bowel obstruction or intestinal ischemia[58] or as a debulking intervention to control CS-symptoms. Interestingly, a recent meta-analysis indicated improved median OS after resection of the primary tumour without curative intent[59]. For liver metastases, surgical resection, vascular embolization or radiofrequency ablation can be considered and sometimes also in combination in order to obtain radicality while preserving residual liver function[10].

Biomarkers

Chromogranin A (CgA) is a protein that is normally stored in intracellular secretory vesicles in neuroendocrine cells. The normal range varies according to the assay used with levels double or triple the upper limit of normal (ULN) considered pathological. In patients with NET, serum CgA-levels are often but not always increased with a recent meta-analysis showing a pooled sensitivity of 0.73 and pooled specificity of 0.95[60], suggesting that S-CgA is better to rule in NET than to rule out NET. However, if elevated at diagnosis, S-CgA is a sensitive biomarker for monitoring of both functioning and non-functioning NET[61]. However, as elevated CgA can be caused by a variety of factors [62,63] including systemic inflammation, use of proton pump inhibitors and renal insufficiency, its use has come into increased scrutiny. CgA is correlated to tumour load[64–66] with increased CgA associated with more advanced and/or progressive disease and worsened survival[61,67] . In addition, and with special significance for this thesis, increased CgA is also correlated with impaired patient-reported physical functioning and overall quality of life[68] . In the follow-up setting, an increase of CgA ≥25% is often used[69–71] to denote progressive or recurrence of NET.

For siNET, the urinary metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), is used to confirm functioning, i.e. hormone producing, status of the tumour[72]. Higher levels of urine 5-HIAA indicates more circulating serotonin which is correlated to increased risk of carcinoid heart disease[73] and worsened CS-symptoms. In patients without treatment with SSA, elevated 5-HIAA >42µmol/24h can predict metastatic siNET disease with a sensitivity of 82% and specificity of 86%[66].

Follow-up

As progression can occur unpredictably and disease recurrence can occur even after a prolonged interval following primary tumour surgery[74], optimal follow-up for siNET is important. An overview of guidelines from the European Neuroendocrine Tumour Society (ENETS) [74] and the European society of medical oncology (ESMO)[75] , North American Neuroendocrine Tumour Society (NANETS)[76] and Swedish guidelines[77] are presented in table 3. Due to a general lack of high-quality evidence, guidelines often make different recommendations. During the study period and in order to detect smaller SSTR-positive lesions, our institution has used SSTR PET-CT, CgA and urine 5-HIAA every 12 months as follow-up for siNET-patients.

Table 3. Guideline recommendations for follow-up of NET. Biochemical markers = urine 5-HIAA and S-CgA.

Disease Status	ENETS Guidelines[73]	NANETS Guidelines[75]	ESMO Guidelines[74]	Swedish Guidelines[76]
Radically Resected Local/ Regional Disease	Imaging (CT/MRI) every 6–12 months for 3–5 years, then annually if stable. Biochemical markers every 6–12 months. Clinical assessment every 6–12 months.	Follow-up for at least 7 years due to risk of late recurrence. Imaging every 6–12 months. Biochemical markers every 6–12 months.	Imaging every 6 months for 2 years, then annuallyif no recurrence. Biochemical markers every 6–12 months. Clinical assessment every 6 months initially, then annually.	Somatostatin receptor PET-CT after 3–6 months, then annual biochemical monitoring for 5–10 years if elevated levels before surgery, otherwise annual CT/MRI.
Radically Resected Metastatic Disease	Imaging every 3–6 monthsfor 2 years, then 6–12 months. Biochemical markers every 3–6 months. Clinical follow-up every 3–6 months.	Follow-up every 3–6 monthswith imaging and biomarkers.	Imaging every 3–6 months for 2 years, then 6–12 months. Biochemical markers every 3–6 months.	PET-CT after 3–6 months, then imaging and biochemical monitoring every 6 months for 2 years, followed by annual follow-up for up to 10 years.
Non-Radically Resected Local/ Regional Disease	Imaging every 3–6 months based on disease burden. Biochemical markers every 3–6 months. Clinical assessment every 3–6 months.	Imaging every 3–6 months. Biochemical markers every 3–6 months. Clinical assessment every 3–6 months.	Imaging every 3–6 months for progressive disease, otherwise every 6 months. Biochemical markers every 3–6 months. Clinical assessment every 3–6 months.	CT/MRI every 3–6 months with biochemical markers and PET-CT if signs of progressive disease. Lifelong follow-up.
Metastatic Disease (Non-Curable)	Imaging every 3–6 months. Biochemical markers every 3–6 months. Clinical assessment every 3–6 months. Adjust follow-up based on therapy response.	Imaging every 3–6 months. Biochemical markers every 3–6 months. Clinical assessment every 3–6 months.	Imaging every 3–6 months for progressive disease, every 6 months if stable. Biochemical markers every 3–6 months. Clinical assessment every 3–6 months.	Individualised as decided on tumour board. Lifelong follow-up.

While follow-up is indicated in NET and imaging is superior to biomarkers[78], the standards for these are not clearly defined. For example, if RECIST (Response Evaluation Criteria in Solid Tumours) with thresholds not suited for the slow development of NET are used, NET might be misclassified as stable[79]. Moreover, whether SRI should be used only in the diagnostic setting or also as follow-up after treatment is still contested by experts[78].

Quality of Life and patient reported outcomes

The earliest known reference to the concept of Quality of Life (QoL) comes from Aristotle's Nichomacean Ethics[80]:

"Both the multitude and persons of refinement … conceive the 'good life' or 'doing well' to be the same thing as 'being happy. But what constitutes happiness is a matter of dispute … some say one thing and some another, indeed very often even the same man says different things at different times: when he falls sick he thinks health is happiness, when he is poor, wealth."

From this text it is evident that Aristotle already understood then what we still debate today – that QoL was is not easily defined and that naturally it is inherently subjective and thus difficult to measure.

Health-related quality of life

WHO defines Quality of Life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[81]. However, in the context of health care and clinical trials, this definition is too broad to be useful. Therefore, the concept of health-related quality of life (HRQoL) is used in these situations instead[82]. Although also quite poorly defined, HRQoL is commonly regarded as a latent construct, i.e. an abstract concept that cannot be observed or measured directly, that reflects the impact of disease on patients' ability to live their life. As diseases and their treatments can affect patients in different and often independent ways, HRQoL is often considered to be multidimensional. This means that HRQoL often includes several different functional domains, symptom intensity of the most common symptoms and global quality of life.

During the last two decades, a greater emphasis has been put on assessment of HRQoL. The main reason for this shift is that HRQoL-studies has provided several important insights[82]:

- For therapies with curative intent, side-effects can lead to diminished HRQoL. If the study shows equal survival for different treatments, HRQoL can be the endpoint that guides which treatment is preferable.
- When studying disease where the intent is palliative, studies using patient-reported outcomes (PROs) can explain which symptoms have the greatest impact on HRQoL. This shifts the focus from providing relief of specific symptoms towards providing relief of that which bothers the patients the most.
- HRQoL-studies can provide a description of what symptoms the patient can expect when diagnosed with a certain disease or when offered a new treatment, thus facilitating expectation management.
- Long-term survivors of cancer can have lasting side-effects from treatment that HRQoL-studies can help illuminate.
- In patients with cancer, low HRQoL is correlated to worse prognosis[83–89].

If we were to elaborate on this last point, the largest 2 studies[83,85], based on prospective data from prospective clinical trials of several different cancer types, have indicated a relatively small added prognostic value (5-6%) of HRQoL when adjusting for performance status, metastatic disease, age and sex. Meanwhile, significant heterogeneity was noted when analysing subsets of the first cohort [83]:

- Physical function was significantly prognostic for melanoma, colorectal cancer, lung cancer, oesophageal cancer, and breast cancer.
- Pain was significantly prognostic for colorectal cancer and lung cancer.
- Appetite loss was significantly prognostic for colorectal cancer and prostate cancer.
- Dyspnoea was significantly prognostic for head and neck cancer.

Therefore, both studies concluded that the prognostic value of HRQoL on survival is probably heterogenous depending on cancer type. Obviously, it is not clear in what direction the causality is working. Is it that more aggressive disease leads to more symptoms and thus lowered HRQoL? Or is it that lower HRQoL in some way can affect the outcome? Whichever way it goes, this information can help guide medical decision making (such as opting to offer more aggressive treatment up-front).

Different global QoL-scales put varying emphasis on the coping process, e.g. some scales ask “how would you rate your overall life?” while others, such as the *Perceived adjustment to chronic illness scale,* ask “how much effort does it cost you to cope with your illness?”[90]. To compensate for the fact that some concepts, such as emotional or social functioning, can mean different things in different cultures

and for different people, these concepts consist of multiple items. Conversely, more easily defined concepts (such as pain) may only consist of one item.

Patient reported outcomes (PROs) is the basis of HRQoL research and is defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's report by a clinician or anyone else"[91]. To achieve this, the method of measuring HRQoL is frequently based on validated questionnaires, also called *instruments.*

HRQoL instruments

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 is a widely used questionnaire for patients diagnosed with cancer[92]. It is a multidimensional instrument covering five functional domains:

- Physical function (PF2) – the need for rest during the day and the ability to care for oneself and/or do strenuous activities.
- Role function (RF) – the ability to carry out work or hobbies.
- Cognitive function (CF) – the ability to concentrate and remember
- Social function (SF) – impact of the disease on relationships with friends and family
- Emotional function (EF) – presence of depressive symptoms and/or anxiety.

The QLQ-C30 also includes questions about nine common symptoms of cancer: fatigue (FA), pain (PA), nausea and vomiting (NV), dyspnoea (DY), loss of appetite (AP), insomnia (SL), constipation (CO), diarrhoea (DI). Finally, it also includes the diseases impact on patients' financial situation (FI) and a global QoL question (QL2).

The QLQ-C30 is modular, meaning that it can be combined with other, more disease-specific instruments. For patients with NET, the module GI.NET21 is used[93]. This instrument complements the QLQ-C30 with an additional social function scale (SF21) and 10 disease-specific symptom scales: endocrine dysfunction i.e. flushing (ED), gastrointestinal symptoms (GI), treatment-related symptoms (TR), disease related worries (DRW), muscle and bone pain (MBP), sexual functioning (SX), information from health care providers (INF), body image (BI), weight loss (WL) and weight gain (WG).

One problem with asking global questions about HRQoL such as "During the last week, how would you describe your overall quality of life?" is its general vagueness. Accordingly, it can be interpreted in different ways, reducing the validity and interpretability. Many researchers therefore argue that, when evaluating overall

QoL, global questions should not be used and that instead QoL should only be presented as a multidimensional construct with every subscale presented separately. However, for studies where HRQoL is the primary outcome, this results in multiple testing which increases the risk of committing a type 1 error. To overcome this, summated scores combining all or some of the subscales are frequently used. For QLQ-C30, seven different summated scores based on different conceptualisations of how the subscales are related to each other were proposed in 2012[94]. A later study, drawing from this work, used structural equation modelling to show that a score using all variables (with all scales having equal weight) except QL2 and FI was the best performing single higher order factor model in terms of known-groups validity and responsiveness to change over time[95]. The model is denoted QLQ-C30 Summary Score and is recommended by the EORTC QLQ-C30 Quality of Life group when HRQoL is the primary endpoint of a study[95].

In HRQoL-research, the term *validity* is central. Validity means that the scale is indeed measuring the underlying latent construct. Internal validity can be tested by comparing the responses of the questions within a specific multi-item scale with each other and calculating the Cronbach-alpha value. External validity is tested by correlating the items with other instruments and scales, e.g. comparing PF2 with WHO performance status. QLQ-C30, GI.NET21 and MSKCC-BFI have all been shown to have good internal and external validity[92,96,97].

When interpreting research on Quality of Life, there is a need to establish what degree of impaired function or increased symptoms that constitute significant change. Previously, research by Osoba et al [98] indicated that a change in 5-10 of the QLQ-C30 indicated a small change, 10-20 indicated moderate change while >20 indicated large change. Recently similar thresholds of clinical importance[99] have been established for cross-sectional studies, which only include one measurement of HRQoL. From this work it is evident that patients are more sensitive to loss of physical function than role- or social functioning and that even occasional bouts of nausea & vomiting constitute clinically relevant symptoms. See figure 6 for details.

Several studies have shown that bowel symptoms are associated with worsened HRQoL in patients with NET[100,101]. Since there is no bowel symptom instrument specifically designed and validated for patients with NET, we searched the literature for instruments used in patients with similar bowel symptoms and found The Memorial Sloan Kettering Cancer Centre Bowel Function Instrument (MSKCC-BFI)[97]. The MSKCC-BFI was developed to evaluate bowel symptoms after rectal cancer surgery and consists of 18 items enquiring broadly and specifically into a range of bowel symptoms.

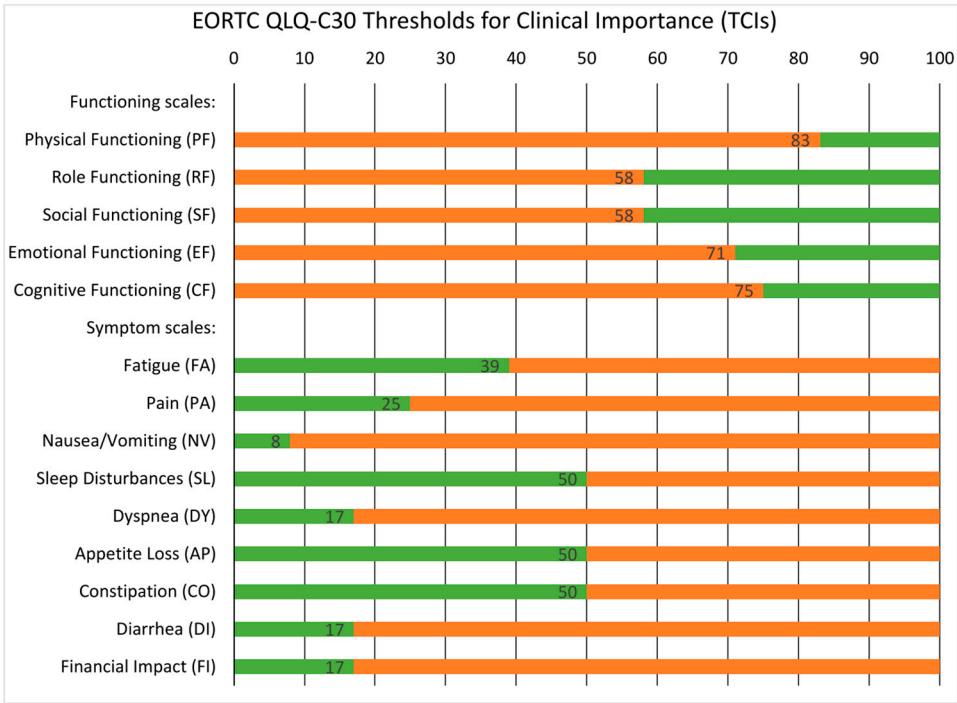

Figure 6. Thresholds of clinical importance for the subscales of the EORTC QLQ-C30.

