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Investigation of treatment modalities and outcomes concerning pancreatic and gastric cancer patients in Europe and the US

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LIST OF ABBREVIATIONS

AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiologists
ASCO	American Society of Clinical Oncology
BCR	Belgian Cancer Registry
C-index	Concordance index
CRN	Cancer Registry of Norway
CRS	Cancer Registry of Slovenia
DCO	Death certificate only
DPCD	Danish Pancreatic Cancer Database
ECOG	Eastern Cooperative Oncology Group
ECR	Estonian Cancer Registry
EiCR	Eindhoven Cancer Registry
ELN	Examined lymph node
ESMO	European Society for Medical Oncology
EUROCARE	EUROpean CAncer REgistry-based study on survival and CARE of cancer patients
GC	Gastric cancer
HR	Hazard ratio
IACR	International Association of Cancer Registries
IARC	International Agency for Research on Cancer
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
IKNL	Netherlands Comprehensive Cancer Organization
ISGPS	International Study Group of Pancreatic Surgery
LN	Lymph node
LNR	Lymph node ratio
MDT	Multidisciplinary team
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCR	The Netherlands Cancer Registry
NOS	Not otherwise specified
NREV	The Swedish National Register for Esophageal and Gastric Cancer
OR	Odds ratio
OS	Overall survival

PaC	Pancreatic cancer
PLN	Positive lymph node
QoL	Quality of life
RCT	Randomized controlled trial
RTOG	Radiation Therapy Oncology Group
SEER	Surveillance, Epidemiology, and End Results
SRC	Signet ring cell carcinoma
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNM	Tumor-node-metastasis
UICC	Union for International Cancer Control
US	United States

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1 INTRODUCTION

1.1 Pancreatic cancer

1.1.1 Epidemiology of pancreatic cancer

(This part has been partly published (Huang *et al.*, 2018a; Huang *et al.*, 2017; Huang *et al.*, 2018b).)
Pancreatic cancer (PaC) is one of the most deadly malignancies and constitutes a major global health burden. In 2018, ~459,000 patients are estimated to be newly diagnosed with PaC and ~432,000 PaC-associated deaths are estimated to occur, accounting for 3% of all new cancer cases and 5% of all cancer-related deaths, respectively (Bray *et al.*, 2018). It is the seventh leading cause of cancer-related mortality worldwide, with mortality closely paralleling incidence (Bray *et al.*, 2018). The incidence of PaC is especially high in developed countries, being the fourth leading cause of cancer-related mortality in Western societies (Ferlay *et al.*, 2013; Malvezzi *et al.*, 2017; Siegel *et al.*, 2017). In the European Union, the incidence of PaC has been stable or moderately increasing over the past decades, and was estimated to have caused 91,500 deaths in 2017, and to cause 111,500 deaths in 2025, potentially becoming the third leading cause of cancer-related deaths (Ferlay *et al.*, 2016). In 2018, 88,900 patients in Europe and 44,300 in the United States (US) are estimated to die from this malignancy (Malvezzi *et al.*, 2018; Siegel *et al.*, 2018). No particularly strong risk factors are universally accepted for PaC, which precludes timely intervention (Malvezzi *et al.*, 2017; Siegel *et al.*, 2017; Vasen *et al.*, 2016). PaC usually occurs at older ages, and more than half of the patients are diagnosed with advanced-stage diseases due to the lack of effective early screening methods and the usually unspecific early symptoms and signs (Canto *et al.*, 2013; Ryan *et al.*, 2014; Wolfgang *et al.*, 2013). Treatment for PaC is thus largely palliative. The long-term survival of PaC patients is poor, even in those with early-stage diseases (Ferlay *et al.*, 2013; Malvezzi *et al.*, 2017; Siegel *et al.*, 2017; Sirri *et al.*, 2016). With 5-year survival of only about 5%, advances in survival of PaC patients have been slow (Siegel *et al.*, 2018), and the prognosis has not markedly improved over the past decades despite numerous efforts in therapeutic modification (Lepage *et al.*, 2015b; Wolfgang *et al.*, 2013). PaC is the only major cancer entity not showing declining mortality rates in both sexes in Europe (Malvezzi *et al.*, 2017).

