



Center for neuroendocrine tumors
Rikshospitalet



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Epidemiology of Neuroendocrine Neoplasms in Norway

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PhD thesis

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“Be like the sun for grace and mercy. Be like the night to cover others' faults. Be like running water for generosity. Be like death for rage and anger. Be like the Earth for modesty. Appear as you are. Be as you appear.”

Jalaluddin Rumi 1207-1273

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ABBREVIATIONS

ASR	Age Standardized Incidence Rate
CgA	Chromogranin A
CI	Confidence Interval
CRN	Cancer Registry of Norway
CT	Computed Tomography
EAPC	Estimated Annual Percentage Change
ENETS	European Neuroendocrine Tumor Society
EUS	Endoscopic Ultrasound
GEP	Gastroenteropancreatic
HIAA	Hydroxyindole-3-Acetic Acid
ICD-O	International Classification of Diseases for Oncology
IQR	Interquartile Range
MEN	Multiple Endocrine Neoplasia
MRI	Magnetic Resonance Imaging
NEC	Neuroendocrine Carcinoma
NEN	Neuroendocrine Neoplasm
NET	Neuroendocrine Tumor
NNTG	Nordic Neuroendocrine Tumor Group
NPR	Norwegian Patient Registry
PCC	Pheochromocytoma
PET	Positron Emission Tomography
PGL	Paraganglioma
P-NEN	Pancreatic Neuroendocrine Neoplasm
SEER	Surveillance, Epidemiology, and End Results program
SRS	Somatostatin Receptor Scintigraphy
SSA	Somatostatin Analogs
SSRT	Somatostatin receptor
TTF-1	Thyroid Transcription Factor
US	Ultrasound
WHO	World Health Organization

PUBLICATIONS INCLUDED

Paper I: Trends in incidence of neuroendocrine neoplasms in Norway: A report of 16,075 cases from 1993 through 2010.

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Paper II: Survival in Neuroendocrine Neoplasms; A report from a large Norwegian Population-based Study

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Paper III: Survival and prognostic factors in well-differentiated pancreatic neuroendocrine tumors

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1. INTRODUCTION

1.1 Neuroendocrine cells

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors that arise from the cells of the neuroendocrine system. There are two groups of neuroendocrine cells; some that form glands (cell types that compose the adenohypophysis, paraganglia, adrenal medulla and parathyroids) and others that are diffusely distributed (the lung, gastrointestinal tract, pancreas, urogenital tract, thyroid, skin, thymus and biliary tract) ¹. NENs are characterized by their ability to produce different peptides and neuroamines that can cause distinct clinical syndromes. Neuroendocrine cells are scattered throughout the body, hence NENs can arise in a wide range of organs. The most common primary sites are in the broncho-pulmonary system, in the gastrointestinal tract, and pancreas. Studies show geographical ²⁻⁵ and racial⁶⁻⁸ differences. A significant number of NENs occur in other anatomical sites⁹, but they are often excluded from population-based studies and our knowledge about their incidence and behavior is sparse.

Siegfried Oberndorfer defined carcinoid tumors (“karzinoide” carcinoma like) of the small bowel in 1907, as these tumors were more indolent than their adenocarcinoma counterparts¹⁰. More than a century later, these tumors remain the most common primary tumor of the small bowel and are usually slow-growing indolent NENs. When that is said, neuroendocrine neoplasms are associated with several morphological types. Historically NENs have been described as benign tumors, but they are now recognized as true neoplasms, and some even with a high malignant potential.

1.2 Classification

During the last decades, the nomenclature and classification of NENs have been changing. Previously, neoplasms have been classified according to their embryologic origin: foregut (respiratory tract, thymus, esophagus, stomach, duodenum, ovaries and pancreas), midgut (jejunum, ileum, appendix, caecum, ascending colon and Meckel’s diverticulum) or hindgut (transvers, descending and sigmoid colon and rectum). NENs have also been classified according to their morphological features, and according to their immunohistochemical properties^{9, 11, 12}. There are no uniform classifications of morphology and grading covering all anatomical sites. The

new classification system for gastroenteropancreatic (GEP) neoplasms is based on the localization of the tumor plus eventual hormone production (e.g. pancreatic NEN with insulin production).

In WHO 2000 classification¹³ the tumors were grouped into three according to tumor differentiation: Well-differentiated endocrine tumors, well-differentiated endocrine carcinomas and poorly-differentiated carcinomas. In 2006, ENETS proposed a new classification for GEP-NENs that was based on mitotic count and Ki-67 index¹⁴. The most recent grading systems for GEP (WHO 2010)¹⁵ and lung NENs (WHO 2015)¹⁶ are now based on registration of the proliferation marker mitotic figures per 10 high power fields in light microscopy or immunohistochemical staining with the monoclonal antibody MIB-1. Based on the number of mitotic figures, or percentage of MIB-1 positive tumor cells (Ki-67 index), NENs are graded from Grade 1 to Grade 3, with Grade 1 being the least aggressive group. Grade 1 and Grade 2 are termed neuroendocrine tumors (NETs). Grade 3 tumors are termed neuroendocrine carcinomas (NECs) and are the least differentiated and most aggressive form of NEN. There is no uniform classification for all anatomical sites, but the classification for GEP and lung NENs can also be indicative for classification for other sites (**Table 1**).

Nomenclature	Grade	Ki-67* (%)	Mitotic Count**	Differentiation
Neuroendocrine Tumor (NET)	G1	≤ 2	<2	Well-differentiated
Neuroendocrine Tumor (NET)	G2	3-20	2-20	Well-differentiated
Neuroendocrine Carcinoma (NEC)	G3	>20	>20	Poorly-differentiated
Small- or large cell types				

Table 1. World Health Organization (WHO) Classification for GEP and Lung NENs. *MIB1 antibody, % of 2000 tumor cells in hot-spot areas (highest nuclear labeling) **10 HPF (high power fields) of total 2 mm², counting at least 40 fields at 40 x magnification in areas of highest mitotic density

During the last decades, there has been debate about the inconsistent nomenclature and changes in classification of NENs. There are numerous different histological codes for NENs in the

International Classification of Diseases for Oncology (ICD-O)¹⁷ The pathologist who examines the tissue specimen from the tumor categorize the tumor based on appearance and characteristics by a one or several of these codes. Various numbers of these codes are included in different studies. Accordingly, it has been difficult to compare epidemiological studies.

Neuroendocrine neoplasms are complex and guidelines are published for what routine pathology report should contain^{18, 19}. These recommendations include tumor characteristics, histology, immunohistochemical markers (Chromogranin A (CgA), synaptophysin), tumor grade, and proliferation markers. Even though the grading of NENs is based entirely on proliferation markers, this information is still not reported in all pathology reports. For example a French group recently reported the results of a prospective one-year survey among French pathologists and found that mitotic count and Ki-67 were reported in only 80% of the cases²⁰.

1.3 Ki-67 index

Ki-67 is a nuclear protein expressed by all human proliferating cells. A study reported that Ki-67 organizes the mitotic chromosome periphery²¹, but the complete function of Ki-67 is still unclear. During the resting phase of the cell cycle (G₀), Ki-67 can exclusively be detected within the nucleus, whereas in active phases of the cell cycle (G₁, S, G₂, and mitosis) most of the protein is located on the surface of the cell. The MIB-1, a monoclonal antibody, targets the Ki-67 protein on the cell surface and stains cells at active stages of the cell cycle²². Accordingly, the relative number of tumor cells with expression of Ki-67 is a marker for the growth fraction of a cell population, indicating the number of cells undergoing active division. This fraction is called the Ki-67 index and is expressed as a percentage of the tumor cell population. The higher Ki-67 index is, the more cells are in cell division and the more aggressive the tumor is. This proliferation index is accepted as a good prognostic marker and is also used to select therapy. Panzuto et al found a 2% increased risk of progression with every unit increase in Ki-67²³. This important marker is also used in other cancers such as breast cancer²⁴.

The gold standard to calculate the Ki-67 index is to count a total of 2000 tumor cells in “hot-spot” areas, areas where the highest density of stained tumor cells is observed. There may be intraobserver and interobserver variations^{25, 26}. There are different methods of calculating Ki-67 index^{27, 28} :

- 1) Manual counting
- 2) Automated counting with digital analysis
- 3) Manual counting of camera-captured/printed image
- 4) Eyeballing with an estimate of the approximate percentage without counting.

A study by Tang²⁸ evaluated different methods and concluded that the first two methods of counting were acceptable standards for Ki-67 assessment, while eyeballing showed low agreement for all NEN grades. Another study that tested all four methods in pancreatic NENs (P-NENs) found that camera-captured/printed image was most reliable with highest reproducibility²⁹.

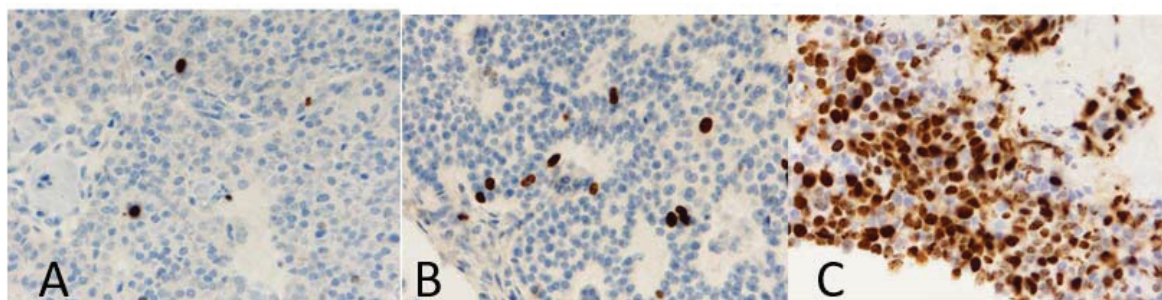


Figure 1. Immunohistochemical staining of Ki-67 antigen

A) Ki-67 1.5% (Pancreas) B) Ki-67 5.6% (Pancreas) C) Ki-67 78.4% (Liver metastasis with unknown primary)
(Courtesy of Department of Pathology, Oslo University Hospital)

The heterogeneity within the neuroendocrine tumor regarding Ki-67 is well accepted³⁰. It is the highest Ki-67 index that decides the grade of the tumor. In the last years, there has been discussion on the difference in Ki-67 in the primary tumor versus the metastases. The Ki-67 is generally higher in the metastases than in the primary tumor³¹. A Russian study found increased Ki-67 index in the

metastases compared to the primaries in 27% of the GEP NENs³² and more than 50% of these needed upgrading from G1 to G2 and G2 to G3. Couvelard et al studied the variety in Ki-67 index among metastases and found the same variations between synchronous metastases as within a single metastasis²⁶.