HRQoL in patients with NET

Patients with NET have a lower median global QoL (67 of 100) than the general population[102,103] (75) and about equal HRQoL as patients with colorectal cancer (67) but higher than patients with hepatobiliary (58) or upper-GI cancer (50) [104,105]. Main determinants for lower HRQoL are symptoms of the carcinoid syndrome (diarrhoea and flushing) and fatigue[106]. Women with NET tend to have more flushing symptoms, more disease related worries and lower global QoL and lower physical function than men (with median values of 58 vs 75 for QL2)[104]. That women have more symptoms as reported on PROs is in line with results from studies on the general population[107]. Other factors generally associated with low HRQoL are low socioeconomic status[108], old age[105] and underlying comorbidities[87].

Qualitative exit-interviews from the TELESTAR-study [46] indicated that symptoms related to bowel movement frequency and urgency had the greatest impact on patients HRQoL, especially within social, occupational, physical, and emotional domains. A post-hoc quantitative analysis of the same study showed that lasting control of bowel symptoms was associated with better HRQoL[109]. In patients with

colorectal cancer, such specific bowel symptoms have been explicitly evaluated[110,111] and found to decrease HRQoL with varying impact.

While debulking surgery can be used to control symptoms of NET[58,112], whether it also leads to improved HRQoL is unclear. In addition, inhibition of tumour hormone secretion by SSA-analogues was not shown to improve QLQ-C30 global QoL[50]. Conversely, PRRT has been reliably shown to improve scores in the QLQ-C30 domains global QoL, diarrhoea, insomnia and appetite loss[113], as well as time to deterioration in other domains[114]. A recently published review noted that no studies had investigated how disease stage and tumour function affected HRQoL in GEP-NET patients[115]. However, one study, not included in the above-mentioned review, did indeed examine the relationship between tumour burden and HRQoL, and reported a moderate correlation between a nonstandard version of tumour stage and total scores of Norfolk QoL-NET and the GI.NET21 module[116]. To summarize, it seems clear that studies on HRQoL and NET suffer from high heterogeneity and non-standardized reporting of HRQoL, which impedes interpretation. Whether better interpretation of HRQoL in patients with NET can be achieved by using a summary score is one concept that this thesis aims to explore further.

Aims

The overall aim of this thesis was to understand the relationship between NET, its related symptoms, and HRQoL and to investigate whether improved follow-up is possible for these patients.

Specific aims:

Paper I	To determine which specific bowel symptoms (i.e. sensitivity to food, soiling, loose stools, etc.) that have the greatest impact on siNET-patient's HRQoL and to compare HRQoL of the cohort with the general population.
Paper II	To determine whether total somatostatin receptor expressing tumour volume on SSTR PET-CT was associated with decreased HRQoL in patients with gastro-entero-pancreatic (GEP) NET.
Paper III	1. To determine the clinical value of SSTR PET-CT in the follow up of patients with siNET. 2. To determine which tumour- or patient factors that are most predictive of major treatment change with the goal of identifying subgroups of patients with high vs. low risks of a change in treatment, perhaps making some SSTR PET-CT scans unnecessary.
Paper IV	To determine whether a summary score of QLQ-C30 can add predictive power to clinical and sociodemographic variables on overall survival in patients with advanced siNET and in a secondary analysis, to explore specific HRQoL domains with the highest predictive power on overall survival.

Patients and methods

Patients

All four papers concern patients with neuroendocrine tumours with follow-up at Skåne University Hospital of Lund:

Paper I

Patients alive on 1 September 2019 in the southern hospital region of Sweden and whose histopathological diagnosis of well-differentiated (G1-G2) NET with origin in the gastrointestinal tract had been established between 1 January 2000 and 31 December 2018 were eligible for inclusion. The following exclusion criteria were used:

- Non-metastasized neuroendocrine tumours (NET) that only required endoscopic resection.
- Appendiceal NET where appendectomy sufficed as the only treatment
- NET found incidentally during resection of another cancer
- Synchronous inoperable colorectal cancer
- Synchronous inflammatory bowel disease

Patients were identified by searching for gastrointestinal NET codes according to the Systematized Nomenclature of Medicine (SNOMED) system in the pathological database of Region Skåne. Eligible patients were invited by regular mail. Patients were sent questionnaires and an informed consent form. If a patient did not reply within one month, one reminder letter was sent to the patient.

Patients who replied that they did not wish to participate, and patients who did not reply within two months after one reminder, were considered non-responders. To minimize heterogeneity in the cohort and since bowel symptoms are most common from tumours with origin in the middle GI-tract, only patients with origin from small intestine and right colon, i.e. the group previously denoted midgut NET, were included in the subsequent analysis.

Paper II

The GEP-NET cohort of 165 patients from Paper I was used with the addition of the following exclusion criteria:

- Patients without evidence of metastatic disease (including lymph node metastasis).
- No ^{68}Ga-DOTA-TATE/TOC PET-CT within one year before or after the date of answering the HRQoL-questionnaires.
- Tumour-modulating treatment (PRRT, surgery, chemotherapy, SIRT, ablation) between ^{68}Ga-DOTA-TATE/TOC PET-CT and answering the questionnaires.

These criteria resulted in a further exclusion of 94 patients: some 92 due to non-metastatic disease, one due to chemotherapy between scan and questionnaire and one subsequently declining to participate. The final cohort included 71 patients.

Paper III

Since the third study did not include HRQoL-data, informed consent was not deemed necessary. All adult (aged 18 years or over) patients with histologically verified siNET who had undergone at least two SRI scans between March 21st 2013 (the date when ^{68}Ga-DOTATATE PET/CT was introduced in our institution) and September 1st 2021 and who were followed at Skåne University Hospital, Lund, were eligible for inclusion in the study. Consequently, compared to the other studies, a more complete coverage with 164 patients could be achieved.

Patients were identified by searching the picture archiving and communication system (PACS) using the procedure codes for ^{68}Ga-DOTA-TATE PET-CT and ^{68}Ga-DOTA-TOC PET-CT, respectively. Histopathological diagnosis was verified by reviewing each patient's electronic medical record.

Paper IV

All 109 patients with siNET in the GEP-NET cohort from paper I were included. Of these, 24 patients were excluded due to non-residual disease. The final cohort consisted of 85 patients with residual siNET, either regional or metastatic.

Methods

HRQoL instruments

For papers I, II and IV, the EORTC QLQ-C30 (version 3.0) cancer generic HRQoL-instrument was used together with the NET-specific adjunct GI.NET21.

For the EORTC-instruments, the scoring procedure starts with adding the scores from the questions within the same domain and dividing by the number of items within the domain, yielding a raw score[117]. The raw score is then linearly transformed into values between 0-100 with 100 indicating high function/perfect QoL. However, for symptoms the scales are reversed so that higher values indicate more severe symptoms. Translated Swedish versions provided by EORTC were used in the study.

In paper I, the MSKCC-BFI was used. Translation from English to Swedish was done by the authors. Items in the MSKCC-BFI enquire how often symptoms occur: never, rarely, often, or always, except for the first item, which asks how many bowel movements a patient has per day. Answers to item 1 were transformed into quintiles, and answers from items 4, 5, 7, 11, and 12 were inverted, so that lower scores reflect more symptoms for all items, as per the reference manual[97]. While a manual exists for incorporating the symptoms into a total score and three domains, as the aim of the study was to evaluate specific symptoms, each symptom was presented and treated separately.

For papers II and IV, the QLQ-C30 Summary Score[95] was used and obtained by taking the mean value of all included subscales of the EORTC QLQ-C30 except QL2 and FI. In paper IV, in order to investigate the added value of NET-specific symptoms, the mean values of non-missing subscales of the EORTC GI.NET21 was included in this average score, yielding two summary scores.

PET-CT protocols

For papers II and III, the methodology included somatostatin receptor imaging with PET/CT. These scans were performed using a Discovery MI or Discovery D690 (GE Healthcare®, Milwaukee, WI, USA) PET-CT system. Ga-DOTA-TATE was used for somatostatin receptor imaging until 2019. For regulatory reasons following the approval of Somakit TOC by the European Medicines Agency in 2019[22], there was a shift in production to ^{68}Ga-DOTA-TOC at Skåne University Hospital. Both ^{68}Ga-DOTA-TATE and ^{68}Ga-DOTA-TOC were prepared according to established techniques[31,118,119]. Intravenous injection of an activity of 2.0-2.5 MBq/kg (minimum administered activity 100 MBq and maximum 300 MBq) was followed 60 minutes later by a PET-CT scan from mid-thigh to the top of the head, and the

PET acquisition time was about 3 min per bed position. Either a low-dose CT scan or a diagnostic CT was performed simultaneously for attenuation correction and anatomic correlation. If a recent diagnostic CT was available, only a low-dose CT was acquired during the PET-CT examination.

Image analysis

For paper II, if a patient had had more than one ^{68}Ga-DOTA-TATE/TOC within the timeframe allowed by the inclusion criteria, the most recent scan was chosen in terms of the date the questionnaires were answered. Images were analysed retrospectively by Anni Gålne and Elin Trägårdh. Semi-automatic segmentation of tumours, i.e. computer-assisted image analysis that requires some level of user interaction to define and refine volumes of interest (VOIs), was performed using the software Hermes® (Hermes Medical Solutions, Stockholm, Sweden). To quantify tumour burden in each, somatostatin receptor expressing tumour volume (SRETV) and total lesion somatostatin receptor expression (TLSRE) was used. SRETV was defined as tumour volume (measured in millilitres, ml) with uptake higher than 50% of maximum standard uptake value (SUVmax) in a VOI. TLSRE was defined as the product of SRETV and mean SUV (SUVmean) per lesion. Pathological uptake of ^{68}Ga-DOTA-TATE/TOC was considered significant for tumour segmentation if SUVmax was >3 and did not correspond to physiological uptake. A relatively high normal background uptake in the liver meant that manually drawn VOIs were often needed to avoid physiological uptake, as previously described[36]. Overlap between tumour volumes was avoided. The sum of all SRETV was calculated within seven separate anatomical sites (liver, pancreas, GI tract, mesenteric lymph nodes, other lymph nodes, skeletal and other).

Total tumour volume for each patient was the sum of these values and denoted as ΣSRETV. Corresponding calculations were made for ΣTLSRE.

Clinical variables

For papers I, II and IV, electronic medical records were searched for relevant information regarding other comorbidities, primary tumour site, presence of distant metastasis or residual tumour, Ki67 index at primary histopathological diagnosis, tumour grade, previous tumour surgeries, treatment with SSA, treatment with anti-diarrhoeal agents or laxatives, levels of 24 hour urine 5-HIAA, levels of serum chromogranin A (S-CgA), years since diagnosis, and previous or ongoing peptide-related radionuclide therapy (PRRT) or chemotherapy. For analyses were a categorical variable was needed, the biomarkers were categorized into below upper limit of normal (ULN), above ULN or missing. The ULN were decided according to the standards of the local laboratory of Skånes University Hospital (SUS). For S-CgA the ULN is 2 nmol/liter and for urine 5-HIAA the ULN is 50μmol/24h.

In order to quantify the burden of comorbidities, the Charlson comorbidity index (Charlson CMI) was used. The Charlson CMI assigns weighted points to a predefined set of diagnoses depending on their severity. The points are then added to obtain the Charlson CMI of the patient. Previous research has shown increased 10-year mortality for each increase of Charlson CMI[120].

For paper III, in addition to the clinical variables mentioned before, tumour distribution on first SRI was documented and based on this parameter, the patient was categorized according to the tumour distribution:

- No visible tumour,
- Tumour only in the small intestine,
- Tumour in the small intestine and mesenteric lymph nodes,
- Presence of intraabdominal metastasis except the liver (i.e peritoneal metastasis, extramesenteric lymph node metastasis, gross tumour), presence of liver metastasis,
- Presence of extra-abdominal/extrahepatic metastasis.

During follow-up, for each subsequent SRI, this information was updated. At the same time, information regarding vital status, latest values of S-CgA and urine 5-HIAA, whether the SRI-report stated progressive disease and if tumour treatment changed (as a result of the SRI) was obtained. "Major change" in treatment was defined as newly added treatments such as the start of SSA therapy, planning for liver ablation, (PRRT) or unplanned withdrawal from treatments.

For paper IV, ICD-codes from the Swedish National Patient Registry including both out-patient and in-patient data until 1 September 2019 were supplied by the Swedish National Board of Social Affairs and Health.

Sociodemographic variables

For Paper IV, we wanted to control for sociodemographic variables which are known confounders in HRQoL-research. Yearly disposable income per consumption unit and highest level of education were supplied by Statistics Sweden (SCB). In order to avoid bias due to shared expenses / or shared income within households, the variable disposable income per consumption unit was chosen. This variable enables comparisons of disposable income between different types of households by using a weight system in which consumption is linked to the composition of the household ("equivalence scale"). The household's economic standard is calculated by dividing the disposable income by the consumption weight that applies for the household. These statistics use a scale established by Statistics Sweden and are adapted to Swedish conditions[121].

For paper IV, date and cause of death were supplied by the Swedish National Cause of Death Register by the Swedish National Board of Social Affairs.

Statistical analysis

STATA/BE® v 16,17,18 (StataCorp LLC, Texas, USA) was used for statistical analysis.

Paper I

To establish whether the research cohort indeed suffered from decreased HRQoL, the difference in values of QL2, function scales and DI between the cohort and the general Swedish population aged 60-79[122] was calculated. A one-sided t-test was used to indicate whether the difference was statistically significant.

To avoid exclusion of patients with missing data from the analysis, multiple imputation was used for missing values concerning bowel function. Multiple imputation is a statistical technique which replaces each missing value with multiple plausible estimates, creating several complete datasets, which are then analyzed separately and combined. Compared to complete-case analysis, statistical power is preserved and compared to other, simpler imputation methods, multiple imputation introduces less bias in the analysis and preserves natural variability of the data . More specifically for our method, values from MSKCC-BFI, were imputed using multiple imputation[123] with predictive mean matching[124], k-nearest neighbour (knn) = 10, and 20 imputations using a fixed random seed number. Missing values for the function scales and QL2 were not imputed since these were considered outcome variables.

To depict the relationship between HRQoL and bowel symptoms, multiple linear regression between each of the bowel symptoms from MSKCC-BFI and each of the outcome variables (QL2, function scales) was performed. Adjustment for confounding was made by including the following clinical variables with $p>0.1$ in any of the models: sex, age, Charlson CMI, Urine 5-HIAA, S-CgA, distant metastasis, residual regional disease, SSA-treatment, BMI, years since diagnosis and type of tumour surgery. The choice of clinical variables was based on biological reasoning that these factors can influence both HRQoL and bowel function. Linear regression was conducted in two steps:

1. The first step included one bowel function item, the clinical variables and the outcome variable (QL2 or one of the function scales).
2. The second step included all bowel function items simultaneously with the clinical variables and the outcome variable (QL2 or one of the function scales).

Paper II

To report the distribution of tumour volume in the cohort, median SRETV was calculated for all patients with tumour in each respective anatomical site. To further illustrate the distribution (as the SRETV in the liver was disproportionately higher than in the other anatomical sites) a ratio between $SRETV_{liver}$ and ΣSRETV was also calculated.