1.1.2 Treatment for pancreatic cancer

(This part except the last two paragraphs has been published (Huang *et al.*, 2018a; Huang *et al.*, 2017; Huang *et al.*, 2018b).)
Primary resection of the primary tumor and regional lymph nodes (LNs) remains the cornerstone of

potentially curative treatment which could markedly improve the long-term survival in selected patients, and is recommended for medically-fit patients with resectable locoregional PaC amenable to surgery, who however comprise only less than one-fifth of all diagnosed cases (Khorana *et al.*, 2016; Khorana *et al.*, 2017a; Khorana *et al.*, 2017b; Wolfgang *et al.*, 2013). Resectability is to a large extent determined by vascular involvement. Only patients with favorable conditions and high probability to achieve curative resection are deemed eligible candidates for resection (Ryan *et al.*, 2014). While resection mostly aims at negative margins, notably, it currently remains controversial how clear-margin (R0) resection should be defined (Konstantinidis *et al.*, 2013; Tempero *et al.*, 2014) and whether and how strongly it is associated with survival (Butturini *et al.*, 2008; Chandrasegaram *et al.*, 2015). The resectability criteria for PaC in the European Society for Medical Oncology (ESMO) guidelines (Ducreux *et al.*, 2015b) follow the US National Comprehensive Cancer Network (NCCN) guidelines (Tempero *et al.*, 2014). According to the current guidelines (Balaban *et al.*, 2016; Ducreux *et al.*, 2015b; Khorana *et al.*, 2016; Sohal *et al.*, 2016; Tempero *et al.*, 2014), only American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) stage I-II PaCs are usually resectable, while for locally-advanced PaCs involving major arteries (T4/stage III according to the TNM staging system) and metastatic (M1/stage IV) cancers, resection should be mostly avoided. However, the resectability criteria are differentially and arguably defined (Balaban *et al.*, 2016; Evans *et al.*, 2015; Wolfgang *et al.*, 2013). Notably, even most of stage I-II PaCs are not *curatively* resectable. Large-scale investigations on surgical resection for PaC are rare (Balaban *et al.*, 2016).

The perioperative mortality is noteworthy. In Germany, it is 10% on the whole population basis and is volume-dependent (5%-6% even in the largest centers), which is mainly influenced by failure to rescue and surgical expertise (Krautz *et al.*, 2017; Nimptsch *et al.*, 2016). Furthermore, postsurgical morbidity remains relatively high (30%-40%) even in high-volume centers (Ceppa *et al.*, 2015). Patients with resectable PaC who undergo resection have much better survival especially in the longer term than those who cannot undergo resection (Ducreux *et al.*, 2015b; Khorana *et al.*, 2016). When counseling a given PaC patient who is considering surgery or who has already undergone resection, it is important to well inform him/her with survival estimates especially for the resected subgroup so that he/she could decide whether or not to undergo resection. However, population-based survival estimates are only available for overall patients without differentiation by resection status or TNM stage (Lepage *et al.*, 2015b), according to which survival however might vary greatly. Survival in resected PaC from institutional reports would be accompanied with relatively high patient selection, which makes the generalizability questionable.

While resection offers the only chance to cure PaC, the 5-year postsurgical survival remains low (8%-16%) if no further adjuvant treatment is administered (Oettle *et al.*, 2013; van der Geest *et al.*, 2016a), as tumors might quickly recur locally and/or distantly (Oettle *et al.*, 2013). Chemotherapy further improves outcomes (Lutz *et al.*, 2017; Neoptolemos *et al.*, 2010; Oettle *et al.*, 2013; Oettle *et*

al., 2007), while the safety and efficacy of adding radiation remains controversial (Hammel *et al.*, 2016; Liao *et al.*, 2013). While chemotherapy has been routinely recommended for resected PaC (Ducreux *et al.*, 2015b; Khorana *et al.*, 2016; Tempero *et al.*, 2017), it remains challenging to get many patients to adjuvant therapy after pancreatectomy (Huang *et al.*, 2018b). Patients with locally-advanced or metastatic diseases are generally not considered candidates for surgery, and palliative treatment remains the mainstay (Sohal *et al.*, 2016). Underuse of therapy with proven efficacies potentially greatly limits survival improvement (Tsai and Evans, 2016). Although the European and US evidence-based guidelines have clearly outlined the role of non-surgical treatment for PaC (Balaban *et al.*, 2016; Ducreux *et al.*, 2015b; Khorana *et al.*, 2016; Sohal *et al.*, 2016; Tempero *et al.*, 2014), its application in the real-world clinical practice has rarely been investigated. While randomized controlled trials (RCTs) on chemotherapy and radiotherapy for PaC have been actively conducted (Hammel *et al.*, 2016; Liao *et al.*, 2013; Lutz *et al.*, 2017; Neoptolemos *et al.*, 2010; Oettle *et al.*, 2007), the implementation of the evidence into the clinical routine remains largely unexplored.