There are differences in survival between the different grades, but the limits of Ki-67 are proposed modified. Scarpa et al³³ found prognostic differences with Ki-67 limits 5% and 20% in pancreatic NENs. The upper limit of G1 proposed increased to 5%. Further there is a controversy as to whether G3 tumors can be well-differentiated^{34,35}. The Nordic NEC study in 2013 found that NEC patients with Ki-67 < 55% were less responsive to platinum based chemotherapy³⁶. Still they had longer survival, indicating separate entities within gastrointestinal NECs. This was followed by the discussion on the possibility of well-differentiated high-grade neuroendocrine tumors³⁷. Our knowledge on NECs is limited, but more studies are emerging in this field. There is likely that new cut-points will be proposed in the future. Meanwhile there are suggested modifications such as separating G3 tumors (high-grade tumors) into two categories: tumors with Ki-67 20-55% and tumors with Ki-67 > 55%³⁷. This discussion also emphasizes the importance of registering the actual Ki-67 index and not only the grade.

1.4 Functionality

All NENs could produce different peptides and neuroamines. While NETs often do, NECs rarely produce hormones. When a clinical syndrome of hormonal overexpression is evident, the neoplasm is classified as functional. Many tumors may be clinically silent though and are classified as non-functional tumors. In the latter instance, peptides or amines are often demonstrable in tissue specimens by immunohistochemical techniques¹³. There are no good correlation between positive staining and functionality. To give an example; a tumor with positive staining of gastrin is not a gastrinoma if the patient has no symptoms or signs of excess gastrin production.

Most of NEN patients presents with symptoms related to the tumor bulk itself. But some patients present with hormone-related symptoms depending on the underlying cellular subtype. In P-NENs,

functional tumors constitute 20-30% of the cases³⁸⁻⁴⁰ and **Table 2** shows different cellular subtypes and associated hormones and symptoms⁴¹.

Functional tumor type	Hormone produced	Symptoms
Insulinoma	Insulin	Hypoglycemia, weight gain, coma
Gastrinoma	Gastrin	Dyspepsia, recurrent peptic ulcers, diarrhea, steatorrhea
Glucagonoma	Glucagon	Diabetes mellitus, migratory necrolytic erythema, thromboembolism
VIPoma	Vasoactive Intestinal Peptide	Watery diarrhea, hypokalemia, achlorhydria, hyperglycemia, metabolic acidosis
Somatostatinoma	Somatostatin	Diabetes mellitus, diarrhea, gallbladder disease
Pancreatic polypeptidoma	Pancreatic polypeptide	Abdominal pain, watery diarrhea
PTHrP-oma	PTH-related peptide	Hypercalcemia (with non-increased PTH)
ACTHoma	ACTH	Cushing's syndrome
GRHoma	Growth releasing hormone peptide	Acromegaly

Table 2. Functional NENs. VIP: Vasoactive Intestinal Peptide. PTH: Parathyroid hormone.

ACTH: Adrenocorticotrophic hormone. GRH: Growth releasing hormone.

In small intestinal, appendiceal and lung NENs, the serotonin production may result in carcinoid syndrome, characterized by diarrhea, flushing, intermittent bronchial wheezing and right heart-valve fibrosis⁴². These manifestations are related to metastatic disease, and mostly liver metastases, which leads to bypassing serotonin from the portal circulation and hepatic clearance of serotonin.

1.5 Diagnosis

The diagnosis of a NEN is based on histopathological examination of tissue specimen from the primary tumor or metastases. The diagnosis can also, to a lesser extent, be based on radiological imaging, laboratory tests and symptoms.

1.5.1 Histopathological diagnosis

The histological pattern of endocrine tumors is characterized by a solid, trabecular or glandular arrangement of well-differentiated cells which may also form pseudo-rosettes or tubulo-acinar structures⁴³. Poorly-differentiated NENs show a patternless arrangement with necrosis and marked cellular atypia. The histological pattern does not distinguish between organs of origin. A biopsy or surgical specimen should be used as cytology is neither sufficient for diagnosis nor calculation of Ki-67⁴⁴. The histological diagnosis of NEN is confirmed by immunohistochemical markers such as chromogranin A (CgA) and synaptophysin⁴⁵⁻⁴⁷. In high-grade neoplasms, CgA is often negative while synaptophysin is positive. In the high-grade neoplasms it can be necessary to combine these markers with less specific markers such as neuron-specific enolase (NSE), CD56 and thyroid transcription factor 1 (TTF-1).

Markers of primary origin are not completely specific but a panel of markers can be in help of the determination of the primary location. As an example, TTF-1 can be indicative of primary location in the lung. Another marker such as cytokeratin 20 (CK-20) is expressed in Merkel cell carcinomas. An important differential diagnosis in Merkel cell carcinoma is metastases from a small cell lung carcinoma. CK-20 is always positive in Merkel cell carcinomas while TTF-1 is negative. CK-20 is negative in small cell carcinomas⁴⁸ and these markers can be used to differentiate between these two morphological entities. But TTF-1 cannot be used to differentiate between pulmonary and extra pulmonary small cell carcinomas. In a study of markers of GI small cell NECs, up to 21.4 % the GI tumors stained positive for TTF-1⁴⁹. Another marker CDX-2 is an intestine-specific marker, but can be found in pancreatic NENs as well. This marker (CDX-2) may also be useful to distinguish between primary ovarian carcinoids and intestinal carcinoids with metastases to the ovary⁵⁰.

PAX8 are positive in pancreatic well-differentiated NENs, but can also label rectal NENs^{51, 52}. The human insulin gene enhancer-binding protein islet-1 (ISL1) has been identified as a marker for pancreatic NENs, but it is found to be positive also in a range of extra pancreatic NENs such as medullary thyroid carcinoma and paraganglioma/pheochromocytoma⁵³.

Peptide hormones should probably only be stained for when a clinical syndrome suggesting a functional tumor is present¹⁹.

1.5.2 Biochemical markers

Chromogranin A (CgA) is a glycoprotein stored in dense-core secretory granules in endocrine and neuroendocrine neoplasms and secreted in the bloodstream and can be analyzed in serum and plasma. CgA is useful in diagnosis of NENs, evaluation of treatment response and early detection of recurrence^{44, 54}. High levels of CgA in GEP-NENs are associated with high tumor burden and poor prognosis⁵⁵. The sensitivity and specificity varies between different types of NENs, between 60-100% and 70-100%, respectively. CgA can also be elevated in other neoplasms than NENs, in organ failure (heart, kidney and liver), inflammatory diseases, chronic atrophic gastritis and in use of proton pump inhibitors (PPI). As food intake may also affect CgA levels it is recommended to do measurements in fasting patients⁴³.

Urinary 5-hydroxyindole-3-acetic acid (5-HIAA) is a breakdown product of serotonin and is elevated in tumors originating from the enterochromaffin cells⁵⁶. The majority of patients (70%) with small intestinal NENs have elevated 5-HIAA¹². There are some diet restrictions days up to urine test, as avoidance of serotonin rich food such as bananas, kiwis, avocados, pineapples, nuts and chocolate⁵⁷. The determination of 5-HIAA has traditionally been done by cumbersome 24-hour urinary samples. In 2013 Gedde-Dahl et al. compared 24-hour sample collection with ~8 hour morning urine sample and found significant correlations⁵⁸.

1.5.3 Imaging

Imaging techniques play an important role in diagnosis, staging, treatment selection and follow-up in NEN patients. The techniques have improved during the last decades. New modalities are in use such as PET, as well as existing ones being more accessible and with better resolution such as CT and MRI.

In patients with NEN several morphological (anatomical) and functional (molecular) imaging techniques are available (**Table 3**). For visualization of primary tumor and evaluation of stage and somatostatin receptor status, a combination of morphological and functional imaging techniques are mandatory⁵⁹. The choice of techniques depends on whether the purpose is diagnosis and staging, choice of therapy or follow up. In the initial diagnostic work-up, CT/MRI in combination with somatostatin receptor imaging (SRS or PET) is used.

Anatomical Imaging	Biological Imaging	Molecular Imaging
<ul style="list-style-type: none">• CT• MRI• US/EUS• Endoscopy	<ul style="list-style-type: none">• CgA• Ki-67• Histology• Gene transcripts	<ul style="list-style-type: none">• SRS• PET<ul style="list-style-type: none">• ⁶⁸Ga-DOTA• ¹⁸F-DOPA• ¹¹C-5-HTP• ¹⁸F-FDG• ⁶⁴Cu-DOTA

Table 3. *Different Imaging techniques for diagnostics and follow-up*

CT/MRI

CT is the basic radiological modality for NEN imaging. It is recommended to scan the thorax, abdomen and pelvis for primary tumor and/or metastases⁴⁴. A triple-phase CT with proper i.v contrast is necessary to visualize NEN lesions. NEN liver metastases are more frequently hyper-vascular than metastases from other solid cancers such as colorectal- and breast cancer, but can be hypo-vascular as well. Both hyper- and hypovascular types can even be found in the same patient. For pancreatic NENs CT has a sensitivity and specificity of 73% and 96% respectively⁵⁹. MRI is superior to CT for imaging small liver and pancreatic lesions⁶⁰. The use of MRI is favorable in younger patients with expected long follow-up time to decrease the radiation exposure. For imaging thoracic lesions, MRI is less suitable because of the low signal-to-noise ratio in the lungs and cardiac- and respiratory movements⁶¹.

US/EUS

Ultrasonography (US) is suited for superficial organs such as thyroid and parathyroid glands and abdominal and retroperitoneal organs. US does not expose the patient for radiation and enables tumor biopsies. It can also be performed during contrast enhancement (CE) using microbubbles, making liver metastases smaller than 5 mm detectable.

Endoscopic ultrasound (EUS) is the most sensitive modality in the diagnosis of pancreatic NEN (detection rate about 90%)⁵⁹. The technique also allows fine needle aspiration for cytology and core biopsies from pancreatic tumors as well as gastric tumors.

Somatostatin Receptor Scintigraphy (SRS)

Most NENs express somatostatin receptors (SSTR). Various somatostatin receptors can be expressed, but SSTR2 is predominant⁶². By using radiolabeled somatostatin analogs NENs can be visualized. Tumors with low density of SSTR such as high grade NENs, or small tumors, may not be detected.

SSTR scintigraphy (SRS) with ^{111}In -DTPA-ocreoitide is the standard method. Planar whole-body images (2D) are taken at 4 and 24 hours and 3D single photon emission computed tomography (SPECT) of the abdomen and/or thorax is performed after 24 hours. SRS in combination with computer tomography (SPECT/CT) secures a better localization where the anatomical CT superimposes onto the functional SPECT images.