Since the distributions of ΣSRETV and ΣTLSRE were highly skewed (skewness values of 3.3 and 2.8, respectively), natural logarithmic transformation to logΣSRETV and logΣTLSRE was performed. Unadjusted linear regression between logΣSRETV and QLQ-C30 Summary Score was performed, followed by regression with inclusion of the confounding covariates age, Charlson CMI, and SSA-treatment. Several sensitivity analyses were conducted excluding patients having undergone Whipple's procedure, those with SSTR PET-CT more than 6 months before or after the questionnaire, those with non siNET and those with recent (<6 months) tumour directed treatment. Subgroup analysis of patients with grade 1 and 2 and diagnosis less than or more than 4 years were also performed. The same procedure was then performed with logΣTLSRE as the independent variable.

The secondary aim was explored by using a correlation table with Pearson's correlation coefficients between logSRETV in each anatomical site and subscales from QLQ-C30 and GI.NET21. A cut-off of r>0.2 was chosen to indicate weak correlation over no correlation.

Paper III

Patients were observed from their second SSTR PET-CT until death or until September 1st 2021. To evaluate whether sex, grade or stage would affect the interval for undergoing ^{68}Ga-DOTA-TOC/TATE PET-CT, the median number of scans per year and median interval between scans in all patients and in each of the above groups was calculated. To illustrate any time-dependent relationship between ^{68}Ga-DOTA-TOC/TATE PET-CT and major change, events were grouped into years and displayed as a bar graph.

In order to explore the primary aim, we wanted to calculate odds ratios for major change after each scan. Each scan was thus considered a separate observation. Since observations of the same patient were not independent, we used mixed-models logistic regression with major change as the outcome variable.

The choice of factors to test in the model was based on biological and clinical reasoning. Since progressive, metastatic disease is the main reason for intensified treatment, tumour distribution at the last ^{68}Ga-DOTA-TOC/TATE PET-CT and whether the report indicated progressive disease were included. Due to the known association between grade[125] and carcinoid heart disease[126] with PFS and the association of CgA with tumour burden[127] and urine 5-HIAA with the carcinoid syndrome[128], these variables were included together with age and Charlson CMI

(since these can be thought to influence the clinician's decision to intensify treatment by indicating increased sensitivity to side-effects). Finally, sex and years since diagnosis were also included. Biomarkers were transformed into below ULN, above ULN or missing.

The first step of creating the model used univariate regression with visual inspection of logit-transformed Locally Weighted Scatterplot Smoothed (LOWESS) smoothed plots to find non-linear relationships with the outcome variable. For the variables that displayed such a relationship, transformation into binary variables using cut-off points chosen to optimise predictive power was done. The next step consisted of entering all variables deemed to be clinically and biologically relevant into a multivariate model. Then, stepwise removal of variables with $p>0.1$ was performed until a final model was created. Finally, sensitivity analysis with exclusion of patients with Ki67% ≥ 15% at baseline was performed.

Weighting of risk factors was based on their respective odds ratio on major change, increasing the total score for each additional risk factor. The percentage of scans leading to major change was obtained for groups of observations based on number of risk factors. From this score, a receiver-operating curve (ROC) with its corresponding c-statistic was acquired. With a cut-off point optimising for sensitivity, the events of the cohort were divided into two groups and the ratio of major change in each group calculated. Based on this, the negative predictive value (NPV), and positive predictive value (PPV) of being high vs low risk were presented.

$$NPV = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Negatives}}$$

$$PPV = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}}$$

Paper IV

To facilitate interpretation of the hazard ratios (HRs) so that each increase in HR corresponds to a clinically relevant increase of HRQoL of 10, each HRQoL-factor was scaled by a factor of one tenth.

Since missing data on HRQoL-factors and levels of biomarkers were judged not to be missing at random, these were not imputed. Instead, patients with missing values for these variables were left out from the respective analyses. However, when calculating the summary scores – as recommended by scoring manuals[129] – the average of available factors was used, leading to no missing data.

In this study, we opted to use the theoretical framework of causal inference[130] when deciding which set of variables that should constitute confounders. Since bias and confounding cannot be controlled for in observational studies, observational studies

require adjustment for confounders. In this situation, causal inference utilises a graphical framework, the directed acyclic graph (DAG) to carefully and explicitly choose the correct set of confounders to adjust for. The relationship between the variables in the DAG is based on à priori assumptions from the existing theory on causal relationships between the underlying variables. For the purposes of this study, a DAG was drawn in the web application dagitty[131] with arrows denoting the proposed underlying causality behind the relationship between survival and HRQoL, see figure 7 below. From the DAG, a minimal set of confounders to include in further analysis was obtained: age, sex, urine 5-HIAA, tumour burden (replaced by surrogate marker S-CgA), presence of distant metastasis, Charlson CMI, highest education level and yearly disposable income per consumption unit.

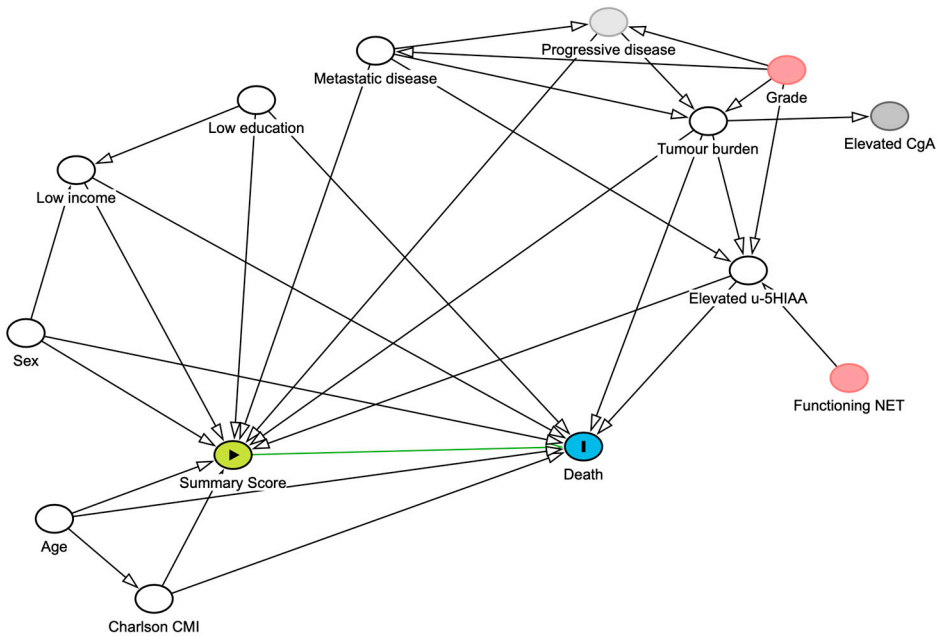

Figure 7 - Directed acyclic graph (DAG) of paper IV.
The DAG depicts the proposed causal relationship between the green exposure variable, Summary Score, and the outcome variable in blue, death. White variables represent adjusted variables, light grey variables represent latent variables, grey represent other variables and red variable represents ancestor of exposure and outcome (for which adjustment is not appropriate). Since tumour burden is not measured, chromogranin A was used as a surrogate marker.

To assess the relationship pictured above, Cox proportional Hazards models with overall survival were used. First, univariate analysis of separate HRQoL-domains and the clinical variables sex, comorbidities (as quantified by the Charlson

comorbidity index), presence of metastatic disease, latest level of urine 5-HIAA, latest level of S-CgA, disposable income, and education level was performed. The proportional hazards assumption was evaluated by visual inspection of -log-log survival probabilities, and by calculating Schoenfeld residuals. A log-rank test was performed for variables that violated the proportional hazards assumption, ruling out confounding by these variables not detected on parametric tests. Then, several multivariate models were analysed in sequence. Initially, all clinical variables were modelled. Then, for the primary aim, clinical models with either the QLQ-C30 Summary Score or the Summary Score including GI.NET21 were modelled. Lastly, for the secondary aim, clinical variables and subdomains of the QLQ-C30 and GI.NET21 with $p < 0.1$ in the univariate analysis were included in a multivariate Cox Regression with backward stepwise exclusion retaining variables with $p < 0.05$. Clinical variables were forced into the model and not excluded.

To evaluate model performance and fit, the predictive accuracy of the three models in the primary aim were compared using Harrells C-index ($0 \leq C \leq 1$). The C-index estimates the proportion of all pairwise patient combinations from the sample data whose survival time can be ordered such that the patient with the highest predicted survival is the one who has survived longer (discrimination) in the observed data set[132]. A C-index of 0.5 represents a random model and 1 represents a perfect model. Furthermore, model fit (while penalizing for model complexity) was evaluated using the Akaike Information Criterion (AIC) with lower scores indicating better model fit. To illustrate the added impact of HRQoL over using only clinical data, a flexible parametric model (adjusted for all clinical variables) using cubic splines with two degrees of freedom was created. From this model, survival probability curves over 3 years with 4 different levels of QLQ-C30 Summary Score (100, 80, 60 and 40) for a simulated typical patient was created.

Use of generative AI

Generative AI using ChatGPT-4o was used when trouble-shooting STATA-code for paper IV. ChatGPT-4o was also used to format tables and graphs from STATA-output and to generate table 3 and figure 10 and 14 in this thesis. Generative AI has not been used to generate any text in this thesis. The author takes full responsibility for the results from using generative AI.

Results

Patients

Between 1 January 2000 and 31 December 2018, some 806 patients had GI-tract NET diagnosis codes. From this, 561 patients were excluded based on pre-defined exclusion criteria. Of the 245 patients invited to participate, 165 patients accepted invitation and returned the questionnaires with answers. This constitutes the cohort from which the 3 sub-cohorts of papers I, II and III are based on. See figure 8 for details.

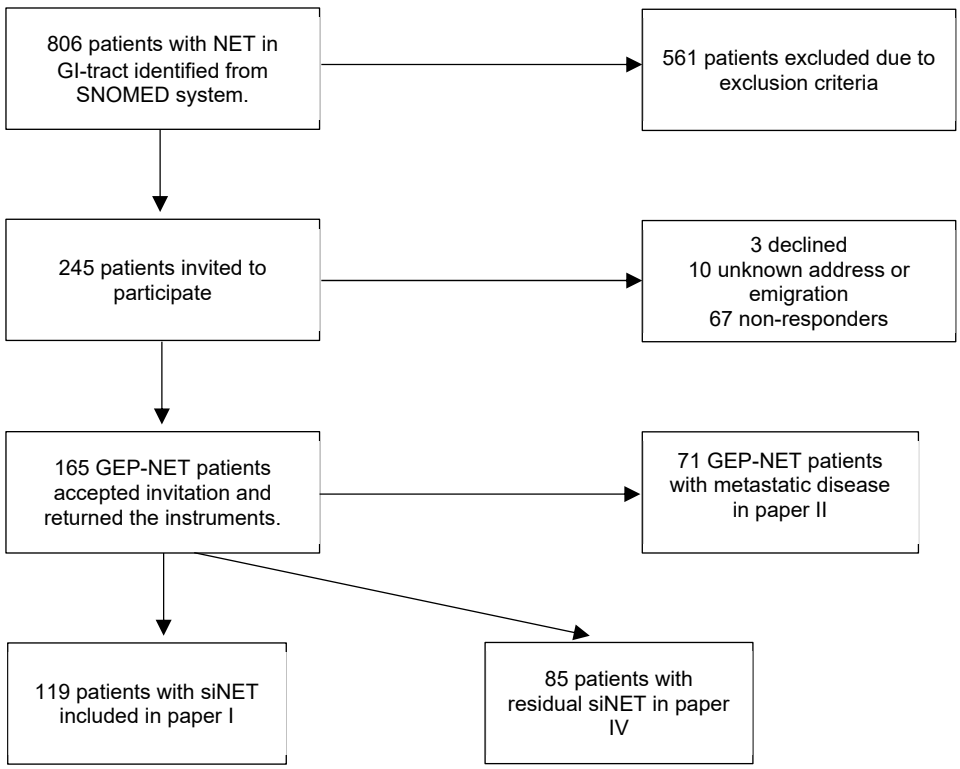

Figure 8. Flowchart for included patients for papers I, II and IV

For paper I, to minimize heterogeneity, only the 119 patients with siNET were included. For paper II, only the 71 patients with metastatic GEP-NET are included. For paper IV, since no deaths occurred in patients without residual disease, only 85 siNET-patients with advanced disease, either metastatic or regional were included. For paper III, since HRQoL was not a factor, the initial inclusion process was instead based on records from the PACS. Consequently, not all 164 patients in this cohort belong to the original cohort of patients completing the questionnaires in 2019. For an illustration of cohort-overlap between the four papers, see figure 9.

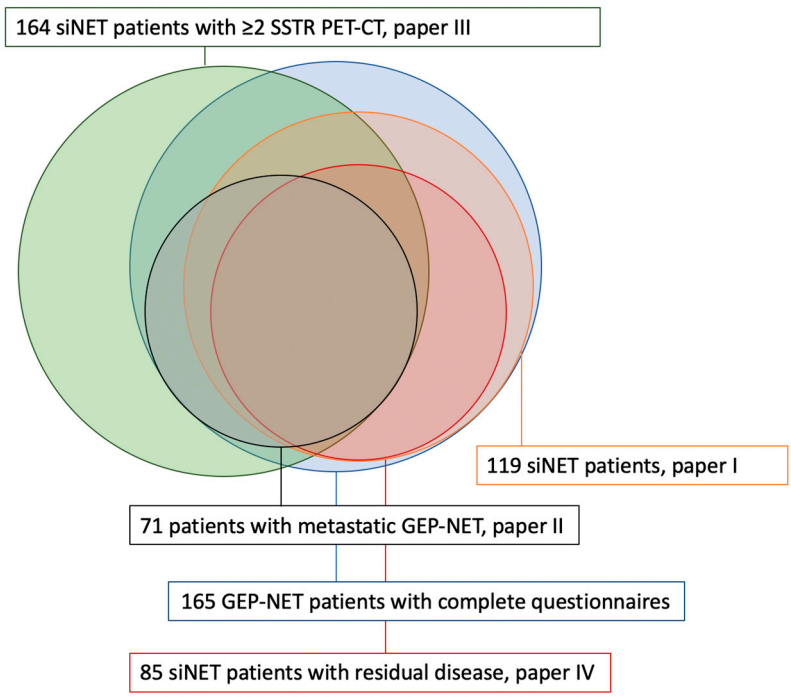

Figure 9. Overview of the included cohorts of the four papers and their overlap.
Sizes of circles correspond to cohort sizes

Paper I

Cohort characteristics

Table 4 displays cohort characteristics. Mean (s.d.) age of the patients was 70.4 (10.7) years and 61% were men and mean (s.d.) time since diagnosis was 6.4 (3.7) years. Some 71 patients (60%) had metastatic disease. Some 59 of these received SSA-therapy and a further 11 without metastatic disease also received SSA. Some

51 patients (43%) had urine 5-HIAA levels above ULN. Some 67 patients had undergone small bowel resection and 58 patients had undergone a right-sided resection (either right hemicolectomy or ileocecal resection). Two patients with siNET metastasis to the pancreas underwent pancreaticoduodenectomy in addition to bowel resection.

Table 4. Cohort characteristics
Values are presented as mean (s.d) for continuous variables and n (%) for binary varibles.