Studying survival-associated factors in patients with resected PaC receiving chemotherapy is difficult due to challenges in accruing adequate and sufficient numbers of operated patients with detailed information. While to date some studies have tried to identify the prognostic factors, most of them reported single institution-/hospital-based case series with <200 long-term survivors, revealing conflicting results (Erdmann *et al.*, 2015; Jouffret *et al.*, 2015; Pindak *et al.*, 2017; Yamamoto *et al.*, 2015). Further insights into the survival-associated factors at the population level would have important implications for treatment and prognosis.

Survival is heterogeneous in resected PaC patients undergoing chemotherapy, and there lacks a model predicting individualized survival for them. Stage is the major prognostic factor for PaC. Notably, survival of patients with disease of the same TNM stage might vary greatly (Jouffret *et al.*, 2015). Other prognostic factors such as patient age and tumor differentiation could improve individualized survival-prediction. A model incorporating all these factors can be intuitively illustrated using a nomogram (Balachandran *et al.*, 2015). Resected patients who receive chemotherapy are selected and have characteristics distinct from those who do not (Huang *et al.*, 2018b). Besides two institutional nomograms predicting postsurgical survival in overall patients (Brennan *et al.*, 2004; Tol *et al.*, 2015), *population-based* survival-predicting models specifically for resected PaC patients receiving chemotherapy with international validations and with robustness have not been found.

1.1.3 Lymph node examination in pancreatic cancer

PaC patients with LN metastases have higher risks of disease recurrence after resection. LN involvement is amongst the strongest indicators for long-term survival and impacts therapeutic decisions in resectable PaC (Khorana *et al.*, 2016; Neoptolemos *et al.*, 2017; Tempero *et al.*, 2017).

LN sampling or dissection might play vital roles in precise nodal staging by identifying the presence of LN involvement and in possibly enhanced treatment effect by clearing potentially metastatic LNs. However, due to the low resection rates (Huang *et al.*, 2017), large international population-based investigations on LN examination in resected PaC remain scarce.

Previous studies have shown contradictory results regarding the association of examined LN (ELN) number with long-term survival in resected PaC (Ashfaq *et al.*, 2014; Hellan *et al.*, 2008; Huebner *et al.*, 2012; Lahat *et al.*, 2016; Michalski *et al.*, 2007; Pedrazzoli *et al.*, 1998; Riall *et al.*, 2005; Slidell *et al.*, 2008; Sun *et al.*, 2014; Tol *et al.*, 2014b; Valsangkar *et al.*, 2013; Wu *et al.*, 2014; Yeo *et al.*, 2002; Yeo *et al.*, 1999). Some small retrospective studies suggested that more ELNs were associated with better prognosis especially in node-negative disease (Ashfaq *et al.*, 2014; Hellan *et al.*, 2008; Huebner *et al.*, 2012; Slidell *et al.*, 2008; Valsangkar *et al.*, 2013), while for node-positive cancer, ELN number was non-prognostic (Lahat *et al.*, 2016; Vuarnesson *et al.*, 2013). However, a secondary analysis of the Radiation Therapy Oncology Group (RTOG)-9704 trial showed that while overall more ELNs were associated with improved survival, there was not such an association in node-negative disease (Showalter *et al.*, 2011). A recent systematic review did not demonstrate a significant association between ELN number and survival (Elshaer *et al.*, 2017). Most previous studies, however, had potential important limitations such as lack of adjustment for confounders, absence of stratified analyses, and limited sample size, resulting in limited robustness. More robust evidence on this topic is therefore needed.