SSTRs are also expressed in other tissues and in inflammation. Scar healing can cause false positive results. The sensitivity and the specificity of SRS vary with the tumor size, anatomical localization and tumor type. The reported sensitivity for abdominal NENs ranges from 46% to 100%. For pancreatic NENs, the overall sensitivity is reported to be 67%⁵⁹. The sensitivity for detecting insulinomas with SRS is generally low.

Positron emission tomography (PET)

PET has replaced SRS in many centers. The positron emitter ^{68}Ga is used to label somatostatin analogs for somatostatin receptor imaging by using PET/CT. Compared to SRS the spatial resolution is 0.5 cm vs 1.5cm and the tissue contrast is better than with SPECT⁶⁰. Due to the fact that the tracer kinetics is faster, PET imaging can be done 30-60 minutes after injection. The most commonly used preparations are ^{68}Ga -DOTATOC, ^{68}Ga -DOTATATE, ^{68}Ga -DOTANOC which shows different affinities for different SSTRs, but they all binds to SSTR2 and SSTR5. The differences in clinical practice seems to be marginal. Their sensitivity and specificity is reported to be more than 90%⁵⁹. False positive results include inflammation and false-negative results include small tumors and tumors with low SSTR expression.

The tracer ^{64}Cu gives the possibility of imaging at a later time (half-life 12.5 hours) than ^{68}Ga but cyclotron is needed for its production. Recently a Danish group compared ^{64}Cu -DOTATATE and ^{68}Ga -DOTATOC PET/CT on a head-to-head basis⁶³. They reported the same patient-based sensitivity, but significantly more lesions were found with ^{64}Cu -DOTATATE. These findings together with the ^{64}Cu -DOTATATEs shelf life of more than 24 hours and a flexible scanning window of at least 3 hour is believed to make the tracer attractive for clinical use.

The tracer ^{18}F FDG is taken up by metabolically highly active tumors and is the preferred tracer in NECs. ^{18}F FDG positivity has been reported to predict early tumor progression and poorer prognosis⁶⁰. Other tracers are ^{18}F -DOPA and ^{11}C -5-HTP, but these have limited availability.

1.5.4 Familial NEN and Genetic Alterations

There are inherited syndromes associated with NENs such as Multiple Endocrine Neoplasia (MEN) 1 and 2, von Hippel-Lindau syndrome (VHL), Neurofibromatosis type 1 (NF1) and Tuberous sclerosis. Up to 20 % of all NENs are part of inherited NENs^{64, 65}. In GEP NENs, pancreaticoduodenal NENs are particularly described to be part of familial syndromes. A Swedish series of familial SI-NENs has been published as well, but the genetic changes is still unknown⁶⁶. If a patient presents with more than one primary GEP lesion, or if there is a family history indicating familial NEN, genetic screening is recommended⁴⁴.

In 2011 Jiao et al⁶⁷ examined 68 sporadic P-NENs and found that the most frequently mutated genes were MEN-1 (44%) and DAXX/ATRX (43%), specifying proteins implicated in chromatin remodeling and found to be associated with better prognosis. They also found mutation in genes in the mammalian target of rapamycin pathway (mTOR) in 14% of the tumors.

Although paragangliomas/pheochromocytomas (PGL/PCCs) are rare, they are more commonly associated with an inherited mutation than any other cancer type⁶⁸. In a cohort of PGL/PCCs patients, up to 41% had an inheritable mutation, and genetic testing is recommended in all patients⁶⁹. In addition to three previously well-known syndromes (VHL, NF1 and MEN-2) there have been identified several susceptibility genes for PGL/PCCs: the Succinate Dehydrogenase (SDH) complex subunit genes (SDHA, SDHB, SDHC, SDHD), TMEM127 and MAX to mention some⁶⁸.

Classical tumor suppressor and oncogenes of many solid tumors do not seem to play a role in NEN pathogenesis⁷⁰. As examples p53, RB and KRAS are rarely altered in NENs⁶⁷.

Epigenetic changes are heritable changes in gene expression without alterations of the underlying DNA⁷⁰ and are known to play an important role in cancer development. The field of epigenetics is evolving in NENs, and since epigenetic changes are reversible, they represent possible therapeutic targets. The main fields of epigenetic modifications are DNA methylation, histone modifications and microRNA (miRNA) expressions⁷⁰. Methylation of RASSF1A is a frequent finding in NENs of different origins and is suggested to have a potential role in the development of these tumors as well as a prognostic impact. It does not seem to play a major role in GEP NECs though. MiRNA signatures and histone modifications can be prognostic markers as well as differentiate between subtypes of NENs as well as differentiate NEN from adenocarcinomas⁷⁰.

1.6 Treatment

The only curative treatment is surgery, but about half of the patients have non-resectable metastases at time of diagnosis and need palliative treatment modalities. The treatment is dependent on tumor localization, grade and symptoms. During the last decade, the treatment options of NENs have increased as new therapeutic alternatives have emerged. In addition, the well-established symptomatic treatment with somatostatin analogs (SSA) has been shown to have anti proliferative effect^{71, 72}.

1.6.1 Surgery

In operable patients, the aim is radical surgery. However, most of the patients have advanced disease at diagnosis and radical surgery may not be possible. The recurrence rate after surgery with curative intent is also high⁵⁴. There is still an ongoing debate whether removal of the primary in advanced disease or debulking surgery improves survival.

In metastasized small intestinal NENs, removal of the primary and/or debulking surgery may be beneficial for control of local and endocrine symptoms⁷³. In advanced well-differentiated pancreatic NENs, the survival benefit of resection of the primary is still unclear. Two similar

reports from the SEER database^{74, 75} found a significant survival benefit in patients who underwent palliative primary resection (HR 0.41, 95% CI [0.25-0.66]). Median survival was 65 months vs. 10 months for those without resection. These studies have limitations, such as selection bias and the lack of information on number of metastases and other treatments used. There is a need for randomized trials to clarify the role of debulking surgery. According to ENETS, debulking surgery in non-functional tumors may be considered if the patients are suffering from symptoms related to tumor burden⁷⁶. Surgery should also be considered in patients with uncontrolled functional tumors.

Studies on treatment of neuroendocrine carcinomas (G3 NENs) in the GEP system are limited and recommendations are often based on treatment on the more common small cell lung carcinomas (SCLC). Curative surgery may be attempted in localized disease. Due to the high relapse rate, adjuvant chemotherapy is recommended. In advanced metastatic disease in high grade NENs, surgery is not recommended⁷⁷.

1.6.2 Molecular targeted therapy

Somatostatin analogs

Somatostatin analogs (SSA) are the cornerstone of treatment of hormonal symptoms in NENs⁷⁸. SSAs are binding to SSTR2 and in some extent to SSTR5 and act as a signal inhibitor. It inhibits the release of serotonin as well as reduces gastrointestinal secretion and peristalsis. Hormone induced diarrhea and flushing are main indications for symptom treatment. SSAs can also be effective in treatment of watery diarrhea in VIP-omas and rash in necrolytic migratory erythema in glukagonoma syndrome. Insulinomas may be more refractory to SSAs as most insulinomas express low levels of SSTR2⁷⁹. In addition, SSAs must be used with caution in insulinoma patients as SSAs also inhibit glucagon and can exacerbate hypoglycemia.

Ocreotide was first developed as immediate-release formulation administered twice to three times daily. Later, long-acting depot formulations of both ocreotide and lanreotide were developed. Ocreotide long-acting repeatable (LAR) is administered intramuscularly (IM) every four weeks in doses of 20-30 mg. Depot lanreotide is available as a prefilled syringe and is administered as a deep subcutaneous injection in doses of 60-120 mg every four weeks. Patients who have increasing

symptoms in the end of the treatment cycle may have effect of increased frequency of administration (i.e. 3 weeks). The maximally tolerated doses have not yet been identified.

In recent years, the antiproliferative effect of SSA has been suggested. In 2009 the results from the PROMID study was published⁷¹. This double-blind randomized prospective study compared ocreotide LAR 30 mg versus placebo in patients with advanced midgut NENs. Time to tumor progression (TTP) increased from 6 months in the placebo arm to 14.3 months in the ocreotide LAR arm. The CLARINET study from 2014⁷² reported significantly prolonged progression-free survival among patients with GEP-NENs with grade 1 and 2 (Ki-67<10%) treated with depot lanreotide, confirming the antiproliferative effect also in pancreatic NENs.

There seems to be no difference in hormonal control between the two formulations ocreotide and lanreotide⁷⁶. The antitumor effect in P-NENs is only documented with lanreotide. Treatment with SSAs is recommended in advanced SI-NENs and P-NENs with Ki-67 less than 10%⁴⁴.

Both ocreotide and lanreotide are well-tolerated agents. Side effects are often mild and include nausea, bloating and steatorrhea. For the latter, pancreatic digestive enzymes may be considered. Long-term use of SSAs can result in sludge or biliary stone formation due to inhibition of gallbladder contractility. Routinely prophylactic cholecystectomy is not recommended though. According to the ENETS Guidelines 2016⁴² prophylactic cholecystectomy should be performed in patients with elective laparotomy if patients are planned to undergo treatment with SSA.

Everolimus

Everolimus, an oral inhibitor of mammalian target of rapamycin (m-TOR) has been shown effective in NENs. As mentioned earlier somatic mutations in the m-TOR pathway genes occur in about 15% of P-NETs, but the drug probably has efficacy also in patients without this mutation as the efficacy rate is higher⁸⁰. The RADIANT 3 study published in 2011⁸⁰ included 410 patient with progressive P-NET patients. One arm received 10 mg of everolimus daily and the other arm received placebo. The progression free survival (PFS) in the everolimus arm was 11.4 months, compared to 5.4 months in the placebo arm. In 2016 RADIANT 4 was published and reported

effect of everolimus also in SI-NETs and bronchial NETs, PFS being 11.0 months vs 3.9 months in the placebo group.

Everolimus has also been shown effective in metastasized insulinomas⁸¹ and is recommended in refractory hypoglycemia. Most frequently seen side effects are stomatitis, diarrhea, rash, hyperglycemia, cytopenias and infections. Dose reduction or temporary interruptions can often be necessary. A common and potentially serious side effect is pneumonitis.

Sunitinib

Neuroendocrine tumors are often well-vascularized tumors frequently expressing the vascular-endothelial growth factor (VEGF)⁸². Increased levels of VEGF have been correlated with tumor progression. Sunitinib, an oral multi-tyrosine kinase inhibitor has its main affinity to the VEGF receptor. Sunitinib is so far only recommended in PNETs. In 2011, Raymond et al reported PFS of 11.4 months in patients with progressive well-differentiated P-NETs receiving daily sunitinib of 37.5 mg vs 5.5 months in patients receiving placebo⁸³. The objective response rate was 9.3%. The most frequent side effects are rash, diarrhea, nausea and fatigue.