Variable	Descriptive statistic
Age	70.4 (10.7)
Charlson Comorbidity Index	3.9 (2.5)
Weight	76.4 (17.5)
Height	171.7 (18.1)
BMI	25.4 (5.3)
Years since diagnosis	6.4 (3.7)
Chromogranin A ≥ ULN	63 (52.9)
Urine 5-HIAA ≥ ULN	51 (42.9)
Male sex	73 (61.3)
Metastatic disease	71 (59.7)

HRQoL and bowel symptoms

When comparing mean values of the cohort with reference values of the general population, the cohort displayed statistically significantly lower QL2, lower function levels (PF2, RF2, EF, CF, SF) and higher levels of diarrhoea (DI) than the general population. However, only for social function (delta -10,7), and diarrhoea (delta 30.5), the differences were large enough to be judged clinically important. See table 5 for details.

Table 5. Levels of HRQoL in the cohort including comparison to general population
Values are presented as mean (s.d) for continuous variables and n (%) for binary varibles. *Age adjusted values 60-79 years from Derogar et al[122] . **Compared to swedish reference population 60-79 years

	Mean (s.d.)	Reference values*	Delta**	p-value for t-test	n (%) with score <50
QL2	72.9 (20.9)	76.7	-3.8	0.03	14 (11.8)
PF2	82.6 (20.1)	86.1	-3.5	0.03	11 (9.2)
RF2	81.5 (28.4)	87.8	-6.3	0.01	17 (14.3)
EF	81.8 (22.3)	87.5	-5.7	0.003	12 (10.0)
CF	84.8 (20.1)	88.0	-3.2	0.05	6 (5.0)
SF	80.6 (26.1)	91.3	-10.7	<0.001	13 (10.9)
DI	35.9 (35.4)	5.4	30.5	<0.001	38 (31.9*)

Mirroring the high prevalence of diarrhoea in the cohort, the presence of bowel symptoms in the cohort was substantial. The mean number of bowel movements (BMs) per day (item nr 1) was 2.7 (range 1-6) with 67 patients experiencing more than three BMs per day. The most frequent symptoms (reported often or always) were loose stool (n=55), not being able to wait 15 min when about to have a bowel movement (n=40), presence of watery stool (n=37) and having another bowel movement within 15 minutes of the last one (n=28). See figure 10 for details.

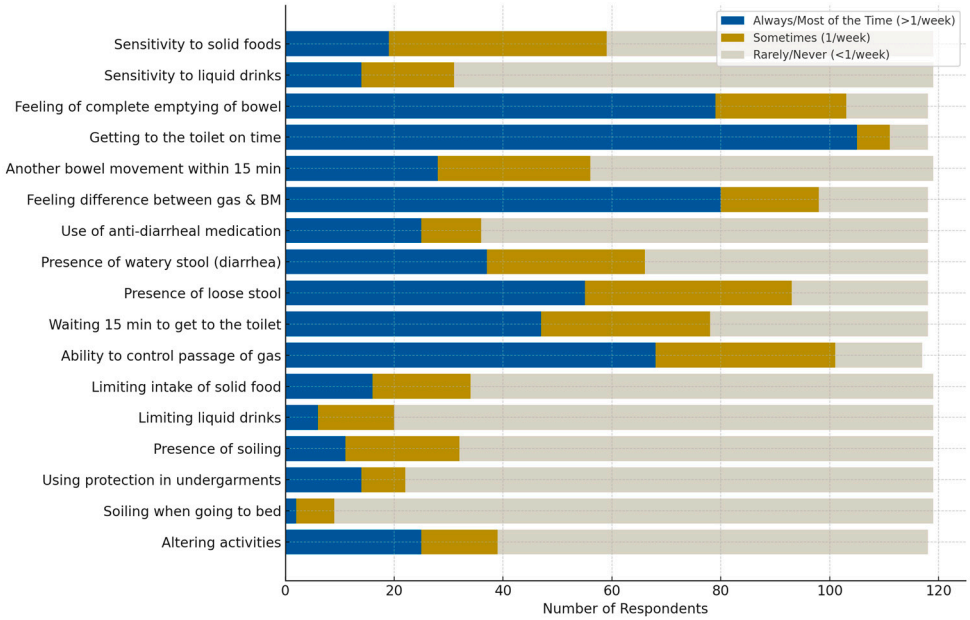

Figure 10. Frequency of bowel symptoms in the cohort
Note that not all questions have the same directions – e.g. getting to the toilet on time is a positive symptom whereas soiling is a negative symptom.

In order to illustrate how elevated urine 5-HIAA was related to 3 or more bowel movements (BM) per day, (MSKCC-BMI item nr 1), a frequency table is shown in table 6. From this table it is evident that while ≥3 BM/day is more common (65%) among those with elevated urine-5-HIAA, the frequency is still significant at 50% in those with normal levels. Since multiple linear regression showed that age, Charlson CMI, presence of metastatic disease, S-CgA above ULN and BMI were independently associated with at least one of the HRQoL outcome variables, these were included in subsequent models.

Table 6. Relationship between bowel movements per day and levels of urine 5-HIAA

BM/day	0-29 (n, %)	Missing (n, %)	≥30 (n, %)	Total (n, %)
0-2	31 (50.00%)	3 (50.00%)	18 (35.29%)	52 (43.70%)
≥3	31 (50.00%)	3 (50.00%)	33 (64.71%)	67 (56.30%)
Total	62 (100.00%)	6 (100.00%)	51 (100.00%)	119 (100.00%)

Results from the adjusted linear regression with each bowel symptom entered separately, shown in table 7, reveal a few different findings: First, that all significant symptoms have a positive correlation with HRQoL, i.e. more bowel symptoms are associated with worse HRQoL. Second, the bowel symptoms with the highest beta-coefficients indicating the most impact on HRQoL were: feeling of incomplete emptying, soiling of undergarments and having to limit certain types of solid foods or drinks. Third, for role function (RF2) and social function (SF), the beta-coefficients for the same symptoms were generally higher than vs other function scales. For example, the beta-coefficient was 13.0, 95% CI: 8.3–17.6 for RF2 vs item 14 (not getting to the toilet on time).

Results from the adjusted linear regression with all bowel symptoms (except item 18) entered simultaneously, only the following symptoms were statistically significant: Item 4 – feeling of incomplete emptying, item 13 – having to limit food to control bowel movements and item 15 – soiling of undergarments. For Global Quality of Life (QL2) and Physical Function (PF2), no symptom was statistically significant.

Table 7. Results from adjusted linear regression between bowel symptoms and HRQoL.
Results presented as beta-coefficients. Adjusted for Age, Charlson Comorbidity Index, Chromogranin A level above reference range, metastatic disease, BMI. Darker colors indicate higher beta-coefficients.*=p<0.05

	QL2	PF2	RF2	EF	CF	SF
Bowel movements per day	4.18*	3.28	4.39*	1.31*	1.61	3.75
Sensitivity to solid foods	3.51	5.77*	6.54*	1.64*	2.32*	5.91*
Sensitivity to liquid drinks	3.48	3.84	4.50	1.72*	3.15	4.18
Feeling of complete emptying of bowel	6.34*	7.14*	9.95*	7.62*	3.83*	8.76*
Getting to the toilet on time	5.21*	7.19*	7.99*	5.28	5.83*	7.99*
Another bowel movement within 15 minutes of the last one	4.02	5.31*	4.83	4.90*	4.01	6.35*
Ability to feel the difference between passage of gas and bowel movement	2.72	1.94	3.44	2.19*	1.98	3.76
Use of antidiarrhoeal medication	5.46*	4.77*	5.63*	4.92*	2.36	4.03*
Presence of watery stool (diarrhoea)	3.80	4.42*	4.27	3.26	3.43	6.60*
Presence of loose stool	1.75*	2.68*	4.82*	-1.04	-1.30	2.15
Being able to wait 15 minutes to get to the toilet when about to have BM	2.66	3.79*	3.29	2.89	2.33	3.78
Ability to control passage of gas	5.49*	4.88*	5.61*	4.40	3.68	7.57*
Having to limit intake of solid food	6.57*	6.16*	10.01*	7.53*	3.73	9.85*
Having to limit liquid drinks	7.79*	8.56*	12.96*	9.91*	5.24*	11.00*
Presence of soling	6.92*	8.80*	12.70*	8.96*	8.18*	11.82*
Having to use protection in undergarments	5.47*	7.28*	8.50*	6.21*	4.42*	7.14*
Soiling when going to bed	10.08*	9.27*	15.00*	11.47*	7.53*	14.61*
Altering of activities	8.65*	8.31*	12.70*	7.46*	5.77*	10.44*

Paper II

Cohort characteristics and tumour volume distribution

Of the 71 patients with metastatic GEP-NET, some 15 patients (21%) had stage III disease, the remaining 56 patients (79%) had stage IV disease. Some 58 patients (82%) were on SSA-treatment and some 32 patients (45%) had elevated urine 5-HIAA. Some 61 patients (86%) had small intestine as their primary tumour site.

Median total SRETV was 9.6 ml (I.Q.R 1.7-45.4 ml) with a maximum value of 539. For the 40 patients with visible liver metastasis of NET on SSRT PET-CT, the median $SRETV_{liver}$ was 18.8 ml (I.Q.R 10.6-112.7). In contrast, for the patients with regional lymph node metastasis or residual tumour in the GI-tract, the median SRETV was only 1.6 and 1.4 ml, respectively. With regards to the patients with

liver metastasis, the median ratio of $SRETV_{liver}/\sum SRETV$ was 0.93 (I.Q.R 0.66-0.99). This indicates that for a majority of patients in the cohort, a substantial proportion of tumour volume was due to liver metastasis. See table 8 for details.

Table 8. Tumour volume distribution.
Frequency of patients and *median (I.Q.R) SRETV in ml for groups of patients with tumour in each anatomical category.

Tumour distribution	n (%)	∑SRETV*
Liver	40 (56.3)	18.8 (10.6-112.7)
Pancreas	15 (21.1)	1.7 (0.7-3-7)
Mesenteric lymph nodes	36 (50.7)	1.6 (0.7-4-3)
GI tract	9 (12.7)	1.4 (1.0-3.3)
Other lymph nodes	31 (43.7)	1.4 (0.5-4.8)
Skeletal	17 (23.9)	1.2 (0.8-6.9)
Other	13 (18.3)	2.4 (1.3-4.2)
Total	71 (100)	10 (2-45)

HRQoL and tumour volume

The results from the primary analysis with simple linear regression (table 9, step 1) between log∑SRETV and QLQ-C30 Summary Score showed no significant correlation. See figure 11 for an illustration of the relationship between ∑SRETV and the summary score. The results did not change after adjustment for age, SSA-treatment and Charlson CMI. Sensitivity analysis with exclusion of patients having undergone the pancreaticoduodenectomy (step 3, n=6), or the patients with more than 6 months between answering the questionnaire and SSRT PET-CT (step 4, n=15), or those with recent PRRT (n=3), or those with non-siNET origin), showed the same results. Similarly, subgroup analysis based on grade and time since diagnosis, failed to show any significant correlation. For log∑TLSRE and QLQ-C30 Summary Score, the same statistical analysis was done, yielding the same results – no correlation.

Table 9. Main analysis of primary aim – linear regression between QLQ-C30 and tumour volume
1. Simple linear regression. 2. Multiple linear regression with adjustment for age, SSA-treatment and Charlson CMI. 3. Sensitivity analysis with exclusion of post-Whipple patients. 4. Sensitiivity analysis with exclusion of patients with >6 months between questionnaire and SSRT PET-CT *Relationship presented as beta-coefficient with 95% CI

	1. Simple linear regression	2. Adjusted multiple linear regression	3.	4.	Both 3 and 4	2,3 and 4
n	71	71	65	56	53	53
∑SRETV *	0.1 (-1.6-1.9)	0.4 (-1.5-2.3)	0.05 (-1.8-1.9)	-1.0 (-3.0-1.0)	-1.2 (-3.4-0.9)	-1.0 (-3.3-1.3)
∑TLSRE *	0.06 (-1.5-1.6)	0.3 (-1.4-1.9)	0.1 (-1.5-1.7)	-0.7 (-2.5-1.1)	-0.8 (-2.7-1.1)	-0.6 (-2.6-1.4)

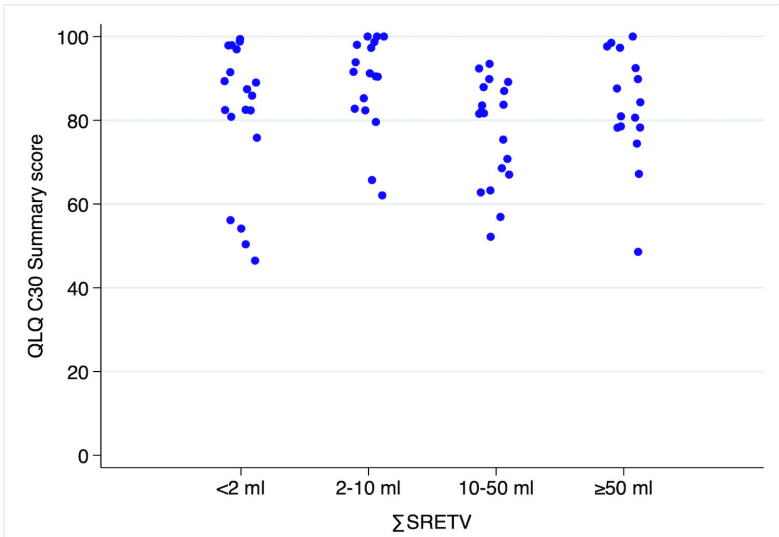

Figure 11. Scatterplot of individual QLQ-C30 summary scores with patients grouped into approximate quartiles of total SRETV.

The secondary aim evaluated correlations between separate domains of QLQ-C30 and GI.NET21, see table 10 for details. The only functional scales that showed a correlation with SRETV across any anatomical site were role function (RF2) and emotional function (EF). Both scales demonstrated correlations with SRETV in mesenteric lymph nodes, with correlation coefficients of r=0.2, and r=0.2, respectively.

For the symptoms constituting the carcinoid syndrome, diarrhoea (DI) and flushing (ED) showed similar patterns of correlation with SRETV across different anatomical sites. DI and ED were most strongly correlated with SRETV in the gastrointestinal tract (r=0.3), liver (r=0.3), other lymph nodes (r=0.2), and other unspecified sites (r=0.3). Naturally, disease-related worries (DRW) showed no

correlation with SRETV in any anatomical site. Additionally, total tumour volume (∑SRETV) displayed weak positive correlations with dyspnoea (r=0.2), diarrhoea (r=0.2), and endocrine dysfunction (r=0.3) as well as information (r=0.3).

Table 10. Correlation matrix between tumour volume at specific anatomical sites and subdomains of QLQ-C30 and GI.NET21.
Yellow color indicate no correlation, red color indicates positive correlation while green color indicates negative correlation.