In general, ELN number is considered an important metric for quality assessment in cancer care (Benson *et al.*, 2017; Benson *et al.*, 2018; Ettinger *et al.*, 2017; Gradishar *et al.*, 2018). In PaC, however, the minimum number of LNs which should be examined as a quality indicator especially to accurately stage cancer or to stratify patient survival has not yet been well-established. The NCCN has not suggested a specific threshold for ELNs in PaC. According to the AJCC and UICC, a minimum of 10 LNs is recommended to be analyzed for nodal staging. The ESMO, however, recommends removal of ≥15 LNs to allow adequate pathologic staging (Ducreux *et al.*, 2015b). The survival impact has not been emphasized in the guidelines. In several small retrospective single-institution univariable analyses, recommendations for ELN number in PaC varied greatly from 11 to 20, and the methods for identifying the cut-off values were not statistically robust (Ashfaq *et al.*, 2014; Huebner *et al.*, 2012; Valsangkar *et al.*, 2013). Single institution/hospital-based findings might not be generalizable to the average real-world population level due to high case selection. The controversies between guidelines and studies need to be further addressed by large international population-based evidence.

1.2 Gastric cancer

1.2.1 Epidemiology of gastric cancer

Despite the overall declines in incidence and mortality (Arnold *et al.*, 2015; Smyth *et al.*, 2016), gastric cancer (GC) remains a significant cancer burden globally (Soerjomataram *et al.*, 2012). Worldwide ~1,034,000 patients are estimated to be newly diagnosed with GC and ~783,000 GC-associated deaths are estimated to occur in 2018, accounting for 6% of all new cancer cases and 8% of all cancer-related deaths and making it the fifth most commonly diagnosed malignancy and the third leading cause of cancer-related mortality (Bray *et al.*, 2018). GC is the fourth leading cause of cancer-related mortality in Europe with ~107,000 deaths in 2012 (Ferlay *et al.*, 2013). GC is anatomically categorized into cardia and non-cardia cancers, whose incidences have been trending in opposite directions over the past decades in Western countries (Colquhoun *et al.*, 2015; Smyth *et al.*, 2016). Alarmingly, cardia cancer with an especially poor prognosis is showing an increasing incidence (Mariette *et al.*, 2011; Torre *et al.*, 2015). Most patients with early-stage GCs for which curative treatment is largely possible are asymptomatic, and many GC patients have advanced disease at diagnosis (Thrumurthy *et al.*, 2013).

1.2.2 Treatment for gastric cancer

Adequate resection remains the cornerstone of potentially curative treatment which can assure long-term survival for medically fit patients with resectable non-metastatic GC (Ajani *et al.*, 2016; Smyth *et al.*, 2016; Songun *et al.*, 2010). Notably, involvement of peri-stomach structures in non-metastatic cancers might preclude resection, while a proportion of patients with metastatic disease undergo resection partly due to detection of metastasis only during or after surgery or for palliative reasons. Regarding non-surgical therapies, the recommendation is perioperative chemotherapy in Europe (Smyth *et al.*, 2016), while adjuvant chemoradiotherapy is preferred in the US (Ajani *et al.*, 2016)

GC shows marked global variations in etiology, incidence, patient and tumor characteristics, management, and outcomes (Ferro *et al.*, 2014; Macdonald, 2011; Strong *et al.*, 2010). GC care has not been well-investigated in Western countries due to its being less prevalent, which potentially hampers the survival improvement. Real-world GC treatment patterns at the population level, which may be directly associated with the overall survival statistics, have remained largely unknown in most Western countries except the Netherlands (Dassen *et al.*, 2013; Nelen *et al.*, 2017). Notably, the application of resection, which is the fundamental treatment for GC, has been rarely studied. International analyses of treatment patterns could help to identify differences and potentially modifiable places in clinical practice, of potential relevance for guiding adequate health policy-making and resource allocation.