Sunitinib and everolimus is considered second line treatment in P-NETs. There are no studies to date that compare the two targeting drugs. In SI-NETs and bronchial-NETs there are no data for Sunitinib, but everolimus is recommended as second or third line treatment.

Interferon

Interferon (IFN) has been known as an antiviral and antitumor agent since the 1960s. In NENs, and specially carcinoids, it has been in use since the early 80s because of its ability to stimulate natural killer cells and control hormone secretion and tumor growth⁸⁴. The most common side effects are flu-like symptoms, fatigue and bone marrow depression. Its use is now limited due to new treatment modalities. According to recommendations from the Nordic Neuroendocrine Tumour Group

(NNTG) interferon can be used as first line or second line treatment in combination with SSA in SI-NENs with Ki-67 < 10%⁴⁴.

1.6.3 Chemotherapy

Chemotherapy targets dividing cells. The response is therefore mostly expected in tumors with higher proliferation index. There are no randomized controlled trials but mostly small case series. Even though chemotherapy is a well-established treatment modality especially in GEP-NENs. Chemotherapy in NETs is used in tumors with higher grades and more aggressive behavior. In advanced pancreatic NENs (P-NENs) chemotherapy is often used as first line treatment. In G1 and G2 P-NENs Streptozocin (STZ) in combination of 5-fluorouracil (5-FU) has been in use since the 1980's. In a retrospective study from Germany⁸⁵ the response rate (RR) was 42.7% and median time to progression 19.4 months.

Combination of temozolomide and capecitabine can be used as first line in metastatic P-NENs. This drug combination, that can be taken orally, has in small studies shown antitumor effect. In a retrospective study from 2011, Strosberg et al⁸⁶ reported a radiological response rate of 70% and median progression free survival (PFS) of 18 months. There are now ongoing prospective trials that study the efficacy of temozolomide with or without capecitabine (NCT01824875) in patients with advanced pancreatic neuroendocrine tumors.

In advanced GEP-NECs, platinum-based chemotherapy combined with etoposide is standard treatment. The Nordic NEC study³⁶ from 2012 found 31% response rate in first-line treatment. The median survival was 11 months in patients treated with chemotherapy compared to one month in patients treated with best supportive care. Poor survival status was the most negative prognostic factor and it is important to start chemotherapy as soon as possible in advanced NEC. In the same study cases with Ki-67 < 55 % were less responsive to platinum based chemotherapy but still had better survival, indicating that not all NECs are one entity, as also mentioned earlier.

1.6.4 Peptide receptor radionuclide therapy (PRRT)

PRRT is promising in inoperable, advanced and progressive NENs with high somatostatin receptor (SSTR) positivity. The majority of neuroendocrine tumors express SSTR on their surface. These receptors are target for somatostatin analogs (SSA). In PRRT a radionuclide (Yttrium-90 or Lutetium-177) is linked to a somatostatin analog via a chelator DOTA. The radiolabeled SSA bind to SSTR and cause localized antitumor effect.

The treatment is usually given as 2-5 cycles with 8-12 weeks intervals⁴⁴. Prior to treatment, patient must have a sufficient bone marrow, kidney and liver function. Response rate is reported between 15-35%⁸⁷. In 2008 Kwekkeboom and colleagues reported the outcome of PRRT in a large group GEP-NENs⁸⁸. The complete and partial tumor remission occurred in 2% and 28%, respectively. Median time to progression was 40 months. This treatment is generally well tolerated. Acute side effects are nausea and abdominal pain. Temporary hair-loss (no-baldness) is reported in 62% of patients treated with Lu-177⁸⁸. Long-term side effects are radiation induced toxicity in bone marrow and kidneys. Severe renal failure (grade 3/4) occurred in 1.5% of the patients in a large retrospective study⁸⁹ from 2015. Myelodysplastic syndrome (MDS) occurred in 2.3% and acute leukemia in 1.1% of the patients. Hematological and renal side effects are observed more frequently after therapy with yttrium-90 than after treatment with Lu-177⁸⁷.

In January 2017, a large phase 3 randomized controlled trial was published in NEJM⁹⁰. This study evaluated the efficacy and safety of Lu-177-Dotate (7.4 GBq every 8 weeks, 4 times in total) compared to high dose octreotide LAR (60 mg every 4 weeks) in the control group. The estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the PRRT group and 10.8% (95% CI, 3.5 to 23.0) in the control group. It was no evidence of renal toxicity during the observed time. Serious hematological side effects (grade 3-4) occurred in less than 10% of the patients in the PRRT group.

1.6.5 Hepatic-directed therapy

The majority of the NEN patients have metastases at time of diagnosis. The most frequent site of metastases is the liver. Resection may be possible when few metastases are present, but most liver metastases are multiple affecting both lobes. Palliative debulking surgery or radiofrequency ablation (RF) may be indicated to decrease local or hormone symptoms.

When the majority of the tumor burden is confined to the liver, different transarterial approaches may be used⁹¹ (**Figure 2**). Hepatic artery embolization or chemoembolization are reported to give relief of hormone symptoms in up to 80% of the patients^{92, 93}. The PFS in different studies are up to 1.5 years^{92, 94} and overall survival 39 months⁹⁴. In a prospective randomized study, there were no significant difference in PFS between hepatic artery embolization and chemoembolization⁹⁵.

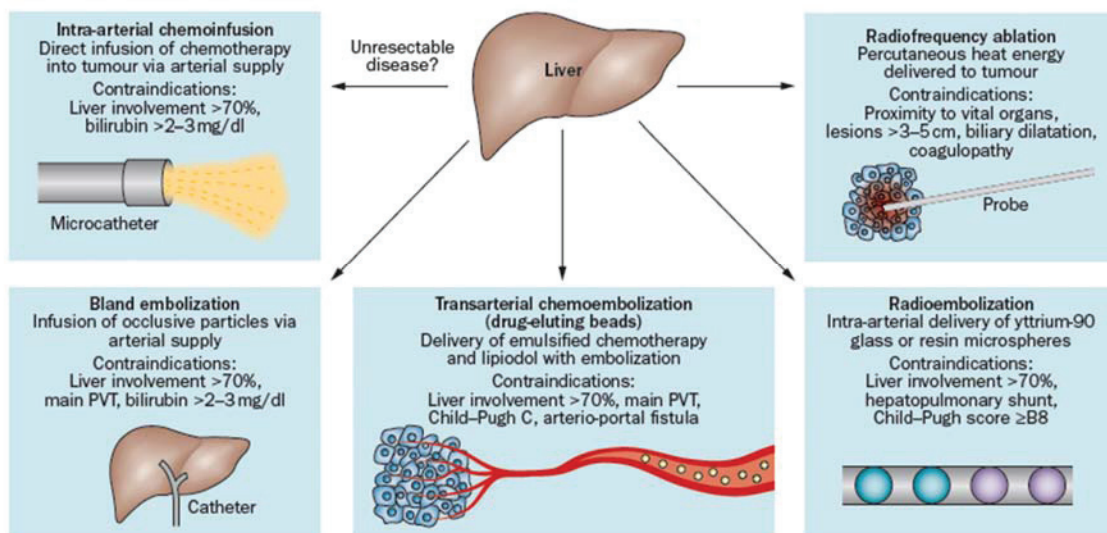


Figure 2. Key transarterial locoregional therapies that are used for primary and secondary hepatic cancers. The figure shows the five main approaches⁹¹ (With permission from Macmillan Publisher).

1.6.6 Liver Transplantation

In metastatic disease confined to the liver, total hepatectomy with consequent liver transplantation has been proposed as a treatment option for decades. However, there are no clear selection criteria and the benefit is still uncertain. The best timing of the transplantation is also unknown. Recently

a group from Milan studied the long-term benefits by collecting 88 patients that met the Milan selection criteria for liver transplantation in patients with NET⁹⁶. The transplant group (42 patients) showed significant advantage over non-transplant strategies (46 patients) at 5 and 10 year survival (97.2% and 88.8% vs. 50.9% and 22.4%, $p < 0.001$). According to this study, the transplant related survival benefit increases over time and maximizes after 10 years. According to the most recent ENETS guidelines⁷⁶ transplantation is not generally recommended as a treatment option but recommended in highly selected patients, preferably in young patients with functional syndromes demonstrating resistance to medical therapy. In Norway, liver transplantation is considered in selected patients after “the Oslo criteria”:

- 1) No known disease other than liver metastases, 2) Ki-67 $\leq 10\%$, 3) 12 months observation after removal of extrahepatic malignancy, 4) Stable disease last 12 months, 5) Age preferably below 65 years and 6) No contraindications against transplantation.

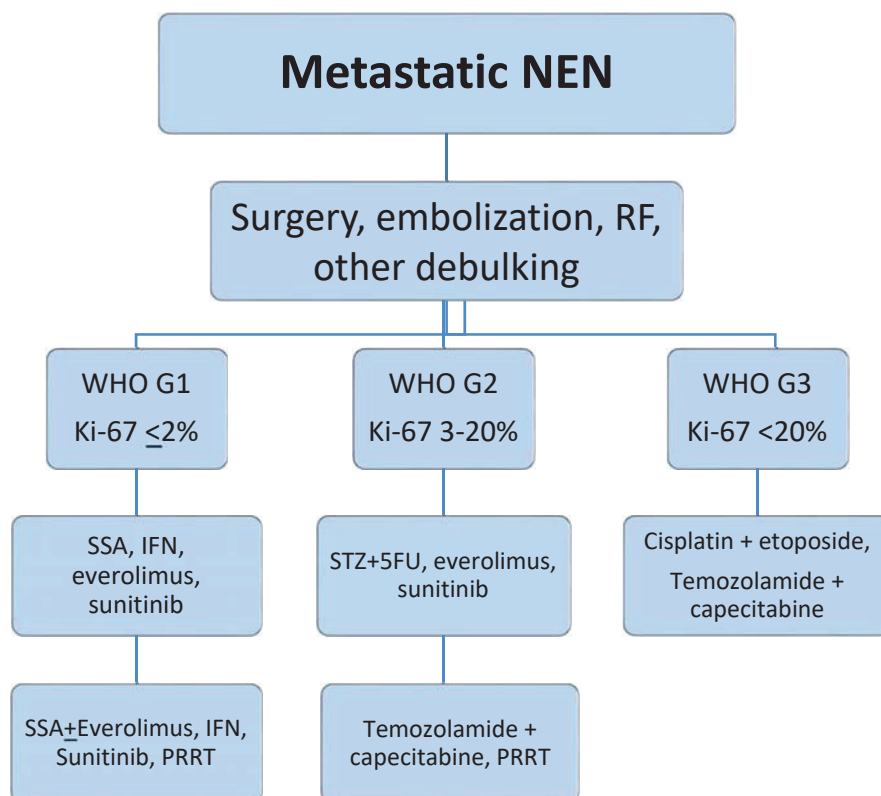


Figure 3. Therapeutic algorithm for the management of metastatic NEN^{12, 76}

1.7 Epidemiology

Neuroendocrine neoplasms are a heterogeneous group of tumors. During the last decades, the nomenclature and classification have been changing. Accordingly, epidemiological studies have been challenging to perform and studies have been difficult to compare. The data sources of information on epidemiology in NENs are local neuroendocrine registries and national population-based cancer registries. The largest and most known national registry is the Surveillance, Epidemiology and End Results (SEER) in the USA. The SEER program has gradually expanded after its initiation in 1973, and covers about 30% of the US population⁹⁷. Up to 1986, “carcinoids” were only registered in the SEER database if distant metastases were clinically evident⁹⁸. Other limitation is that it only covers some geographical areas and not the whole country. In addition, people that move out of these areas will be missed. Other national registries reporting on NEN originate from European countries such as the Netherlands, Sweden, UK and Norway. There are also reports from national cancer registries in Taiwan and Australia and regional registries such as Girona in Spain and Tuscany in Italy. In Germany and France there are also national NEN registries, these are not population-based.