	Liver	Pancreas	GI tract	Mesenteric lymphnodes	Other lymph nodes	Skeletal	Other	Total
Global QoL QL2	-0.1	0.2	0.1	0.0	0.0	0.1	0.0	0.0
Physical function PF2	0.0	0.0	0.0	0.1	0.1	-0.1	0.1	0.0
Role function RF2	0.0	0.1	0.1	0.2	0.2	0.1	0.0	0.1
Emotional function EF	0.0	0.2	0.1	0.2	0.2	0.0	0.0	0.1
Cognitive function CF	-0.1	0.0	0.1	0.0	0.0	-0.1	0.0	-0.1
Social function SF	0.0	0.2	0.0	0.1	0.1	0.0	0.0	0.1
Fatigue FA	0.1	-0.2	0.0	0.1	-0.1	0.0	0.0	0.0
Nausea and vomiting NV	0.1	-0.1	0.0	-0.1	-0.3	-0.2	-0.2	0.0
Pain PA	-0.1	-0.2	0.0	0.0	-0.2	-0.1	0.1	-0.2
Dyspnoea DY	0.3	-0.1	0.0	0.0	0.1	0.0	0.0	0.2
Sleep disturbance SL	0.1	-0.2	0.1	0.0	-0.1	-0.1	0.2	0.0
Appetite loss AP	0.2	0.0	0.0	0.0	-0.3	-0.2	0.2	0.2
Constipation CO	0.0	-0.1	-0.1	-0.1	-0.1	0.0	-0.1	-0.1
Diarrhoea DI	0.3	-0.1	0.3	0.1	0.2	-0.1	0.3	0.2
Endocrine dysfunction ED	0.3	0.0	0.3	0.1	0.0	0.0	0.2	0.3
Gastrointestinal GI	0.1	-0.1	0.0	0.2	0.1	-0.1	0.0	0.1
Treatment-related TR	-0.1	-0.2	0.1	0.2	0.0	-0.3	0.1	-0.1
Disease-related worries DRW	-0.1	-0.1	-0.2	-0.1	0.1	0.1	-0.1	-0.2
Social function NET SFNET	0.1	-0.1	-0.1	0.0	0.0	0.0	0.1	0.1
Weight loss WL	0.1	-0.2	0.1	0.2	0.2	0.0	0.2	0.1
Weight gain WG	-0.2	0.0	0.0	-0.3	-0.3	-0.3	0.0	-0.2
Muscle and bone pain MBP	0.1	-0.1	0.2	0.2	0.0	-0.1	0.1	0.1
Information INF	0.3	0.0	-0.1	0.0	0.3	0.2	0.2	0.3
Sexual dysfunction SX	0.2	-0.1	0.1	0.2	0.2	0.3	0.3	0.1
n with tumour on each site	**40**	**15**	**9**	**36**	**31**	**17**	**13**	**71**

Paper III

Cohort characteristics at baseline

From the initial search in the computerised imaging system, 1019 individual patients could be identified as having undergone a SSTR PET-CT. Some 467 patients had undergone more than one SSTR PET-CT. From this group, 284 patients did not have a siNET diagnosis and 13 patients were not followed at Skåne University Hospital, Lund. Furthermore, seven patients had major change due to side-effect or toxicity from treatment and were thus excluded. This resulted in a final cohort of 164 patients with a combined total of 570 SSTR PET-CT scans (observations). In 383 instances, the ^{68}Ga-DOTA-TATE protocol was used and in the remaining 187 scans, ^{68}Ga-DOTA-TOC was used.

Median age was 76 years and 61% of patients were male. Median (IQR) time since diagnosis in the cohort was 1.3 (0.8-4.2) years. Fifty-six percent of the cohort were on SSA-treatment and half of the cohort had elevated urine 5-HIAA at baseline. Two thirds of patients had stage IV disease, see table 11 for details about stage at baseline. Some 155 patients had undergone primary tumour surgery and nine patients had also undergone metastasis surgery.

Table 11. Baseline stage at first SSTR PET-CT
Presented as number of patients and (%) within each stage.

	n (%)
No visible tumour	20 (12.2)
Tumour only in small intestine	1 (0.6)
Tumour in mesenteric lymph nodes	34 (20.7)
Total localized disease	**55 (33.5)**
Abdominal metastasis	20 (12.2)
Liver metastasis	46 (28.1)
Distant extrahepatic metastasis	43 (26.2)
Total distant metastatic disease	**109 (66.5)**
Total	**164 (100)**

Follow-up

Median (I.Q.R) duration of follow-up was 3.1 (1.8-5.0) years. During this period, 82 scans (14%) led to a major change in treatment. See figure 12 for the distribution of scans and major change during follow-up. The median number of scans per year was 1.1 and neither sex, tumour grade nor stage at baseline were related to the

frequency of scans per year. The most common treatment changes constituting major change were start of SSA, PRRT or start of chemotherapy (see table 12). Some 46 patients died during follow-up.

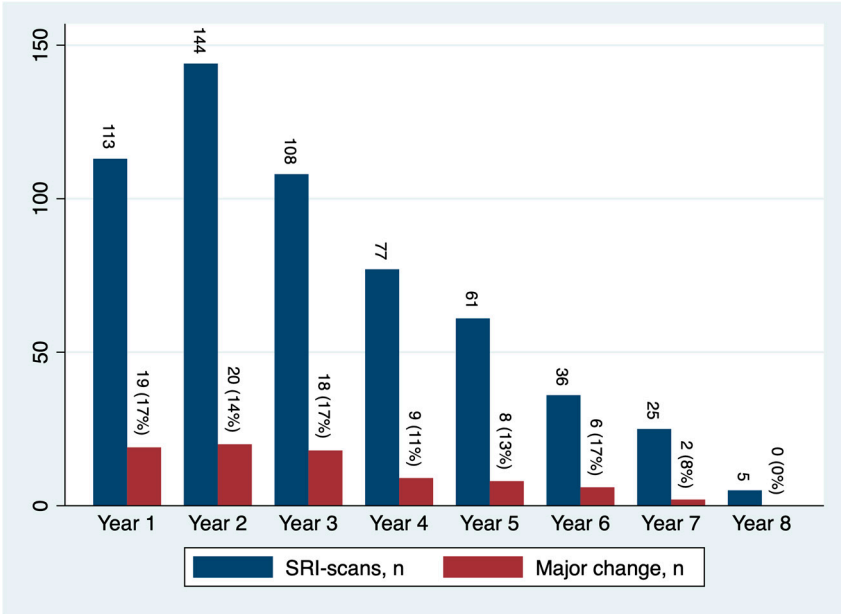

Figure 12. Bar chart of distribution of SSTR PET-CT.
Number and of scans per year (dark blue) and number of events (inlcuding % of scans that year) with major change (red) since baseline.

Table 12. Treatment changes constituting major change

	n(%)
Start SSA	18 (21.95)
Stop SSA	5 (6.1)
Start chemotherapy	17 (20.73)
Start PRRT	17 (20.73)
Plan for non-liver Surgery	6 (7.32)
Start liver directed therapy	5 (6.1)
Start radiotherapy	4 (4.88)
Start M-Tor inhibitor	7 (8.54)
Start Lenvatinib	2 (2.44)
Stop chemotherapy/M-tor	1 (1.22)
Total	82 (100)

Factors associated with major change

Univariate mixed models logistic regression with joint smoothed plots indicated that for age, years since diagnosis and Charlson comorbidity index, the odds ratios for major change was increased using the following cut-off points: 75 years of age, more than 4 years since diagnosis and more than 6 points in Charlson comorbidity index. See figure 13 for an example using age. Consequently, these variables were transformed into dichotomous versions using these cut-off points. For tumour distribution on previous SSTR PET-CT, no clear increase in OR was shown except for with distant extrahepatic metastasis. This variable was consequently transformed to whether distant extrahepatic metastasis was present or not.

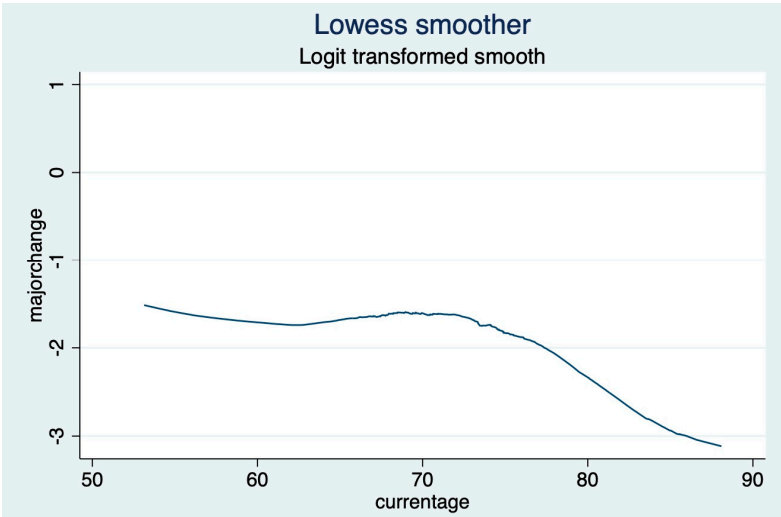

Figure 13. Lowess smoothed plot of odds for major change vs age
Smoothed trend of major change probability on a logit scale. The y-axis represents log-odds, with a fitted LOWESS curve for trend estimation. As the odds are continous from 53 years to 75 years and then gradually decrease, we estimated that a cut off point at 75 years of age was appropriate for dichotomization of the age variable.

After inclusion of the ten biologically and clinically relevant variables into a multivariate mixed model regression with stepwise exclusion, six variables remained: sex, age, S-CgA, urine 5-HIAA, distant extrahepatic metastasis and progress on last scan. From these results, shown in table 13, we can see that both male sex and age above 75 years are associated with about half the odds for major change with odds ratios of 0.62 and 0.52, respectively. For the other 4 variables, presence of the factor was roughly equal to a doubling of the odds with odds ratios for CgA>ULN, urine 5-HIAA>ULN, presence of distant extrahepatic metastasis and progress of last scan with odds ratios at 2.4, 2.5, 2.1 and 1.7, respectively.

Table 13. Results from multivariate mixed models logistic regression with stepwise exclusion

	Odds Ratio	95 % CI	p-value
Female sex	reference		
Male sex	0.62	0.37-1.04	0.07
No extrahepatic metastasis	reference		
Extrahepatic metastasis	2.06	1.15-3.7	0.01
Chromogranin A <2 mmol/L	reference		
Chromogranin A unknown	1.08	0.22-5.21	0.93
Chromogranin A ≥2 mmol/L	2.42	1.15-5.07	0.02
Urine 5-HIAA <30 mmol/L	reference		
Urine 5-HIAA unknown	5.32	1.41-20.1	0.01
Urine 5-HIAA ≥30 mmol/L	2.48	1.25-4.92	0.01
No progress on last scan	reference		
Progress not evaluated	2.22	1.10-4.50	0.03
Progress on last scan	1.69	0.95-2.99	0.07
Age < 75 years	reference		
Age ≥ 75 years	0.52	0.29-0.94	0.03

Taken together, absence of any risk factor mentioned above, age < 75 years or female sex were all associated with about half the odds for major change. Utilising the fact that the factors had about the same weight on major change, the total number of risk factors for each event was calculated, see figure 14.

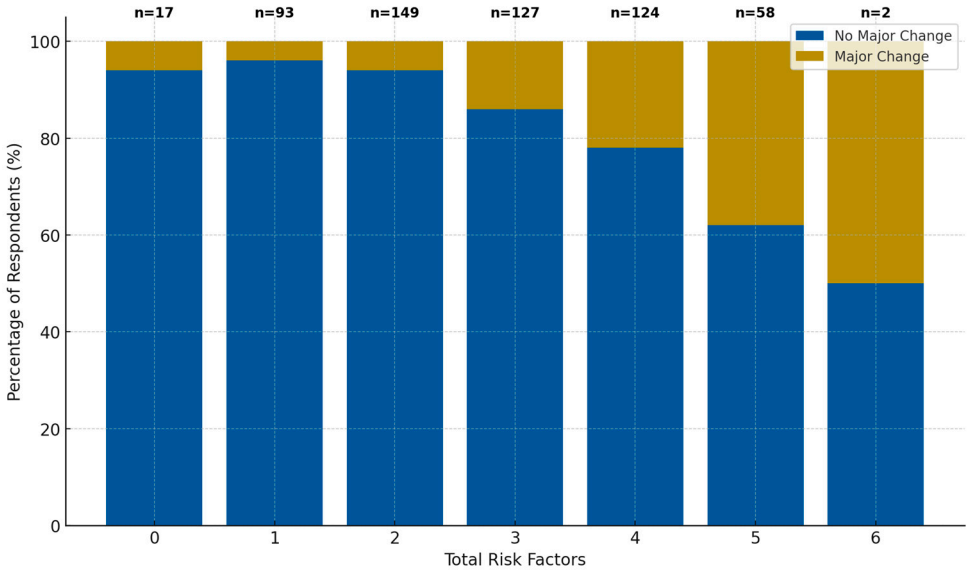

Figure 14. Proportion of Major vs No Major treatment change by number of total risk factors

From figure 14 it is evident that for observations with 0-2 risk factors, major change occurred in 4-6% of cases. From three risk factors and above, a continuous increase in the frequency of major change can be seen for each additional risk factor, e.g. 14% at 3 risk factors and 38% at 5 risk factors. When evaluating the discriminatory ability of the model to accurately classify observations into low- or high risk using a receiver-operating-curve (ROC), the area under the curve or c-statistic was 0.72 (95% CI 0.66-0.78), indicating good discrimination, see figure 15. As the goal of the model was to reduce unnecessary use of SSTR PET-CT while keeping the false-negative rate as low as possible, we wanted to optimise for sensitivity and also divide the group into approximately two equally size groups. Therefore, we chose a cut-off point for high risk for major change at ≥ 2 risk factors. Using this cut-off point, the model would correctly classify 245 of 259 observations as no major change in the low risk group, resulting in an excellent NPV of 0.95. Conversely, as the cut-off point was not chosen to optimise for this, PPV was poor at 0.22, only being able to correctly classify 68 of 311 events in the high-risk group as major change. See table 14 for details.

Table 14. Proportion of major change in low vs high risk group

	no major change, n (%)	major change, n (%)	Total, n
Low risk (≤2 risk factors)	245 (95)	14 (5)	259
High risk (>2 risk factors)	243 (78)	68 (22)	311

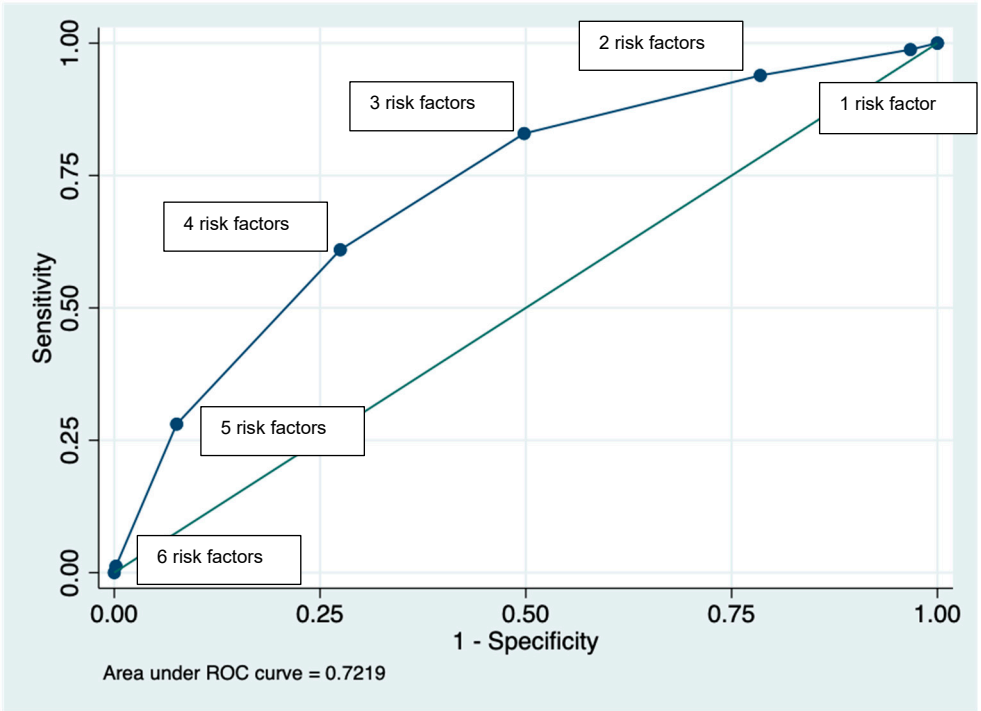

Figure 15.
Reciever-operating curve with sensitivity and 1-specificity using from 1 to 6 risk factors as cut-off point. The area under the curve, corresponding to the c-statistic, is 0.72.