1.3 Study questions and aims

Using real-world data from multiple European national population-based cancer registries and the US

Surveillance, Epidemiology, and End Results (SEER) Program (SEER, 2018), this thesis/dissertation aims to investigate the treatment and outcomes for PaC and GC in Europe and the US in the early 21st century. The research questions are detailed as follows:

1.3.1 Pancreatic cancer

- To explore the application of surgical resection for PaC in various European countries and the US;
- To assess chemotherapy and radiotherapy use across countries for resected and unresected PaC;
- To comprehensively and robustly provide 1-month to 5-year overall survival estimates at the population level for overall (resected and unresected) and resected PaC patients in Europe and the US stratified by TNM stage and age;
- To explore the survival trends over time in each country;
- To investigate factors associated with survival in patients with resected TNM stage I-II PaC receiving chemotherapy;
- To construct a population-based survival-predicting model with international validations;
- To further investigate the association of ELN number with staging and survival in resected PaC through overall and stratified analyses of resected PaC patients from the US and the Netherlands;
- To determine and to validate the minimal and optimal thresholds for the ELN number, using a multivariable approach.

1.3.2 Gastric cancer

- To investigate the application of resection for both non-metastatic and metastatic GCs and explore the treatment-associated factors;
- To come up with some potential explanations for the observed trends.

2 MATERIALS AND METHODS

2.1 Data sources and quality

2.1.1 Data sources

(This part has been published (Huang *et al.*, 2018a; Huang *et al.*, 2017; Huang *et al.*, 2018b).)
For robustness, only data from population-based cancer registries were included in the analyses for this thesis. Institution-based data were not included due to the relatively high risk of patient selection bias. An extensive attempt was made to find and contact population-based cancer registries, and formal invitations were sent to the population-based participants of the EUROpean CAncer REgistry-based study on survival and CARE of cancer patients (EUROCARE) project (Lepage *et al.*, 2015a) and other population-based registries based on extensive PubMed and internet search. The response rate was relatively high, but only national population-based registries able to provide high quality data on TNM staging, treatment (resection, chemotherapy, and radiotherapy), and survival were eligible. A list showing the selection of the contacted European national population-based cancer registries together with the reasons for exclusion is shown in **Table 1**. Finally, population-based data of PaC patients from seven European national population-based cancer registries (the Netherlands, Belgium, Norway, Denmark, Sweden, Slovenia, and Estonia) and the US SEER-18 Program database were obtained for this large international real-world observational study series. The participating European population-based national registries, located in Western, Northern, Southern, and Eastern Europe, respectively, were those able to provide data of relatively high quality according to a standardized uniform data-request sheet with variable lists, to ensure the robustness of the results. All variables were uniformly (re)coded across registries. All patient-level data were anonymous. No individual patient data were reported. This real-world observational study was approved by the Ethics Committee of the Medical Faculty Heidelberg, conducted according to the Declaration of Helsinki (World Medical, 2013), and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Table 1. Selection of contacted European national population-based cancer registries[1] (Huang *et al.*, 2018a)

Country of contacted registry	Included in pancreatic cancer study	Included in gastric cancer study	Comment if not initially included	Comment if initially included but not included in one or more further analyses
Northern Europe				
Finland	No	No	Surgical treatment not validated	
Sweden	No	Yes	Pancreatic cancer: national data not statistically validated	
Norway	Yes	Yes		
Iceland	No	No	No national population-based data on treatment	
Denmark	Yes	No	Gastric cancer: required variables not readily prepared	Pancreatic cancer: consent withdrawn due to legislation issues
Western Europe				
The UK	No	No	No ready-to-use national population-based data on treatment or TNM stage	
Ireland	No	No	No further response after initial contact	
The Netherlands	Yes	Yes		
Belgium	Yes	Yes		
Southern Europe				
Bulgaria	No	No	No national population-based data on treatment	
Serbia	No	No	No response	
Slovenia	Yes	Yes		
Croatia	No	No	No national population-based data on surgical treatment	
Eastern Europe				
Estonia	Yes	Yes		Small number of resected cases and short incidence periods recorded not allowing for robust survival analysis
Latvia	No	No	No national population-based data on treatment	
Lithuania	No	No	No response	
Ukraine	No	No	Insufficient resources for data collection	
Slovakia	No	No	No response	
Central Europe				
Poland	No	No	No response	
Czech Republic	No	No	No national population-based data on treatment	
Austria	No	No	No national population-based data on treatment	

[1]For the other countries and regions in Europe (*e.g.*, France, Italy, and Germany) not listed in this table, no corresponding national population-based registries were found through careful search.

2.1.2 Data quality

(This part except the description of the Swedish registry has been published (Huang *et al.*, 2017).)
The included registries generally follow the international standards and classifications, and are controlled for quality using the International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR) rules. The data analyzed are generally of high quality.