The median age at diagnosis is around 60 and the female-male ratio is close to one except from the Netherlands⁹⁹ where it was a male predominance (62%) and higher median age (64 years for females and 68 years for males). The most common primary sites are in the lungs and the GEP-system. Studies show geographical and racial differences^{2-8, 98}. While the lungs are the most frequent primary site in white Americans and in some European countries, rectum is the most frequent primary site in black Americans and in South-East Asia.

Studies show an increase in incidence^{2, 6, 98-102} for NENs. Yao et al⁷ reported incidence of NETs up to 5.25 per 100.000 in 2004. There is also a rise in diagnosis of incidental NENs, which is NENs detected while performing investigations for other conditions. A population-based analysis of pancreatic NENs of ≤ 2 cm from the SEER database from 1988-2010 showed an increase of 710.4%¹⁰³.

Whether this increase in NEN incidence is real or due to increased detection rate is under discussion. Hallet et al¹⁰⁴ found increase in incidence while the proportion of metastatic disease

decreased, suggesting that the rise in incidence could be explained by earlier detection of NENs. A Dutch group suggest that the rise might be due to shifting in pathology classification⁹⁹. There are some findings supporting a real increase in incidence. The incidence is increasing in both small intestinal and colorectal NENs, also in countries without colorectal cancer screening. Further Mocellin et al found an increase in mortality similar to the incidence trend¹⁰⁰, indicating true increase in incidence.

The 5-year survival rates have been reported in the range of 4-80% depending on the grade, stage and primary sites^{4, 7, 99, 102, 104}. In neuroendocrine tumors (grade 1 and 2) the 5-year survival rate has been reported in the range of 50-80%^{4, 6, 8, 102, 104}. In neuroendocrine carcinomas the 5-year survival in large cell NECs is 20% and small cell NECs 6%⁹⁹. There are only few reports on trends in NEN survival. Two of the largest studies^{7, 99} report improved survival only in metastatic NENs and attributed this to treatment with octreotide that was introduced in the end of the 80's.

2. AIMS

The overall aim of this thesis is to investigate epidemiology of neuroendocrine neoplasms in Norway and to explore prognostic factors in pancreatic NENs treated at a tertiary referral center.

Paper I

Investigate trends in incidence of neuroendocrine tumors in Norway from 1993 through 2010 including rare types and highly malignant forms.

Paper II

Investigate survival in all NENs diagnosed in Norway from 1993 through 2015, and study changes in survival during the study period.

Paper III

Study survival and prognostic factors in well-differentiated pancreatic NENs treated at a tertiary referral center.

3. SUMMERY OF THE RESULTS

Paper I: Trends in Incidence of Neuroendocrine Neoplasms in Norway: A Report of 16,075 Cases from 1993 through 2010

Our analyses were based on cancer cases diagnosed between 1993 and 2010 and reported to the national population-based Cancer Registry of Norway. A total of 65 ICD-O morphological codes were identified as neuroendocrine and stratified into three different groups of aggressiveness; low (adenomas), intermediate (roughly corresponding to WHO grade 1 and 2) and high (roughly corresponding WHO grade 3). We identified 16,075 NENs of which 49.5% were in women. Median age at diagnosis was 65 years. The most common primary sites were the lung (48.1%) and the gastroenteropancreatic system (18.0%). Stage at diagnosis was local in 40.4% of the cases, regional in 17.5% and distant in 42.1%. The stage distribution was stable throughout the study period. Age standardized (European) incidence rate (per 100,000 person years) increased from 13.3 to 21.3 from 1993 to 2010 with an estimated annual increase of 5.1% in women and 2.1% in men. The increase was most pronounced for tumors of intermediate aggressiveness from 3.3 in 1993 to 7.3 in 2010. Largest annual increases were estimated for adrenal gland (8.8%), pancreas (6.9%) and lung (6.1%). The overall incidence rate for tumors of high aggressiveness was stable around 9.

Paper II: Survival in Neuroendocrine Neoplasms; A report from a large Norwegian Population-based Study

We used the cancer cases diagnosed from 1993 through 2015 and reported to the national population-based Cancer Registry of Norway. We included 70 ICD-O morphological codes. According to morphological characteristics and known disease behavior, we stratified the tumors into three different groups of aggressiveness: benign (adenomas), low/intermediate and high. A total of 21,411 NENs were analyzed. Median age was 65 years and 49.9% of the patients were females. The 5-year relative survival in patients with benign NENs was 98.9% (95% CI, 97.2-99.5), in patients with low/intermediate aggressive NENs 64.8% (95% CI, 63.3-66.2) and high aggressive NENs 8.4% (95% CI, 7.8-9.1). Primary site in the lungs had a poor prognosis compared to localization in the GEP system. In multivariable analysis of patients with low/intermediate and

high aggressive tumors, gender, age at diagnosis, time of diagnosis, stage and primary sites were all predictors of outcome. Men had poorer prognosis than women, regardless of their tumor stage or aggressiveness. The survival improved in all stages and age groups during our study period.

Paper III: Survival and Prognostic Factors in Well-differentiated Pancreatic Neuroendocrine Tumors

The aim of this study was to investigate survival and prognostic factors in patients with well-differentiated pancreatic neuroendocrine tumors (P-NETs) treated at a tertiary referral center. We retrospectively reviewed the medical records of 114 patients diagnosed with well-differentiated P-NETs from 1982 through 2010. All relevant data were recorded in a database. We studied demographic, clinical, radiological, and histopathological characteristics. Median age at diagnosis was 57 years (range 32-83), 53% were men and 78% had non-functional tumors. The most common presenting symptoms were abdominal pain (41%), weight loss (36%) and diarrhea (25%); 19% of the tumors were incidental findings. At diagnosis 32.5% patients had local, 22.8% regional and 44.7% distant disease. During follow up, another 25% of the P-NET patients developed metastases, most often in the liver. Men had more often distant disease at diagnosis ($p=0.02$). Overall 5-year survival was 53.9% (95% CI 43.4-63.3). For patients with local disease the 5-year survival rate was 70.2% (95% CI 49.9-83.6) vs 33.0% (95% CI 19.7-46.7) for patients with distant disease at diagnosis. Surgery with curative intent was performed on 46 (40%) patients. Liver metastases were diagnosed up to 10 years after surgery in this group. In patients with metastases, palliative surgery (debulking) did not have a statistically significant effect on survival compared to those who had no surgery. Distant metastases, Ki-67 > 2%, non-functional tumors, elevated CgA were associated with poor survival.

4. MATERIALS AND METHODOLOGICAL CONSIDERATIONS

4.1 Paper I + II

In the incidence and survival studies, we used registry data. Cancer Registry of Norway (CRN) was established in 1953 and is one of the oldest cancer registries in the world¹⁰⁵. CRN covers the entire Norwegian population (5.2 million in 2016). All medical doctors are mandated by law to report all new cancer cases as well as benign and premalignant neoplasms of the central nervous system. CRN coding is performed by trained personnel based on reports from several different sources such as clinician reports, pathology and autopsy reports and death certificates¹⁰⁶ (**Figure 4**). The degree of completeness is estimated to be 98.8%¹⁰⁷. We used cancer registry information on topography, morphology and disease dissemination at the time of diagnosis.

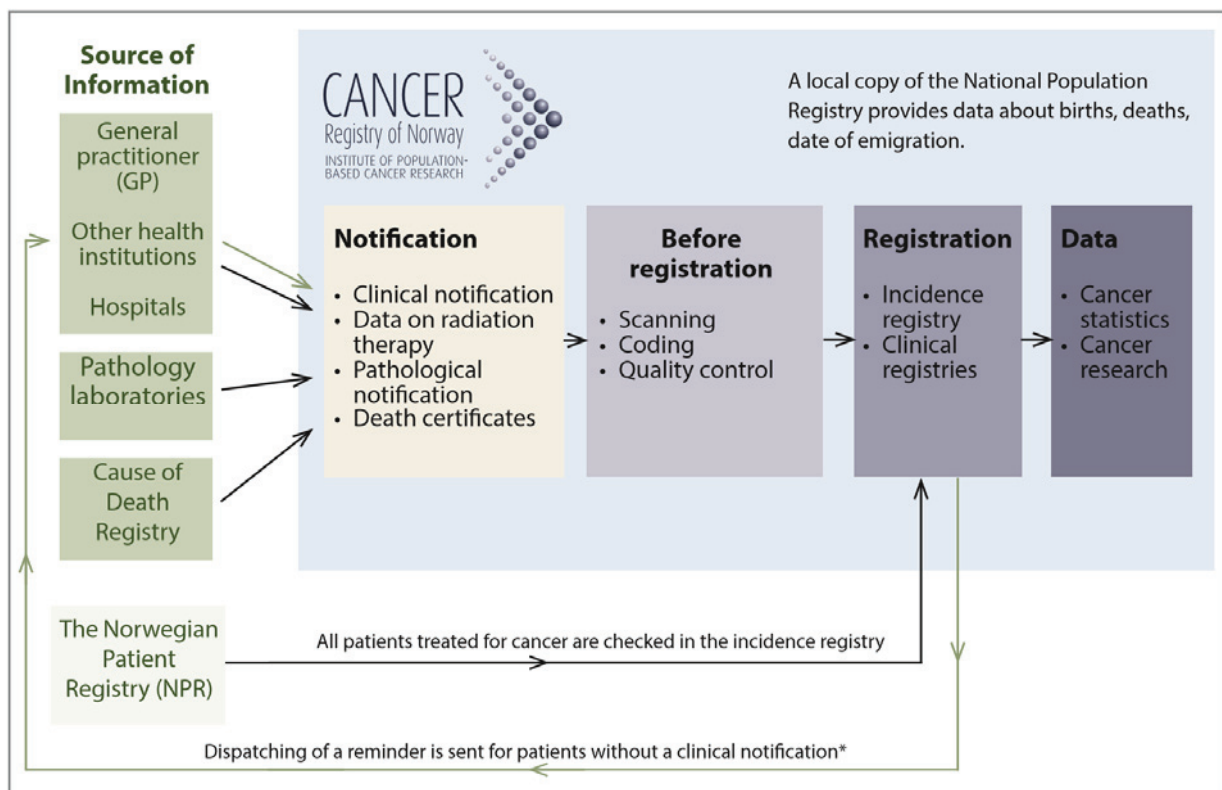


Figure 4. Sources of cancer registration at the CRN. *Dispatching of reminders for clinical notifications are sent for cases only notified from the NPR or cases only notified by a pathology notification/death certificate on radiation therapy data¹⁰⁶ (Cancer in Norway 2015).