Paper IV

Cohort characteristics

In this study, 85 patients with siNET and residual disease at follow-up were included. Some 64 patients (75%) had stage IV disease. The total number of patients with SSA-treatment was 67 (79%). Some 41 patients had hormonally active tumours with elevated urine 5-HIAA above 50µmol/day. Median values of both QLQ-C30 Summary score and the summary score including GI.NET21 was 84. This indicates that, on average, the level of HRQoL in the cohort was only moderately lowered. However, some 33 and 38 patients had scores below 80, indicating significantly decreased HRQoL. Median follow-up time was 39 months.

Survival analysis of primary aim

In the unadjusted univariate Cox proportional hazards analysis of the clinical variables, age, male sex, urine 5-HIAA and S-CgA were all associated with decreased overall survival. Presence of distant metastasis and Charlson comorbidity index trended towards association with shorter OS with p-values at 0.11 and 0.09, respectively. The sociodemographic variables did not show statistically significant association with overall survival and furthermore, after visual inspection – the proportional hazards assumption was not fulfilled. Log-rank test for these three variables were not significant, indicating that these variables were not confounders in our cohort. In order to not over-parametrise the model with non-informative variables, these were left out from the latter adjusted multivariate analysis. Unadjusted QLQ-C30 Summary Score and the summary score including GI.NET21 were both associated with overall survival with unadjusted hazard ratios of 0.58 (95% CI 0.46-0.74) and 0.50 (95% CI 0.37-0.67) for each 10-point increase in summary score, respectively. See table 15 for further details.

Table 15. Univariate unadjusted Cox Regression on overall survival.

	Hazard ratio	95% CI	p-value
Male sex	3.50	1.03-12.0	0.045
Age	1.09	1.03-1.16	0.004
Charlson CMI	1.27	0.96-1.69	0.09
Education level	0.87	0.66-1.14	0.32
Income level	1.00	1.00-1.00	0.29
Serum Chromogranin A	1.08	1.05-1.11	<0.001
Urine 5-HIAA	1.002	1.001-1.003	0.001
Distant metastasis	3.27	0.76-14.1	0.11
QLQ-C30 Summary Score	0.58	0.46-0.74	<0.001
QLQ-C30 with GI.NET21 summary score	0.50	0.37-0.67	<0.001

The results from the multivariate Cox regression with adjustment for clinical confounding variables showed that the QLQ-C30 Summary Score and the summary score including GI.NET 21 were still significantly associated with overall survival with a hazard ratio of 0.67 (95% CI 0.51-0.90) and 0.60 (95% CI 0.43-0.85), respectively. See table 16 below for details (only QLQ-C30 summary score shown). The flexible parametric model of survival probability for a simulated typical 74-year old male patient with metastatic disease and biomarkers at ULN is shown in figure 16. This illustrates that while controlling for clinical variables, a decrease in QLQ-C30 Summary Score of 40 is associated with a lowered survival probability at 3 years from 90% to 65% for such a patient. For comparison, the observed

unadjusted values of the whole cohort divided into above or below QLQ-C30 Summary Score 80 is depicted in a Kaplan-Meier curve, figure 17.

Table 16. Multivariate Cox regression
First model with clinical variables alone and second model with inclusion of QLQ-C30 Summary Score. The same procedure was done with similar results for the summary score including GI.NET21 (not shown).

	Clinical variables			Clinical variables & Summary Score		
	HR	95% CI	P-value	HR	95% CI	P-value
Male sex	3.06	0.85–11.03	0.09	2.79	0.78–9.98	0.11
Age	1.08	1.02–1.16	0.02	1.09	1.02–1.16	0.02
Urine 5-HIAA	1.00	1.00–1.00	0.28	1.00	1.00–1.01	0.07
S-Chromogranin A	1.06	1.02–1.10	0.00	1.04	1.00–1.09	0.05
Distant metastasis	2.53	0.57–11.26	0.22	1.19	0.24–6.04	0.83
Charlson CMI	0.92	0.66–1.29	0.65	0.96	0.68–1.37	0.83
QLQ- C30 Summary Score				0.67	0.51–0.90	0.01

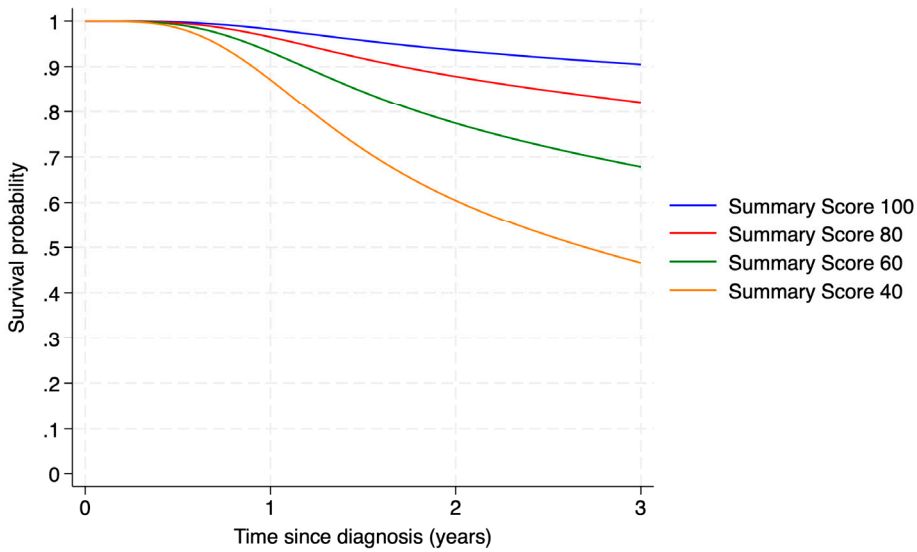

Figure 16. Flexible parametric model of survival probability
The graph depicts the modeled survival probability of a simulated 74 year old male patient with metastatic disease with CgA at 2nmol/l and urine 5-HIAA at 50 µmol/day.

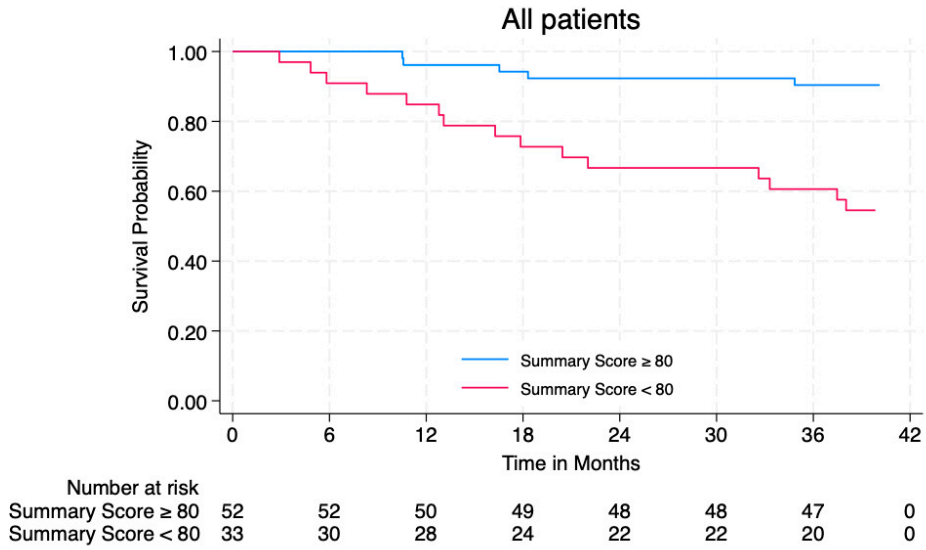

Figure 17. Kaplan-Meier curve of observed survival for whole cohort
Divided by QLQ-C30 Summary Score at baseline (above or below 80).

During model evaluation, Harrells C for clinical variables was 0.82, a 64% increase compared to the null model containing no variables. When adding the QLQ-C30 Summary Score or the summary score including GI.NET21, Harrells C improved to 0.86, constituting an increase of 8 percentage points over clinical variables alone. Results from model fit evaluation using the AIC, which penalizes overly complex models, showed that inclusion of either summary score gave the best fit with AIC 142 compared to 148 for clinical variables alone. The difference in AIC of 6 is substantial and the model with higher AIC generally has low support, according to the literature[133]. Table 17 depicts the results from model evaluation.

Table 17. Results from model evaluation.

	Harrells C	Increase from null model	AIC
Null model	0.5	reference	
Clinical variables	0.82	64%	148
Clinical variables + QLQ C30 Summary Score	0.86	72%	142

Secondary aim

For the subdomains of the QLQ-C30 and GI.NET21, all scales had p-values <0.1 and were thus included in the subsequent analysis. However, during the course of model estimation and stepwise exclusion, the algorithm encountered a flat region,

indicating it could not decide which variable to exclude next. Since the clinical variables were fixed, we judged this to be due to overparameterization in relation to cohort size. We therefore chose to remove the clinical variable with the weakest correlation with OS, the Charlson Comorbidity index. Hereafter, the process continued and after exclusion, Physical function (PF2), Role Function (RF2), Emotional Function (EF), Weight Loss (WL), Sleep loss (SL), Social Function (SF), Nausea and Vomiting (NV), GI-symptoms and Pain (PA) remained in the model.

Discussion

To summarize, this thesis has demonstrated a few important findings:

To start with, for patients with siNET, HRQoL is lower than the general population, especially within social domains. Although bowel symptoms concerning urgency and frequency are most common, other more socially stigmatizing symptoms such as soiling and insensitivity to certain food and/or beverages impact HRQoL more. This is especially pertinent, unsurprisingly, within social domains.

Secondly, in a cohort with metastatic siNET, tumour volume as measured on SSTR PET-CT did not seem to be related to overall HRQoL as measured by a summary score. However, some symptoms of the carcinoid syndrome seemed to be weakly correlated with tumour volume.

Thirdly, for GEP-NET patients undergoing SSTR PET-CT as follow-up in order to detect recurrence or progression, only a minority of scans (14%) led to a clinically relevant change in treatment. Six risk factors with clinical and biological relevance (sex, age, level of urine 5-HIAA, level of S-CgA, presence of extrahepatic metastasis, progressive disease on last scan) seemed to predict whether the scan would lead to major change or not.

Lastly, for patients with siNET and residual disease (either metastatic or local), lower scores on the QLQ-C30 summary score was associated with shorter overall survival, even after adjusting for clinical variables. Apparently, she summary score seemed to add important predictive information over using clinical variables alone.

Obviously, the studies have several limitations which will be discussed further on. However, if we take the results from the thesis at face value, the findings should raise several questions:

1. If tumour volume is not related to HRQoL, what other biological explanations are possible to understand the decreased HRQoL of siNET-patients?
2. If poor HRQoL is related to worse OS, are progressive disease and HRQoL related in some way? Should HRQoL be considered a causal factor or a marker for overall survival?
3. Is the QLQ-C30 Summary Score a sensible method of describing HRQoL in patients with NET or do we need to use a more NET-specific instrument?

4. If only a minority of SSTR PET-CT scans lead to change in treatment, which scans can be safely omitted?
5. Can regular, standardized measurement of HRQoL play a role or replace parts of follow-up of siNET as we now know it?
6. Is there room for improvement in the treatment of patients with siNET where curative intent is not possible?

We will now elaborate further on these six questions and meanwhile, discuss future implications of this thesis.

Possible explanations for lower HRQoL

Before conducting study II, our hypothesis was that growth of tumour volume would lead to more symptoms which would give lower HRQoL on the symptom scales and then also affect the patient's functional status, further reducing HRQoL. While our study cohort included patients with, on average, rather low tumour volumes with a median ∑SRETV of 10 ml (I.Q.R 2-45 ml), which might disguise this relationship, other explanations are also possible. Adaptation level theory[134,135] states that adverse life events not always lead to worse QoL if patients can learn to cope with the illness, sometimes by finding acceptance of its symptoms. Thus, while symptoms from the disease can still be severe, the resulting overall Summary Score may not be affected. This might explain the findings in the secondary analysis of paper II where weak correlation between symptoms of the carcinoid syndrome and tumour volume was found and also the contrasting findings of Vinik et al[116] where tumour burden, using a non-standard definition, was related to total score of EORTC GI.NET21.

A large Canadian study[136] on 2721 patients with NET using Edmonton Symptom Assessment System scores showed stable proportion of patients with moderate or severe symptoms over the first 5 years after diagnosis. These results were distinct from similar studies on other malignancies where the proportion of patients with symptoms typically increase each year after diagnosis. The slow-growing nature of siNET is probably a factor here and might provide a unique opportunity for patients with siNET to cope with their malignancy over a prolonged time, thereby affecting HRQoL less for a given tumour burden.

The fact that Tirosh et al showed that urine 5-HIAA correlates strongly with SRETV on SSTR PET-CT, $r=0.7$ $p<0.001$) indicates that larger tumours produce more hormones which in theory should give more symptoms. However, modern treatment with SSA[101,137] and other anti-diarrhoeal medications might alleviate the most debilitating symptoms from CS, further obscuring the relationship between absolute tumour volume and HRQoL.

The multi-facetted concept of HRQoL should also be considered here. The results from paper I indicated that for the functional domains, while role function and emotional function had scores moderately below the general population of delta -6, only the lower level of social function of delta -10 was clinically relevant[98]. The social function subscale concerns two questions about how the illness 1) disrupts interactions with family or household activities, 2) interferes with spending time with friends, participating in community events, or engaging in social gatherings. Interestingly, Fröjd et al[102] reported a delta for social function at -12 one year after diagnosis for a similar cohort. For role function, delta was -16. Presence of diarrhoea was comparable to our cohort with delta +25. While role function was not as severely affected in our cohort, this still point to that human interactions seem most disrupted by a NET diagnosis. The results from paper I suggest that bowel symptoms probably play an important role here by disrupting the ability to interact with friends and family due to food intolerance or stigmatizing faecal soiling.

HRQoL as causal factor or marker of progressive disease and mortality?