2.1.2.1 European population-based registries

The European national population-based cancer registries included in this thesis participate in the EUROCARE, whose criteria for inclusion, quality checks, *etc.* have been extensively described (Rossi *et al.*, 2015).

The Netherlands Cancer Registry (NCR)

The Netherlands Cancer Registry (NCR)/Netherlands Comprehensive Cancer Organization (IKNL) is a national organization and is the quality institute for oncologic research and practice. “The objective of IKNL is to serve the public interest by promoting the fight against cancer, particularly by helping those suffering from cancer.” The NCR/IKNL supports this objective through the following four main processes: 1) Record: Information about every patient with cancer in the Netherlands is gathered in the NCR. 2) Report: The data in NCR are then reported in three domains: the public (science), political (the Ministry of Health, Welfare and Sport, and the National Health Care Institute), and care domains (hospitals/care institutions, professionals, and patients). 3) Improve: The effect of all the improvement initiatives (*e.g.*, training) is evaluated in the NCR/IKNL. The IKNL responds to developments in the field by shifting its focus from a general to a tumor-specific approach to oncologic care. 4) Regulate: Guidelines are deployed to improve quality and efficiency and to reduce unwanted variation in care (NCR, 2017).

Belgian Cancer Registry (BCR)

The Belgian Cancer Registry (BCR) is a national population-based registry which has covered the entire country since 2004 and which relies on two major data sources: oncologic care programs and pathology laboratories. It has a legal basis to use the national registration number which allows accurate linkage and follow-up. Detailed information about diagnostic and therapeutic procedures is obtained through linkage with administrative and clinical databases for an active involvement in quality of care studies.

Cancer Registry of Norway (CRN)

Records in the Cancer Registry of Norway (CRN) are complete and nationwide, and the CRN has since 1953 kept a complete registration of all new cases of malignancies. Regulated by the Norwegian law, medical practitioners are required to report cancerous and pre-cancerous lesions to the registry, and five sources of information are available: 1) copies of all pathology and autopsy reports from all

laboratories in Norway, 2) registration forms filled in by clinicians providing the location and extent of disease and treatment, 3) copies of all death certificates that mention neoplastic disease, 4) hospital discharge data and outpatient diagnoses from all hospitals, and 5) radiotherapy data from all treating centers. The CRN has documented a high degree of data quality including key aspects such as comparability, completeness, and validity (Larsen *et al.*, 2009).

Danish Pancreatic Cancer Database (DPCD)

The Danish PaC data are based on the Danish national registries for pathology and treatment, which are well documented with a high data validity (Erichsen *et al.*, 2010; Pedersen, 2011; Schmidt *et al.*, 2014; Schmidt *et al.*, 2015). In Denmark, all hospitals are required to register diagnosis and treatment information for every patient contact in the Danish National Patient Registry. All histological and cytological specimens are likewise required to be registered in the National Pathology Register. The Danish Civil Registry keeps track of the vital status of all Danes. The Danish Pancreatic Cancer Database (DPCD) gets data from all these three registers and combines the data. The combined data for each patient are validated by the relevant surgical and oncological department regarding diagnosis and treatment. The completeness of clinical validation has been around 70%. The completeness regarding patients with a diagnosis of PaC is close to 100%.

The Swedish National Register for Esophageal and Gastric Cancer (NREV)

In 2006 The Swedish Association for Upper Gastro-Intestinal Surgery closed two previous registers, SWEGIR (https://www.swegir.com/) for GC and SECC, another research-based register for esophageal and cardia cancer, which later merged and formed The Swedish National Register for Esophageal and Gastric Cancer (NREV) on January 1st, 2006. NREV receives yearly financial support from the Swedish Government. The Steering Committee of the NREV consists of surgeons, oncologists, nurses, a pathologist, patients, and statisticians with representativeness from both university and regional/county hospitals. The Steering Committee of the NREV is also responsible for establishing the national guidelines of care for patients with esophageal and gastric cancer, which are updated every second year. The main objectives of the NREV are to compile data and information to monitor the diagnostic process, to evaluate the treatment regimens, and to improve the care of patients with esophageal cancer and/or GC. The NREV also serves to facilitate research, and yearly publishes the results for the previous year. The register has been validated and shown to have a high level of completeness, accuracy, and concordance compared to the mandatory Swedish Cancer Registry (Linder *et al.*, 2016).