All inhabitants in Norway are given a unique 11-digit personal identification number (at time of birth or immigration) that ensures unequivocal identification. Accordingly, very few patients are lost to follow up. Data from CRN is linked to the Norwegian Population Register (NPR) to obtain dates of death.

Morphological groups included as NENs in this study were small cell carcinoma, large cell neuroendocrine carcinoma, Merkel cell carcinoma, carcinoid, islet cell neoplasms, pheochromocytoma/paraganglioma, medullary carcinoma of the thyroid, neural/ neuroblastic neoplasms, and “NEN not otherwise specified”. Mixed neuroendocrine-exocrine tumors (both components of at least 30%) were included while exocrine tumors such as adenocarcinoma with neuroendocrine differentiation (neuroendocrine components less than 30%) were excluded. In the survival study we excluded the neuroblastomas due to their heterogeneous survival. In addition, we excluded mixed forms and goblet cell carcinoid in appendix in concordance with the most recent ENETS guidelines where these tumors no longer are recognized as neuroendocrine¹⁰⁸.

WHO grading based on the proliferation indexes Ki-67 and mitotic count^{15, 16, 109} was not possible as reporting of proliferation indexes was not done until recently. Complete data on tumor differentiation was not available. We categorized the tumors according to tumor morphology (ICD-O) and known disease behavior into three groups of aggressiveness. In paper I the tumors were categorized into low, intermediate and high aggressiveness. The intermediate aggressiveness group roughly corresponding to WHO grade 1 and 2, and high aggressiveness group roughly corresponding to WHO grade 3 (carcinomas). The benign tumors, the adenomas, were classified into the low aggressiveness group in paper I, but to avoid the possible confusion with G1 tumors, we changed the terminology to “benign” in paper II (**table 4**). In neoplasms, where the categorization was not straightforward, we searched the literature for behavior and survival before categorization into one of the three groups^{108, 110-115}. This approach may have led to some degree of misclassification in aggressiveness. In survival analysis, it might have underestimated the survival in the intermediate group and overestimated the survival in the high aggressiveness group.

	Adenomas	G1 /G2	G3
Paper I	Low	Intermediate	High
Paper II	Benign	Low/intermediate	High

Table 4. Stratification of tumors in Paper I+II according to tumor aggressiveness

The ICD-O morphology code is composed of 6 digits where the specific histological term is given by the first four digits. The behavior is given by the fifth digit and differentiation is given by the sixth digit. The behavior code /0 is used for benign form, /1 is unspecified, borderline or uncertain borderline, and /3 is malignant. Insulinomas, pheochromocytomas/paragangliomas and appendiceal NENs have traditionally been classified as benign or malignant based on the absence or presence of metastases. The use of the term “benign” is under debate, and these NENs are now accepted to have a malignant potential. We chose to include these tumors in the intermediate aggressiveness group, whether they had metastasized or not. In the intermediate aggressiveness group in paper II, the amount of cases with /0 was 3.8% and the amount of cases with /1 15.9%. Previous studies only included “malignant” forms, and this can explain some of the differences in both incidence and survival.

Stage at diagnosis presented in paper I and II as local, regional and distant were based on the aggregation of 10 CRN categories of dissemination. No disease spread is categorized as localized disease. Regional disease is per definition when tumor grows microscopically or macroscopically into a neighboring structure or lymph nodes of the same body segment as the primary tumor. Distant disease includes metastases to lymph nodes or organs in a body segment other than that of the primary tumor. Stage was missing in 11.7% of the patients in paper III. In comparison, in one of the largest reports from the SEER data by Yao et al⁷, stage was missing in 20% of the cases.

4.2 Paper III

Our hospital is a tertiary referral center in Oslo, serving approximately 54% of the Norwegian population. Altogether 714 patients with NEN were treated at our hospital from 1982-2010, of whom 114 (16%) had well-differentiated pancreatic neuroendocrine tumors (grade 1 and 2). Patients were prospectively registered in a database, hence very few patients admitted to our hospital were missed. However, as a tertiary referral center our patients are selected. Some patients

with tumors that were completely resected at local hospitals, and some patients in their terminal stage of the disease, were probably not referred. As a consequence of this, we might have missed some of the patients with the best, and some of the patients with the worst, prognosis.

We retrospectively recorded demographical, clinical, radiological and histopathological characteristics in a database. Variables registered included age at diagnosis, gender, symptoms, biochemistry, proliferation index, tumor size, tumor functionality, stage and therapy.

We divided stage in local, regional and distant disease. Local disease was defined as the tumor confined to the pancreas. Regional disease was defined as extension of tumor into adjacent tissue or spread to regional lymph nodes. Distant disease was defined as the presence of metastases in other parts of the body⁷. During follow-up, most of the patients underwent CT scan with arterial and portal venous phases. MRI and ultrasound were used to a lesser extent.

The proliferation index, Ki-67, was retrieved from pathology reports of surgical specimens or liver biopsies. Ki-67 was not a routine test until the last decade. In cases where more than one tissue sample were analyzed for Ki-67 we used the highest value for grading according to WHO 2010¹⁵. The Ki-67 was missing in 35 patients, mostly due to lack of remaining tumor specimens for estimating the Ki-67. Due to the missing Ki-67 values, we might have included G3 tumors in our analyses. This could have influenced the survival rates.

A P-NEN was defined as functional when a clinical syndrome of hormonal overexpression was evident. It was not sufficient to have positive staining for hormones in the tumor tissue sample. We registered genetic syndromes in cases where this was known, but our patients were not routinely tested for genetic syndromes.

4.3 Statistical analysis

Paper I+II

Missing information on tumor stage is a common problem in population-based cancer registries and multiple imputation has become the standard method to obtain estimates from such data. We emphasize that the observed total incidence (trends) is unrelated to the cancer registry's internal

coding of stage, and thus unrelated to any imputation of stage. Due to missing data on tumor stage, ranging from 17% missing in year 2000 to 4% missing in year 2010, tumor stage were imputed using multiple imputation techniques. The imputation model was a multinomial logistic regression¹¹⁶⁻¹¹⁸ stratified by primary site and tumor aggressiveness, with continuous (c) and indicator (i) predictors: age at diagnosis (c), year of diagnosis (i), time to death or censoring (c) and an indicator of death/censoring (i). For analysis of time trends in stage distribution the imputation model included two additional predictors; morphological group (i) and an indicator of metastasis (i). The reason for imputing missing stage is to obtain unbiased and potentially also more precise estimates of the stage distribution (and time trends in the distribution of stage). To obtain unbiased estimates, the "missing at random" assumption need to be fulfilled. This is an untestable assumption. Given the imputation model used we believe that the MAR assumption can be justified i.e. data are missing completely at random after conditioning on the covariates in the imputation model.

In incidence studies, different standard populations have been used. Studies we have used for comparison have mostly used the European standard population. As exception, the reports from the SEER data have used the US standard population. We also did estimations with the US standard population and found that the incidence rates were similar. We chose not to use the World standard population as that is a younger population than the Norwegian population. Accordingly age-standardized incidence (per 100,000 person-years) rates (ASR) were calculated using direct standardization with the European standard population¹¹⁹ as weights.

Confidence intervals (CI) for the ASRs were calculated using the modified gamma limits proposed by Tiwari, Clegg and Zou¹²⁰ as implemented in the Stata¹²¹ program *distrat*¹²². Estimated annual percentage change (EAPC) was calculated using Poisson regression with adjustment for age.

Relative survival is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals. The more precise term, net survival, is not used to avoid the potential confusion with the abbreviation for neuroendocrine tumor. Relative survival was estimated using the consistent non-parametric estimator proposed by Pohar-Perme et al¹²³. To examine which prognostic factors that would affect cancer survival, a flexible parametric proportional excess hazard model¹²⁴ was estimated with sex,

period of diagnosis, age at diagnosis, disease stage and primary site (grouped into eight categories; lung, stomach, small intestine, colon/rectum, appendix, pancreas, adrenal gland and all others) included as independent categorical variables. The model was also estimated separately for intermediate and high aggressive NENs. The baseline cumulative excess hazard was modelled using restricted cubic splines with three internal knots placed at the quartiles of the distribution of the log of the uncensored survival times. The statistical analyses were performed using Stata 14.2¹²¹.

Paper III

The statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, Illinois, USA) and STATA 10 (StataCorp LP, College Station, Texas, USA). To compare groups Mann-Whitney, Kruskal-Wallis and Chi-square were used. P-values < 0.05 were considered statistically significant. For survival analyses, we used Kaplan-Meier and log-rank. We obtained information on time of death by linkage of our data to Statistics Norway. The survival analyses were performed by a statistician. No corrections for multiple comparisons were made and multivariable analysis could not be done due to small numbers.

4.4 Ethical considerations

All studies in this thesis were conducted according to principles of the Declaration of Helsinki and approved by the Regional Committee for Medical and Health Research Ethics.

5. GENERAL DISCUSSION

This thesis is based on three original research articles exploring the epidemiology of neuroendocrine neoplasms. In our population-based studies, the first and second papers, we report on the epidemiology of neuroendocrine neoplasms arising from all organ systems, of all grades, and give a more comprehensive overview on incidence and survival than most previous studies. In the third paper, we present the survival and prognostic factors in well-differentiated pancreatic NENs treated at a tertiary referral hospital.