In paper IV the QLQ-C30 Summary score was associated with overall survival in patients with siNET after adjusting for clinical confounders. As this relationship has been shown previously for other malignancies, several credible explanations for this already exist:

- Clinician-reported outcomes might miss out on important symptoms from either the disease or from treatment as some patients might withhold symptoms from their healthcare provider for varying reasons. One study showed that oncologists missed up to 50% of toxicity symptoms during routine cancer treatment[138,139].
- Patient reported outcomes are more detailed than routine open-ended questions at the clinic and can therefore possibly be more sensitive to small changes in patient symptomatology, reflecting real changes in tumour progression before these are visible on follow-up imaging[140].
- High quality of life correlates with positive behaviour such as healthy eating habits, physical exercise, stronger social relationships and higher adherence to treatment[141] reflecting a latent construct of “general fitness” which can be thought of as an unmeasured confounder.
- Patients with higher HRQoL might have better coping strategies and thus lower stress which in turn leads to lower levels of stress hormones. In women with metastatic breast cancer, dysregulation of diurnal cortisol levels was associated with shorter OS [142].

As the last explanation is the one with the best opportunity for intervention, we might expand on the findings underlying this concept. In 2008, a landmark randomized trial on women with breast cancer by Andersen et al. [143] showed that the group receiving psychological intervention before start of adjuvant therapy had better OS with HR of 0.51 (p=0.03). Results from a follow-up study on the patients from the cohort with a recurrence indicated that although both groups responded with severe stress when having their recurrence, only the patients in the intervention showed declining stress levels. Also, patients in the intervention group were more successful at securing emotional support from their spouse or family, a factor with known importance for coping with cancer[144]. Similar results have also been shown in patients with malignant melanoma[145]. The biological basis for these results is thought to be driven by excess stress from the diagnosis leading to increased sympathetic nervous system activity, dysregulation of the pituitary adrenal axis with ensuing inflammation and decreased cellular immunity[146], resulting in less clearance of cancer cells by the immune system. Evidence of this pathway was found in the study on recurrent breast cancer with patients in the intervention group displaying higher levels of natural killer cell cytotoxicity and T-cell blastogenesis – two factors associated with survival in cancer[147] .

On a similar note, growing evidence is emerging that active palliative treatment in patients with cancer is safe and is associated with improved quality of life[148]. Although not reproduced, a study by Temel et al on patients with lung cancer even showed improved overall survival (11 vs 9 months) with this strategy [149]. This points to a new direction in treatment of palliative cancer patients where length of life[150] and quality of life doesn't necessarily need to be at odds with one another.

With these findings in mind, the results from paper IV might serve as a validation of the HRQoL-concept in patients with NET. Consequently, while HRQoL can be thought of as a marker for better health, it can also act as an avenue on which to organise better psychological support for patients with siNET, primarily with the goal of increasing end-of-life HRQoL, but possibly also increasing length of life.

On the use of the QLQ-C30 Summary score in siNET patients

When conducting retrospective observational studies using HRQoL as either the independent (paper I, paper II) or dependent variable (paper IV), one problem is the multi-facetted concept that is HRQoL. The QLQ-C30 consists of 1 global QoL scale, 5 function scales and 9 symptom scales. If we also want to combine it with NET-specific symptoms using GI.NET21, this adds a further 9 symptoms and 1 function scale (SFNET), yielding a total of 26 domains to test for. On the one hand, the breadth of scales is helpful in an exploratory, hypothesis generating situation

where the patients' situation needs to be portrayed with as much detail as possible. On the other hand, in a hypothesis testing situation, the many subdomains create a problem of multiple testing, increasing the risk of committing a type 2 error where the null hypothesis is wrongly rejected. As paper I aimed to describe bowel symptoms of siNET-patients, multiple testing was deemed sufficient. However, the interpretation of the statistical significance of the results was more difficult. So, while we can say that the beta-coefficients of soiling and food intolerance was higher than for the other symptoms, indicating higher impact on patients' functioning, whether this relationship is statistically significant is harder to establish, as correction for multiple testing using for example Bonferroni correction was not possible due to the small cohort size.

The use of the QLQ-C30 summary score which incorporates all function scales and symptom scales except QL2 and FI, as established using factor analysis[95], might overcome this problem. This is the basis for us using the QLQ-C30 Summary Score in paper II and IV. However, using a summary scale has other problems:

Firstly, a summary score makes the rather strong assumption of equal weight of subdomains. While this might be true for the group as a whole, in the real world, the weight of different symptoms probably varies considerably between patients, as evident by the varying thresholds of clinical importance for different subscales in the work of Giesinger et al.[99].

Secondly, mixing function scales and symptom scales makes interpretation of what the summary score actually portrays less straight-forward. As the summary score is an average of 13 subdomains, high function or low symptom burden can mask severe symptoms in other areas. The results from paper II, where no correlation between tumour volume and the summary score was seen but correlation between tumour volume and specific symptoms was evident, are illustrative of this. With this in mind, the summary score, being the best performing aggregate score[95], is probably still the best compromise.

Lastly, for patients with a specific malignancy, such as siNET, the summary score does not inquire about specific NET-symptoms. This was the case in paper IV where we chose to create our own, non-validated summary score consisting of the average of all domains in the QLQ-C30 Summary Score together with all non-missing domains in GI.NET21. Our results did point to a slightly lower HR of 0.60 (95% CI 0.43-0.85) vs 0.67 (95% CI 0.51-0.90) when using the combined summary score compared to the validated QLQ-C30 version, pointing to important information from the added symptoms. This is reflected by studies showing an association with symptom severity of the carcinoid syndrome on OS[151,152] and that changes in GI.NET21 reflect response after therapy[93]. However, the difference in HR was so small and model fit so similar that we did not judge this to be outweighed by the increased complexity and the non-validated method. Compared to using subdomains as in the methods of Ediebah et al [153] and Quinten et al[83] , we judged

that the summary score was more scientifically honest than the stepwise exclusion of symptoms based solely on p-values which we used in the secondary analysis. Predictably, the results from this analysis where physical function, role function, emotional function, weight loss, insomnia, social function, nausea and vomiting, GI-symptoms and pain were all statistically significant, are not easy to interpret, especially since they differ from previous studies on other malignancies which in turn also show conflicting results [83]. This is in line with a recent study on a wide cohort of cancer patients where the QLQ-C30 Summary Score had lower HR on OS than global quality of life and physical function[140].

SSTR PET-CT scans during follow-up

In paper III, only 14% of SSTR PET-CT scans resulted in a major change of treatment. Using six risk factors (age, sex, latest level of urine 5-HIAA, latest level of S-CgA, presence of extrahepatic metastasis, whether last scan showed progressive disease) the cohort could be divided into a low- and high-risk group for major change (with 3 or more risk factors indicating high-risk). In the low risk group, 5% of scans led to major change whereas in the high-risk group, 22% of scans led to major change. It could be argued that overfitting is a factor and that the generalisability of the findings into guidelines is not appropriate. However, except for male sex, each risk factor has a sound clinical basis for actually being related to major change:

- High age is associated with increasing frailty and lower tolerance to side-effects from more aggressive treatment. Also, shorter remaining expected life span can also tip the risk/reward scale towards conservative treatment.
- Chromogranin A is known to correlate with tumour burden and shorter survival[62,69,154,155], higher levels probably therefore reflect more disseminated disease, increasing the likelihood for intensified treatment.
- Urine 5-HIAA adds further prognostic information to S-CgA, possibly by indicating functional tumour and hormone production, which by the symptoms of the carcinoid syndrome, often necessitates more aggressive treatment[128].
- Extrahepatic metastasis and progressive disease both signal an active disease process with worsened PFS[125,156]

As high-quality evidence for follow-up in siNET is lacking[157], the optimal follow-up of patients with siNET is unclear. Meanwhile, disease related worries and emotional distress are common[37] in patients with NET, suggesting that better management of follow-up and its associated fear of recurrence/progression is warranted. The results from paper III might indicate that if risk-stratification can be

implanted safely, some patients can benefit from follow-up with longer intervals than one year. The use of a risk score as outlined in paper III can serve to identify such low-risk patients. While our model was not developed to predict progressive disease, most of the patients in the cohort had major change due to progressive disease. Hence, if the NPV of 95% for our risk model can be replicated in another cohort, this is on par with recent developments in measurement of circulating NET-DNA and mRNA, the NETest®[158] , which demonstrated a NPV of 96% on progressive disease when used in combination with S-CgA[159]. As level of NETest has been shown to correlate well with imaging[160], the methods can potentially complement each other, perhaps by measuring NETest® and S-CgA at regular intervals as determined by the patient's risk profile and then using SSTR PET-CT to confirm recurrence or progress in order to guide further intervention when the biomarkers are elevated.

Towards regular measurement of HRQoL during follow-up of siNET?

If we accept that the results from paper III indicate that some patients with siNET might benefit from less intense follow-up and that the results from paper IV indicate that there is some inherent, additional value of HRQoL when predicting survival in patients with advanced siNET, one clinical application of this could be to include standardized, regular monitoring of HRQoL in the follow-up protocol of advanced siNET-patients. While a review of siNET in 2014 noted that the QLQ-C30 Summary Score has yet not been validated as a marker for progressive disease[79], the NETTER trial[114,161] of PRRT showed that time to deterioration of HRQoL and PFS was both improved for the treatment-arm. Other studies have showed that GI.NET21 changes in accordance to expected clinical outcome after therapy[93]. Ideally, a study evaluating the relationship between deterioration of QoL and its relationship to PFS should first be undertaken. If such a study could confirm this relationship, regular HRQoL can be integrated into follow-up protocols in a randomised prospective study setting.

Interestingly, Basch et al conducted a prospective trial that randomised patients undergoing routine cancer treatment of metastatic solid tumours to one of two groups: The intervention group filled in regular, web-based PROs to monitor symptoms and when symptoms deteriorated below a certain threshold, a nurse was notified by e-mail and a report concerning results from the PRO was made available to the treating oncologist before each scheduled visit. The usual care group received standard follow-up with routine visits and the option to be able to call a nurse about concerning symptoms. Regular PRO improved HRQoL among more participants in the intervention group than usual care (34% v 18%) and worsened among fewer (38% v 53%; $P < .001$). Regular PRO was also associated with less visits to the ER,

less frequent hospitalization and longer duration on chemotherapy. Moreover, the group using PROs had better median OS (31 vs 26 months, p=0.03) with an adjusted HR of 0.83 (p=0.04)[162]. A systematic review of the impact of using PROs in an oncologic setting demonstrated that regular use of PROs improved patient/physician communication, monitoring of treatment response as well as detection of unrecognized problems[163]. For patients with siNET, who often experience a prolonged course of malignant symptoms, standardized follow-up with this approach might be a course of action worth exploring. As internet increasingly permeates society and as logistically easier modes of collecting PROs such as the EORTC Cat Core[164] (which gathers information on QLQ-C30 by using adaptive questions and provides results as accurate as the old version) become available, the threshold for clinical implementation lowers. Then, with information gathering becoming less cumbersome, health-care providers are left to decide what to do with the new information. As care of patients with siNET becomes increasingly complex, this is not an easy question. However, except for the subject on the treatment of bowel symptoms, it is also beyond the scope of this thesis.

Is better treatment of bowel symptoms possible?

The results from paper I, which indicated a high prevalence of bowel symptoms in our cohort with siNET-patients, also indicated that faecal soiling and food intolerance adversely interfered with patients' ability to socially interact with family and friends. As frequency of faecal soiling varies depending on stool consistency[165], one might think of soiling as a consequence from the underlying cause of diarrhoea. For patients with the carcinoid syndrome, a decrease of transit time through the large intestine by half[166] due to decreased colonic compliance[42] is thought to be an important factor here. This biological basis might explain that a significant proportion of patients in our cohort was not able to wait 15 minutes when about to have a bowel movement or had to have another bowel movement within 15 minutes of the last one, practically mimicking symptoms of the low anterior resection syndrome[111] in patients having undergone surgery for rectal cancer. For cases where CS is a factor, more aggressive tumour directed therapy such as shorter interval between SSA doses or start if PRRT can be considered. For patients where this is not successful, telotristat ethyl (an inhibitor of serotonin production), can be tested. As results from phase 3 trials indicated improved HRQoL after using this treatment[167], it is probably safe to assume that not all patients with CS have adequate control of their bowel symptoms, suggesting room for improvement.

In our cohort, 43% of patients had elevated urine 5-HIAA above ULN and 56% of patients had more than 3 bowel movements per day. A post-hoc analysis tabulating these variables with each other (table 6) indicates that while ≥3 BM/day is more common (65%) among those with functioning tumours, 50% of patients with non-

functioning tumours also experience significant diarrhoea. This indicates that while the carcinoid syndrome probably affects some patients, other factors than the carcinoid syndrome are also important to understand presence of bowel symptoms in our cohort and for siNET-patients in general. This necessitates a thorough workup of each patient, using methods described in previous work[168]. To summarize, after evaluating whether syndrome from functioning tumour is a factor, the following differential diagnoses should be considered:

- Diarrhoea secondary to surgery such as pancreatic exocrine insufficiency after pancreaticoduodenectomy and short bowel syndrome after extensive intestinal resection (>100 cm small intestine).
- Diarrhoea secondary to SSA-treatment, here pancreatic exocrine insufficiency is the most common cause, leading to steatorrhea which can be treated with pancreatic enzyme replacement therapy (pancrelipase).
- Diarrhoea secondary to bile acid malabsorption due to right-sided hemicolectomy or ileocecal resection allowing for bile acid to reach the colon where it exerts a secretory effect. High clinical suspicion can warrant empiric treatment with bile acid sequestrants such as cholestyramine.
- Diarrhoea secondary to other antineoplastic treatments such as chemotherapy-induced diarrhoea. In these cases, more general treatments such as loperamide are indicated.

When the complexity of care for patients with siNET increase, health-care providers might struggle to keep up with the latest guidelines as delineated above. However, as social function and role function are the two most commonly affected domains of HRQoL in patients with siNET[102], bowel symptoms might provide a focus point where the return on improved HRQoL from spent healthcare resources are highest.

Strengths and limitations

Inclusion process

Overall, the studies in this thesis included patients by use of either a pathological database, SNOMED, or picture archiving and communication system. This resulted in inclusion of all eligible patients. Compared to using inclusion by information distributed by patient groups such as in the study on HRQoL in NET by Singh et al[169], this results in less selection bias. However, in papers I, II and IV, patients had to give informed consent and complete the HRQoL-instruments. For this, the response rate was 67%, which can be considered adequate and on par with similar studies[110]. Nevertheless, when exclusion of non-responders leads to a loss of one

third of patients, significant effects on the results from selection bias cannot be ruled out. Unfortunately, as analysis of non-responders was not included in the ethical application, whether these patients on general were more or less ill cannot be established. When comparing the cohort to that from Fröjd et al[102], a study where response rate is not reported but should in other ways be similar (Swedish population in the catchment area of a University hospital), the patients in our cohort had better HRQoL within most domains. This suggests that the non-responders might have more symptoms and lower function, which might stop them from filling out the instruments and mailing it to us. The question should then be whether this hypothetical selection bias actually significantly affects the conclusions. For paper I, inclusion of more sick patients with lower function and more symptoms would probably move the results towards stronger associations between bowel symptoms and HRQoL. For paper II, it is possible that exclusion of the most ill patients masks a *weak* correlation between tumour volume and the QLQ-C30 Summary Score. However, as no correlation was seen for the patients in the study, it is unlikely that selection bias would mask a *moderate or strong* correlation.