Cancer Registry of Slovenia (CRS)

The quality and completeness indices of the Cancer Registry of Slovenia (CRS) suggest that cancer registration in Slovenia adequately covers the entire population. To assure the completeness and to obtain additional information on registered cancer cases, the CRS is linked with several governmental and health databases. The synchronization of data between different sources is based on comparing the unique personal identification number which is assigned to every resident in Slovenia and recorded in

every state registry including the CRS. Using unique personal identification numbers guaranties data integrity and quality, and prevents data duplication. The CRS links with the Central Register of Population instantaneously through secure on-line connection (24/7 availability) and daily updates information on vital status and address for each person registered by the CRS. The electronic linkage to the national Mortality Database is performed several times every year (Zadnik *et al.*, 2017).

Estonian Cancer Registry (ECR)

In Estonia, the overall completeness of reporting cancer cases has been estimated to be approximately 95%-98%. The Estonian Cancer Registry (ECR) regularly performs data linkage with the Estonian Causes of Death Registry. Additionally, the ECR regularly compares its database with the databases of the two biggest hospitals responsible for PaC surgical treatment for assurance of the completeness. Data are received on clinical and pathology notification forms. Data input and coding are done within the registry. The registry has been regularly using the IARC Check Program for checking the internal consistency of data. The data quality is evaluated using standard indicators for population-based registries (Innos *et al.*, 2014).

2.1.2.2 The Surveillance, Epidemiology, and End Results Program

The SEER Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer epidemiology in the US, and collects data from population-based cancer registries. The SEER Program registries routinely collect data on patient demographics, primary tumor site, morphology, stage, the first course of treatment, and follow-up for vital status. The SEER Program is the only comprehensive source of population-based information in the US that includes stage of cancer at the time of diagnosis. The SEER data are updated annually and provided as a public service. The NCI staff work with the North American Association of Central Cancer Registries to guide all state registries to achieve data content and compatibility acceptable for pooling data and improving national estimates.

The SEER Program is viewed as the standard for quality among cancer registries around the world. Each SEER Program registry has a contractual obligation to meet the specifically defined data quality goals on an ongoing basis. The SEER Program has also developed an extensive set of field edits which prevent and correct errors in the data. Electronic edits provide the means to authenticate codes, to check for missing data, and to check for interrelated data item errors. The joint efforts with national committees and national data standards contribute to the high data quality (SEER, 2018).

2.2 Pancreatic cancer

The overall inclusion and exclusion criteria and the overall collected information and definition are first described, and the study-specific methods are then detailed in each specific subsection with the

corresponding heading. Data in each country were analyzed separately and results were described for each country separately without pooling, considering the potential heterogeneity across countries and to avoid the impact of any single large patient cohort. Numeric data are presented as mean ± standard deviation and/or median (interquartile range) where appropriate, and categorical data as count (percentage). The SAS software (v. 9.4; SAS Institute Inc., Cary, NC) was used for analysis if not otherwise specified, and statistical significance was defined by two-sided P <0.05.

2.2.1 Overall inclusion and exclusion criteria

(This part has been partly published (Huang *et al.*, 2018a; Huang *et al.*, 2017; Huang *et al.*, 2018b).) Only patients with diagnoses of primary invasive malignancies of the exocrine pancreas were selected. Cases were initially included regardless of being eligible for resection. Patients were initially included irrespective of being microscopically diagnosed or not in this real-world study following the EUROCARE studies (De Angelis *et al.*, 2014; Lepage *et al.*, 2015b), since consensus has been reached by the International Study Group of Pancreatic Surgery (ISGPS) that, in the presence of a solid mass suspicious for malignancy, biopsy proof has not been and is not required before proceeding with resection (Asbun *et al.*, 2014). Patients with benign/premalignant tumors, non-pancreatic neoplasms involving the pancreas, neuroendocrine tumors/carcinoids, stromal tumors/sarcomas, germ-cell neoplasms, lymphomas, or peri-ampullar tumors were excluded (**Table 2**). Patients with diagnosis based on death certificate only (DCO) or autopsy were also excluded. As the fifth and prior editions of the TNM staging system were not compatible with the later versions (sixth or seventh) in effect during 2003-2017 (Ducreux *et al.*, 2015b), only patients with PaC diagnosed from 2003 or the first year when resection status was registered until 2016/2017 (depending on the year when the specific part of analyses were done) or the most recent year of registration were included in each registry.