Local registries versus population based registries

Neuroendocrine tumors do not have their own ICD codes and are identified by morphological codes. An important part of our work (paper I+ II) was to define and categorize the tumors with neuroendocrine characteristics. We used the ICD-O 3 to find neuroendocrine tumors based on morphology. The types included are listed in table 1 in both paper I+II. The completeness of ICD-O 3 codes is entirely based on the precision of the reporting pathologist. In the population registry it is very likely that some NENs have been missed and some tumors, due to inconsistent or misleading pathology reports, have erroneously been classified as NENs. In the local registries, however, all pathology reports has been controlled, or even reexamined, to avoid misclassification of patients.

The local registry comprise of a selected group of patients; the patients that were admitted to our center. One can assume that the some of the patients with the most advanced stages of disease were not admitted as one would expect that local doctors would consider these patients beyond the reach of tumor targeted therapy and only candidates for supportive treatment. Some patients regarded as cured by surgery would probably not be admitted as they were not considered in need of further therapy or follow-up examinations. As a consequence we might have missed some of the patients with the best, and some of the patients with the worst, prognosis in our local registry.

The completeness in CRN on the other hand is close to 100%¹⁰⁷. Trained personnel at CRN collects information from clinicians, pathologist and death registry as previously shown in figure 4. All

patients treated for cancer are checked in the incidence registry, and if clinical notification is missing, a reminder is sent. Information is actively collected until the reports are completed.

While the completeness is better in a population-based study, the amount and type of data that can be extracted is limited. For example information regarding symptoms, laboratory findings, exact localization and extension of disease, disease progression and treatment modalities used is not recorded. The quality of data and the granularity is better in a single center study where we had access to medical records including, laboratory findings, pathology reports, radiology reports, development of the disease and treatment modalities used.

In the local registry we had information on tumor size in contrary to CRN where tumor size was not registered. The missing of tumor size was one of the most serious limitations in our population-based studies. Changes in median primary tumor size at diagnosis over time could indicate changes in how extensive the disease had developed at diagnosis. Smaller tumors could indicate earlier diagnosis and indirectly support the notion that at least some of the increase in incidence could be due to more widespread use of diagnostic procedures. Another serious limitation was that grading of the tumors could not be based on proliferation markers (Ki-67 or mitotic count) as recommended by the WHO grading system. Up to date estimation of proliferation markers is not done routinely in all pathology reports²⁰. Even studies based on histopathological classification have high percentages of missing Ki-67 values¹²⁵. Furthermore, Ki-67 % was not routinely analyzed until the last decade and first included in WHO grading as late as 2010. Ki-67 was not registered in CRN. In Paper I and II we had to grade the tumors according to morphological characteristics and known disease behavior of the actual neoplasms. This might have led to some degree of misclassification, probably underestimating the survival in the intermediate group and overestimating the survival in the highly aggressive group.

Real increase in incidence?

The incidence rate of NENs in Norway increased from 13.3 in 1993 to 21.3 in 2010. The increase was most pronounced for intermediate aggressive NENs (corresponding to WHO grade 1 and 2) with the steepest increases for adrenal gland, pancreas and lung (estimated annual change of 6.1-

8.8%). There is an ongoing debate whether the rise in incidence is real or due to changes in classification, an increase in detection rate or a combination of these factors.

Better classification

The increased awareness and knowledge regarding NENs have improved the pathological diagnosis the last decades. This might have influenced the quality of the pathology reports and thereby increased the number of tumors being reported as NENs. The panel of immunohistochemical markers used to identify NENs has increased²⁰ improving the diagnostic precision. This increased quality of pathology is evident at our tertiary referral center. The need for re-investigations of incomplete pathology reports from other hospitals by our dedicated NEN pathologists is less required than for a few years ago. Changes in classification might also lead to more tumors being diagnosed as NENs. For example in G3 tumors it might be a shift in classification. In a Dutch study⁹⁹ the increasing incidence was mainly due to the increase observed in the subgroup of large cell neuroendocrine carcinomas. They suggested that changes in classification in 2001 with the introduction of the ICD-O code M8013 (large cell neuroendocrine carcinoma) may explain this tendency as these tumors were previously classified as “large cell carcinomas” and “undifferentiated carcinomas”.

Increase in detection

Many NETs are indolent tumors that could be asymptomatic for decades. Any diagnostic procedure performed for other indications could incidentally detect a NET in an asymptomatic phase. The number of radiological procedures has increased (**Figure 5**). From 1993 to 2008, the use of CT scanning in Norway increased almost four-fold from 50 to 194 examinations per 1,000 inhabitants per year. Between 2002 and 2008, the use of MRI increased from 61 to 126 examinations per 1,000 inhabitants per year¹²⁶. Improvements in the CT and MRI technologies together with refinements in the use of contrast in the same period have increased the resolution of the procedures.

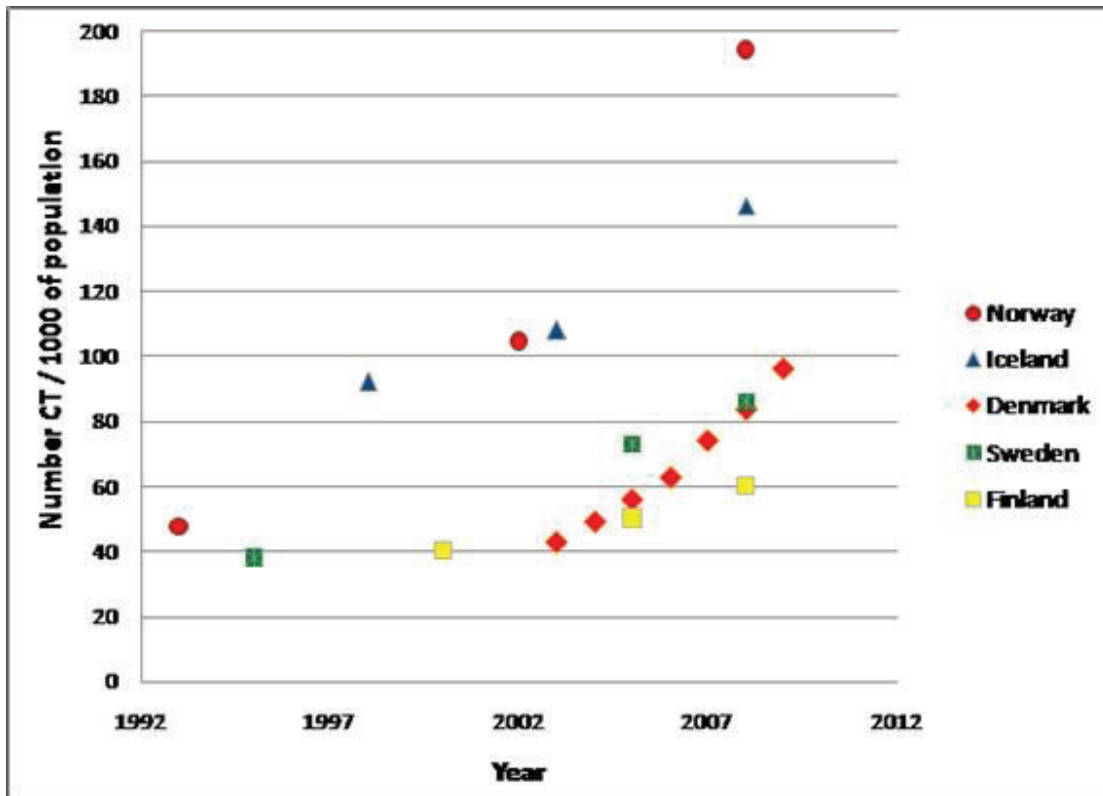


Figure 5. *The trends in the number of computed tomography (CT) procedures, per 1000 inhabitants in the Nordic Countries during 1993 to 2010¹²⁷.*

The number of endoscopic procedures has also increased substantially. For colonoscopies in Norway the number of procedures has increased almost four-fold from 17.437 in 1999 to 70.219 in 2013 (Datasource: Norwegian Patient Registry) (**Figure 6**). The quality of the endoscopes and the resolution of the images have also increased.

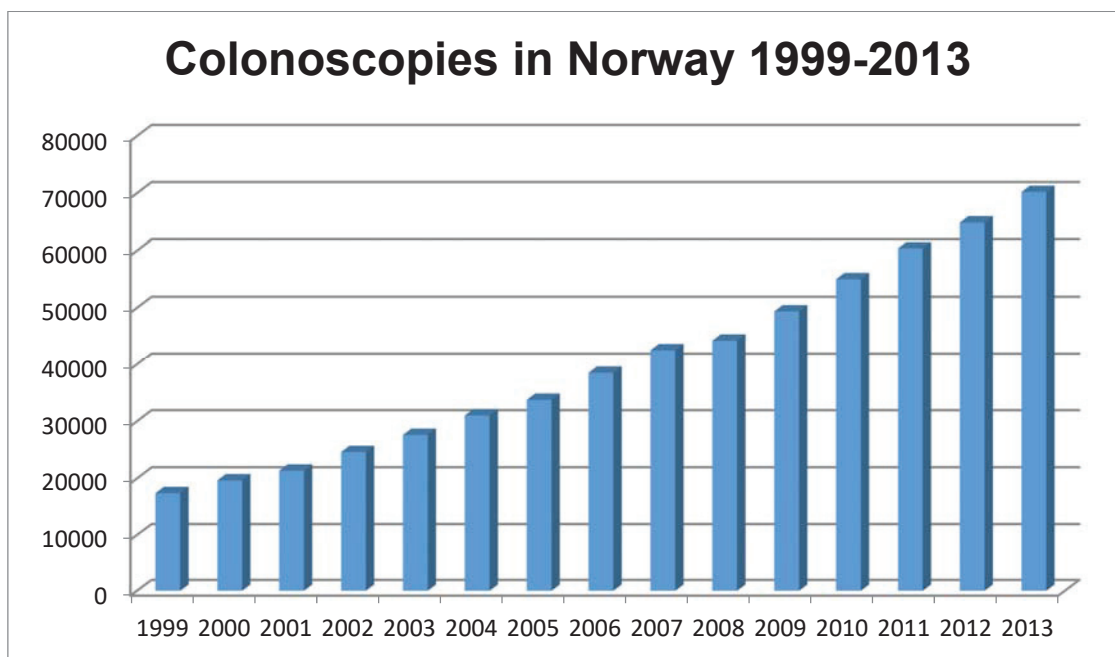


Figure 6. *Trend in colonoscopies in Norway 1999- 2013 (Data source: Norwegian Patient Registry)*

Real increase in incidence?