For paper III, as informed consent was not deemed necessary by ethical review, all 164 eligible patients with 570 observations were included in the analysis. This results in a rather large cohort size which should indicate more robust results. However, as the cohort only includes patients from one Swedish centre, it is possible that local clinical customs contribute to the use of regular, yearly SSTR PET-CT. The fact that no guidelines explicitly recommend using SSTR PET-CT in the follow-up of metastatic siNET supports this and might indicate that the results are not entirely representative of siNET-patients in other geographical areas.

The use of different inclusion criteria in the four cohorts can undoubtedly be criticized and should therefore be scrutinized. In short, as the research questions differed, we had to strike different balances between on one side homogeneity (resulting in more exclusion) and on the other side power and having a representative (and somewhat) heterogenic cohort:

- Paper I – Inclusion of all siNET-patients as they have often undergone similar surgical procedures and similar reasons for bowel symptoms. As patients can have diarrhoea for other reasons than CS, resected non-metastatic cases should also be included.
- Paper II – As tumour volume was the independent variable, only patients with metastatic disease were eligible. However, to increase power and as the study inquired into HRQoL in a broader sense, all patients with GEP-NET were to be included.
- Paper III – Since HRQoL was not a factor, we wanted to include all patients undergoing SSTR PET-CT due to siNET. As other GEP-NET than siNET

differ significantly in their treatment and prognosis, we judged that they could not be included-.

- Paper IV – Based on the cohort from paper I, we chose to exclude the patients having undergone surgery with successful radical resection. The rationale for this is that the group are known to have an excellent prognosis which was reflected by no deaths during follow-up of this subgroup. We therefore judged that their HRQoL would not be related to OS.

HRQoL-instruments

The QLQ-C30 and GI.NET21 are both validated and well-regarded HRQoL with ample previous use. The QLQ-C30 Summary Score has also been shown to have comparable and sometimes higher validity and responsiveness compared to the underlying subscales[95]. This is obviously a strength with the studies using HRQoL as a key variable. On the other hand, the MSKCC-BFI is not validated for use in patients with siNET. Also, as no Swedish translation is available, we had to translate it ourselves which naturally carries some risk of content validity where the translated items may not exactly capture the same concepts as the original. However, as the items were presented in the study as the actual question to the patient and not as an abstract underlying concept, we deem the risk for this to be low. Moreover, as only the single items were used and not the aggregate scores, construct validity should not be affected (which concerns relationships between items and underlying constructs). Lastly, while recall bias can never be ruled out in studies using self-reported outcomes, all instruments asked about "the last week or last 4 weeks", which would result in low recall bias.

Another limitation is the single time-point where HRQoL was measured which makes evolution of symptoms impossible to evaluate. However, a large study on NET-patients using repeated, regular measures of symptoms, showed rather stable symptom prevalence over time[136], suggesting that one measurement might be "good enough".

Methodological considerations

The data collected from the electronic healthcare records, was obtained by medical students doing their bachelor thesis. As they had no previous schooling in NET, this might introduce room for error. To overcome this, the data collection was supervised by the main author and corrected when necessary. In general, data quality was deemed having adequate quality.

One strength of the thesis is the low degree of missing data and transparent, clear plans for either multiple imputation, as used in paper I, or creation of categorical

variables reflecting clinical practice (below ULN, missing or above ULN), as used in paper III.

Other methodological strengths and limitations are:

- Paper I: Different multiple linear regression models gave similar results, making interpretation easier. However, unadjusted coefficients could also have been obtained in order to measure the total effect from bowel symptoms on functional domains.
- Paper II: Complete transparency regarding tumour volume distribution and volume, enabling results to be more easily interpretable. Multiple sensitivity analyses gave the same results, indicating robust findings.
- Paper III: Relatively large sample size with 164 patients and 570 observations. Biological foundation for all risk factors indicates that results can be generalized but as no validation cohort (external or internal) was used, overfitting could be a factor.
- Paper IV: Rigorous adjustment for confounders with causal inference and DAG and models evaluated with both Harrells C and AIC suggests reliable results. However, as no bootstrapping was conducted, robust results cannot be guaranteed. Also, the small sample size yielded computational problems during the secondary analysis so that all confounders could not be included, making these results less reliable. Lastly, as patients did not complete HRQoL-instruments in relation to their diagnosis date, survivorship bias (where patients with poor prognosis were not included before dying) cannot be ruled out.

Conclusions

Previous studies have shown that patients with siNET have lower HRQoL than the general population with relationships with friends and family being most severely affected. Our results confirm this and show that this HRQoL-gap in large parts might be explained by socially stigmatizing bowel symptoms such as faecal soiling and intolerance to certain foods or beverages. The findings suggest that the psychosocial impact of NET has been underappreciated and emphasize the importance of increased knowledge among health-care providers about the rather complex differential diagnostic procedure for bowel symptoms in patients with siNET.

Moreover, tumour volume in patients with GEP-NET does not seem to correlate with overall HRQoL. However, symptoms from the carcinoid syndrome show weak correlation with total tumour volume and tumour volume in the liver. This points to other psychological or biological causes for decreased HRQoL in patients with siNET such as differing coping strategies or that it is progressive disease in itself, regardless of tumour burden, that cause decreased HRQoL. The results from the first study could also suggest that bowel symptoms, regardless of their cause, drives decreased HRQoL more than objective measures, such as tumour volume.

An overall measure of HRQoL, measured as a summary score of QLQ-C30 at a random time-point after diagnosis, is associated with overall survival in patients with advanced siNET, even after adjusting for clinical variables. Regular follow-up with SSTR PET-CT in patients with siNET only lead to major change in treatment in a minority of cases. Six readily available clinical risk factors can possibly be used to guide risk-stratification when deciding for which patients imaging can safely be omitted. If further studies can establish HRQoL as a marker for progressive disease in patients with siNET, taken together, the findings from this thesis might suggest that a more integrated approach of patients with advanced siNET is preferable where:

- Follow-up is tailored according to trends of HRQoL together with other clinical risk factors.
- Regular HRQoL can act as an early warning system for disease progression.
- When HRQoL declines despite maximal symptom management, early psychosocial intervention is initiated.

Ethical concerns

All studies were conducted in accordance with the Helsinki declaration and ethical approval was obtained from the Swedish Ethical Review Authority. Informed consent was obtained for all patients in paper I, II and IV. Due to the retrospective nature of paper III and in accordance with Swedish law, informed consent was not deemed necessary. This was confirmed by ethical review.

The addition of mortality- and sociodemographic data from Statistics Sweden (SCB) and Swedish National Board of Health and Welfare in paper IV was not included in the information to patients since this project was not conceived when patients were informed. Since some patients had died after inclusion, new informed consent was not possible and as the sociodemographic and mortality data was very specific, patient integrity was not deemed to be severely harmed in relation to the scientific value of the project. This was also confirmed by ethical review.

All patient data was handled anonymously with access limited to the medical student and author for papers I, II and III and limited to only the author for paper IV. Patient data was only analysed on aggregate level. Patient integrity is deemed to have been preserved during the whole process. However, a few patients that had forgotten about or who were never informed about having NET at the time of pathological diagnosis (possibly since it required no further treatment than the surgical procedure they had already undergone) reacted negatively when contacted by mail. This was handled by personal explanations from the author by telephone after which the patients seemed content.

Populärvetenskaplig sammanfattning

Neuroendokrina tumörer (NET) är en ovanlig typ av tumör som främst förekommer i mag-tarmkanalen. Denna avhandling handlar nästan uteslutande om NET i tunntarmen, så kallas siNET (small intestinal NET). Till skillnad från andra tumörer, som t ex tjocktarmscancer, växer siNET ofta långsamt och patienter kan därför överleva under en förhållandevis lång period, ofta upp till 10 år, även om tumören spritt sig till levern eller andra ställen i kroppen. Av denna anledning kallades NET tidigare carcinoid, ”cancer-lik”, för att tumören bara delvis betedde sig som cancer. Den bästa behandlingen för NET är att operera bort det tarmavsnitt där tumören eller tumörerna sitter. Om man får bort allt kan patienten bli botad med även om man inte får bort allt (t ex om tumören sitter nära viktiga kärl eller har spritt sig till stora delar av levern) är det sannolikt så att man åtminstone förlänger patientens liv med en operation.

siNET har sitt ursprung från celler i tunntarmens neuroendokrina system, ett system som verkar för att koordinera tarmrörelserna för att innehållet ska ta sig igenom lagom snabbt beroende på exempelvis näringsinnehåll eller om maten är dålig av någon anledning. En unik egenskap hos NET är att tumören ofta liknar de celler den har sitt ursprung från i så hög grad att tumören fortsätter att producera det hormon, serotonin, som cellerna normalt använder för att signalera med omgivningen. Om tumören sprider sig till levern kan serotoninet nå resten av blodcirkulationen och ge upphov till mycket besvärande symtom. Dessa symtom består främst av kraftiga, vattniga diarréer, blossande kinder (flushing) och hormonet kan även drabba hjärtat så att klaffarna fungerar sämre och börjar läcka. Detta tillstånd kallas det carcinoida syndromet och har sedan ca 30 år kunnat behandlas med läkemedel, så kallade somatostatinanaloger, som fäster till somatostatinreceptorerna på tumören och hämmar både tillväxten av NET och även hämmar utsöndringen av serotonin. En annan behandling som utnyttjar att NET uttrycker somatostatinreceptorer är målinriktad strålbehandling där man kopplat ihop Lutetium, ett ämne som utsöndrar joniserande strålning med en somatostatinanalog (som fäster på NET). Detta gör att strålningen anhopas där tumören finns vilket bromsar förloppet och gör att patienterna lever längre. Uttrycket av somatostatinreceptorer utnyttjas även när man vill kartlägga hur stor utbredning NET har i kroppen. I detta fall kopplas somatostatinanalogen ihop med Gallium-68 som utsöndrar en annan, icke-skadlig, typ av joniserande strålning. Efter att ämnet injicerats i patienten kan man med hjälp av speciell röntgenutrustning (Gallium PET-CT) skapa bilder över tumörens

utbredning. Detta är framförallt viktigt för att avgöra om tumören har spridit sig. Om man upprepar undersökningen med jämna mellanrum kan man även avgöra om tumören växer (vilket ofta betyder att man behöver sätta in ytterligare behandling) eller om sjukdomen är stabil (vilket betyder att man kan fortsätta på samma spår).

I takt med att patienter med olika cancerdiagnoser tack vare bättre behandling lever längre har begreppet hälsorelaterad livskvalitet blivit alltmer viktigt. Detta är i allra högsta grad relevant för patienter med NET där man även med metastaser kan överleva 10 år. Ett av de vanligaste sätten att studera livskvalitet är med hjälp av enkäter som patienterna själva får fylla i. Enkäterna har som mål att belysa patienternas liv i förhållande till sjukdomen på ett så heltäckande sätt som möjligt och består därför av flera områden: fysisk, social, emotionell, kognitiv funktionsförmåga samt förmåga att klara av yrkesliv och dagliga ansvarsområden. Därtill ingår frågor kring intensiteten av de vanligaste symtom som patienter med cancer lider av.

Arbete 1

Eftersom patienter med NET i tunntarmen i stor utsträckning lider av tarmsymtom som diarré, men det var oklart på vilket sätt detta faktiskt leder till påverkad livskvalitet, var målet med avhandlingens första arbete att studera detta samband. Vi skickade därför ut enkäter där patienterna dels fick uppge vilka exakta tarmsymtom de haft den senaste månaden och dels hur deras livskvalitet varit. Föga förvånande kunde man se att de vanligaste tarmsymtomen var att avföringen var lös eller att man behövde gå många gånger på toaletten. Ett mer intressant fynd var att vi med hjälp av statistisk analys kunde vi visa att andra, mer stigmatiserande symtom (avföringsläckage eller intolerans mot särskild föda eller dryck) hade den starkaste kopplingen till sänkt livskvalitet och då särskilt inom förmåga att umgås med familj eller att klara av yrkesliv eller andra dagliga ansvarsområden. Förhoppningsvis kan dessa fynd leda till ökat fokus från sjukvården att hjälpa patienterna med dessa tarmsymtom.

Arbete 2

Man kan hypotetiskt tänka sig att för patienter med obotlig NET så borde mer tumörvävnad ge sämre livskvalitet (genom att det då finns fler tumörceller som kan producera hormon och fler tumörceller som kan störa kroppens normala processer). Tillsammans med en forskargrupp med röntgenläkare som gjort mätningar av total tumörvolym enligt Gallium PET-CT för varje patient, studerade vi detta samband med hjälp av olika statistiska metoder. Något förvånande kunde vi inte se ens ett svagt samband mellan tumörvolym och livskvalitet, däremot kunde man se ett svagt samband mellan symtom från det carcinoida syndromet (diarré, flushing, andfåddhet) och tumörvolym i levern. Vi tolkar resultaten som att vi antingen inte

har fångat alla patienter med våra enkäter eller att patienternas olika förmåga att vänja sig vid symtomen gör att orsakssambandet mellan livskvalitet och tumörvolym suddas ut.

Arbete 3

I samband med metastaserad NET är det många patienter som genomgår regelbunden uppföljning med Gallium PET-CT. Eftersom sjukdomen i många fall är ganska stabil var det oklart hur ofta dessa kostsamma undersökningar faktiskt bidrar med så pass viktig information att behandlingen för patienterna ändrades. I detta arbete studerade vi journalerna för 164 patienter som totalt gjort 570 undersökningar med Gallium PET-CT. Av dessa 570 var det bara 14% som ledde till påtaglig förändring av patientens behandling. Statistisk analys visade att följande faktorer, oberoende från varandra, vardera sänkte risken att undersökningen skulle leda till förändring med ca hälften.

- normala hormonnivåer
- normala nivåer av tumörmarkören Kromogranin A
- ålder över 70 år
- kvinnligt kön
- ingen tillväxt av tumören vid senaste undersökningen
- ingen spridning av tumör utanför lever eller tarm

Vid fler än 5 faktorer var risken så pass låg att man eventuellt kan överväga att avstå Gallium PET-CT eller åtminstone glesa ut intervallen. Eftersom studien bara gjorts vid ett center behöver dock resultaten bekräftas i ytterligare studier innan förändring av klinisk rutin sker.

Arbete 4

Tidigare stora studier av målstyrd strålbehandling av metastaserad NET har visat att behandlingen både förbättrar livskvalitet och överlevnad. Detta tyder på att ett samband mellan nedsatt livskvalitet och överlevnad kan finnas. För andra cancerdiagnoser har man visat just detta resultat. I vår fjärde studie kunde vi visa att detta samband även gäller för patienter med obotlig NET, även om man justerar för vanliga andra faktorer hos patienten som ålder och hur mycket tumören spridit sig. Vi tolkar resultaten som att mätning av livskvalitet ger kompletterande information till sjukvården om patientens underliggande motståndskraft. Förhoppningsvis kan detta vara första steget mot att mer regelbundet följa upp NET-patienter med standardiserad mätning av livskvalitet för att vid tecken till sjunkande nivå snabbare kunna sätta in adekvat behandling eller psykosocial stöttning.

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