The observed incidence increased for all sites of low/intermediate NENs, also for sites not easily detected incidentally by radiology or endoscopy such as small intestinal tumors. This supports the assumption of a true increase in incidence. We found no increase in the incidence of NECs. Most NECs are aggressive tumors growing fast and giving symptoms within few weeks/months. The likelihood of detecting a NEC incidentally would therefore be less than for a slow growing NET. This could indicate that the increased incidence for NETs could, to a large extent, be due to increased utility of diagnostic procedures detecting NETs incidentally. This assumption, however, would be based on the notion that NETs and NECs have the same biology and that any changes in real incidence would be the same for both subgroups. We do not have sufficient knowledge to support this notion.

With the increase in quantity and quality of radiological and endoscopic procedures an increased detection rate of NENs and a shift towards more patients being diagnosed with small tumors and

localized disease would be expected. As previously mentioned, the size of the primary tumor at diagnosis is unfortunately not reported in the CRC. We observed a stable stage distribution through the observation period. This might indicate a true increase in incidence. This observation, however, could also be explained by higher quality and better resolution in the imaging procedures having a higher detection rate for small metastases at the time of diagnosis. Some patients diagnosed with only local or regional disease in the nineties would probably have more widespread disease detected if the imaging technology of today had been applied.

Based on our studies it is not possible to give a clear answer to why the incidence of NENs has increased. It would however, be reasonable to assume that the increase is due to a combination of higher awareness, better classification, more use of diagnostic procedures and a real increase in incidence.

Gender

In paper III, we report that there were a non-statistical trend towards men with P-NETs, even with the same grade, having more advanced disease at diagnosis and reduced survival compared to women. Another study from our center also reported that male gender was associated with decreased survival in patients with small intestinal NETs¹²⁸. We observed the same interesting trend in our population-based study (Paper II) where we found gender to be an important predictor of outcome. This confirms the finding in previous epidemiological studies^{7, 104}.

The gender difference has also been reported in other cancers such as malignant melanoma and lung cancer¹⁰⁶. In malignant melanoma men had more advanced stage at diagnosis which explains the difference in survival. The gender difference in survival has been explained by a different health-care seeking behavior among men compared to women. Men might endure symptoms for a longer period than women before contacting the health services, and hence, presenting with a higher tumor burden and a less favorable prognosis¹²⁹. Information on symptom duration before diagnosis was not registered in CRN. In our single center study the difference in stage could not be

explained by patient delay as men had shorter duration of symptoms before diagnosis of P-NEN than women did (Paper III).

Recently Khedhar et al¹³⁰ reported on the gender difference in lung cancer risk. The clinical features in lung cancer are different in women than in men and biological differences have been considered a possibility. They looked into the association between menstrual and reproductive factors and lung cancer. Women who were postmenopausal had increased risk compared to premenopausal women. Hormonal factors seem to play a role in lung cancer, but the mechanisms are not fully understood and confounding by smoking is possible. In our population-based study, there was a difference in stage distribution among males and females, but even after adjusting for these differences (multivariable analysis) males had 31% higher mortality than females in low/intermediate aggressive tumors, and 11% higher mortality in highly aggressive tumors. These findings might indicate different tumor biology and the need of more aggressive treatment approaches in males.

Age

The relative survival rates differed according to primary sites, tumor aggressiveness, stage, gender and age (Paper II). We found age to be a significant predictor of outcome in both univariable and multivariable analyses with decreasing relative survival rates with increasing age, even after the correction for stage. We know that younger patients may tolerate treatments such as extensive surgery and chemotherapy better and might receive, and endure, more aggressive treatment modalities than older patients. This could explain at least some of the differences in the high aggressiveness group where heavy chemotherapy is the mainstay of palliative treatment. We do not, however, believe that tolerance to therapy could be important in explaining the differences in survival in the low/intermediate aggressiveness group as most of the treatments offered to this group are well tolerated across age groups.

Age is also reported as a prognostic factor for survival in other cancer types. In ovarian cancer age < 45 is related to better survival¹³¹, but the reasons are not known. In renal cell carcinoma young

age (≤ 45) is found to be a favorable prognostic factor and in one study this is related to the presence of a favorable translocation (Xp11)¹³².

The age effect in NENs has also been described by Yao et al⁷ who categorized their patients into three age groups (≤ 30 , 31-60 and >60 years) and found better survival in the youngest patients. The reasons are not explored in detail in NEN. Our study design is not suitable to explore etiological factors, but our findings might indicate different tumor biology and genetic alterations in different age groups.

Trends in survival

The relative survival rate differed according to primary site. Small intestinal NENs had the most favorable survival. We found improved survival in both low/intermediate and highly aggressive NENs after year 2000, regardless of tumor stage, gender and age group. There are few reports on trends in NEN survival, but our findings are supported by studies from USA in 2008⁷ and from the Netherlands in 2013⁹⁹ that reported improved survival in metastatic NENs.

Increased awareness and better care for these patients together with new treatment modalities such as molecular targeted therapy, peptide receptor radionuclide therapy and new better tolerated chemotherapy regimens (such as temozolomide based regimens) could explain the improved survival. Some of the improved survival, at least for NETs, could, however, also be related to lead time bias. The survival time is the time from diagnosis to death. If the neoplasms were diagnosed earlier due to increased use of diagnostic procedures, the survival time would increase, even if the patient's life was not prolonged¹³³ (**Figure 7**).

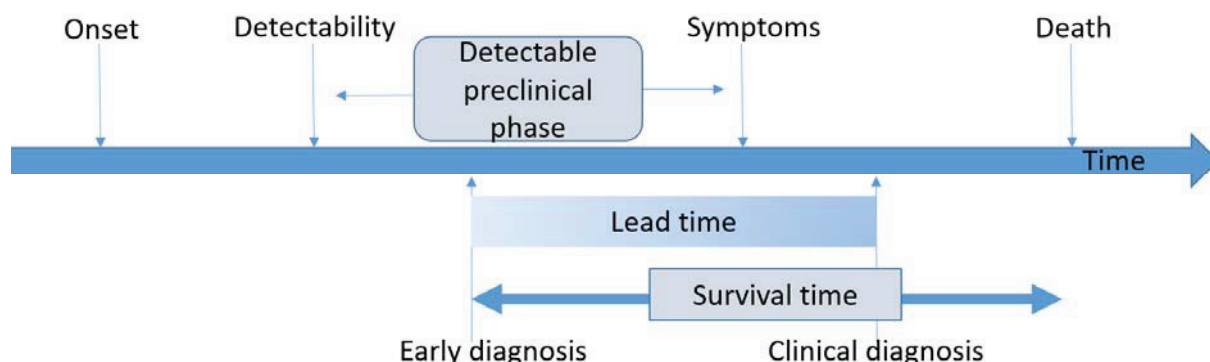


Figure 7. *Natural history of cancer and calculation of survival times for patients diagnosed through screening. Survival time will be increased (lead time) even if the date of death remained unchanged. Adjusted from Dickman et al¹³³ (published with permission from Blackwell publishing)*

P-NENs

In our single center study (paper III) we found that distant metastases, Ki-67 > 2%, non-functional tumors, elevated CgA and non-curative treatment were associated with poor outcome. In localized P-NENs the 5-year overall survival rate was 70% vs 33% in distant disease. In comparison, the 5-year relative survival rates in our population-based study (paper II) were 94.0% in localized disease vs 30.7% in distant disease (**Table 5**). A population-based study includes all reported cases (CRN completeness is reported to be almost 99%¹⁰⁷). In a tertiary referral center, some patients that were completely resected and some patients with advanced disease in terminal stage of the disease, were probably not referred. For example we know that some patients with small resected primaries, especially insulinomas, were not referred as they were assumed to be cured with no need for follow-up. Had these patients been included, the 5-year survival would have been longer. Comparison between the two patient populations is presented in Table 5.

	Population-based study (paper II)	Single center study (paper III)
Male gender (%)	55.2	53
Median age (years)	61	57
Stage (local/distant %)	29.0 / 52.0	32.5 / 44.7

Table 5. Comparison of the P-NEN populations in paper II and III.

In our single center study distant disease was present at diagnosis in 45% of the P-NEN patients. During the follow up, additional 25 % of the P-NEN patients developed distant metastases, most often in the liver. Some of the patients had liver metastases detected up to 10 years after surgery with curative intent. This supports the recommendation for long-time surveillance, even in those patients that are considered cured by surgery. As a consequence of this study, we have implemented 15 years of follow-up of patients believed to be cured by surgery.

Future Perspectives

In CRN more than 32 000 new cancer cases are reported each year. The number of variables recorded are limited. The most important variable in grading NENs, the proliferation index, is not recorded. The CRN has extended the variables recorded for some types of malignancies, as colorectal cancer. A similar extended registration for NENs has been planned but due to lack of resources been postponed. Such an extended registration could increase the granularity of the registry and might give more precise answers to changes in disease behavior over time.

Some of the findings in our studies are interesting. Further studies exploring the differences in survival according to gender and age, looking into risk factors and genetic alterations may give us answers that could be translated into therapeutic and diagnostic options. These findings highlight the utility of registries and the importance of systematic registration of diseases. Especially for rare diseases, as neuroendocrine tumors, the importance of systematic registration can hardly be overestimated. To find leads to etiological and epidemiological factors large numbers of cases must be studied. Ideally, one could hope for international registries as proposed by the European Neuroendocrine Tumor Society (ENETS).

7. CONCLUSIONS

Paper I

Most primary tumors were found in the lungs and in the gastroenteropancreatic system. The incidence of NENs increased. The increase in incidence differed according to primary site, gender and tumor aggressiveness. Our study shows stable distribution of stage and stable incidence of highly malignant NENs. Based on our findings we are not able to conclude whether the observed increase in NEN incidence rates are due to a true increase in occurrence, due to more extensive use of radiological and endoscopic procedures, due to increased awareness among pathologists and clinicians, due to improved histopathological classification or to a combination of these factors.

Paper II

Females, younger age, diagnosis after year 2000 and localized disease were all predictors of better survival. The survival improved in all stages and age groups during our study period. Men had poorer prognosis than women, regardless of their tumor stage or aggressiveness. This might indicate different tumor biology and the need of more aggressive treatment approaches in males.

Paper III

In our single center study, 45% of the patients had advanced disease at diagnosis, similar to the findings in our population-based study. An additional 25% were diagnosed with metastases during follow-up. Distant metastases, Ki-67 > 2%, non-functional tumors, elevated CgA and palliative treatment were associated with poor survival. Some patients were diagnosed with metastases more than 10 years after intended curative surgery, emphasizing the importance of long-term follow up.

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