Table 2. Inclusion and exclusion codes for pancreatic cancer according to the International Classification of Diseases for Oncology, Third Edition (Huang *et al.*, 2017)

Category		Code
Topography	Inclusion	C25.0 (head of pancreas), C25.1 (body of pancreas), C25.2 (tail of pancreas), C25.3 (pancreas duct), C25.7 (other specified parts of pancreas), C25.8 (overlapping lesion of pancreas), C25.9 (pancreas, NOS)
	Exclusion	C25.4
Morphology	Inclusion[1]	8000-8009 (unspecified neoplasms), 8010-8049 (epithelial neoplasms, NOS), 8050-8089 (squamous cell neoplasms), 8140-8389 (adenomas and adenocarcinomas), 8440-8499 (cystic, mucinous, and serous neoplasms), 8500-8549 (ductal and lobular neoplasms), 8550-8559 (acinar cell neoplasms), 8560-8579 (complex epithelial neoplasms)
	Exclusion	8013, 8150-8153, 8155-8157, 8160, 8162, 8170, 8180, 8240-8243, 8246-8249, 8312, 8680, 8700, 8800-8802, 8810, 8825, 8830, 8851, 8852, 8858, 8890, 8891, 8900, 8920, 8936, 8982, 9043, 9100, 9120, 9250, 9364, 9473, 9500, 9591, 9673, 9680, 9687, 9691, 9695, 9702
Behavior	Inclusion	3 (invasive malignant tumor)
	Exclusion	0, 1, 2

[1]Based on the Surveillance, Epidemiology, and End Results (SEER) Program broad groupings.
NOS, not otherwise specified.

2.2.2 Overall collected information and definition

(This part has been partly published (Huang *et al.*, 2018a; Huang *et al.*, 2017; Huang *et al.*, 2018b).) Information on patient (year of diagnosis/surgery, sex, and age) and cancer characteristics (microscopic confirmation, topography, morphology, TNM stages, and differentiation), treatment (resection and (neo)adjuvant/palliative chemotherapy and radiotherapy), and outcome variables (follow-up time and survival status) was obtained from all participating countries.

Specific covariates were only available in certain national population-based registries. Race/ethnicity and marital status were available in SEER-18. Tumor size was available in the US. Comorbidity information at diagnosis was recorded in the Eindhoven Cancer Registry (EiCR), which is part of the national Netherlands Cancer Registry and which contributes to more than one-tenth of the records in the Netherlands Cancer Registry. Belgium and Denmark provided Eastern Cooperative Oncology Group (ECOG) performance status score. Chemotherapy information was not available in SEER-18 for the 2015 submission. For the 2016 and 2017 SEER-18 submission, non-surgical therapies were reported with low sensitivity. Neoadjuvant and adjuvant chemotherapy/radiotherapy was not distinguishable in Estonia, and neoadjuvant and adjuvant chemotherapy was not distinguishable in the US in the submission versions with available information. Information on neoadjuvant chemotherapy and radiotherapy was not available in Norway. Time intervals between diagnosis/surgery and chemotherapy/radiotherapy application were available in the Netherlands, Belgium, and Slovenia. Information on hospital type was available in the Netherlands and Belgium. In resected patients, data on positive and harvested lymph node numbers and resection type were retrievable in the US and the Netherlands. Data on resection margin were available in the Netherlands and Slovenia. For SEER-18, sub-registry information was additionally retrieved.

Tumor stage was defined according to the AJCC/UICC TNM staging system, Sixth or Seventh Edition (both editions are identical to each other) (Ducreux *et al.*, 2015b). Tumor topography, morphology, and behavior were coded based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) (WHO, 2018). Tumor location included pancreas head (C25.0), body (C25.1), tail (C25.2), overlapping lesion (C25.8), and other (pancreas duct, overlapping lesion, or not otherwise specified (NOS) tumor). Tumor histology was categorized into adenocarcinoma, not otherwise specified (8140-8389), ductal/lobular neoplasms (8500-8549), cystic/mucinous/serous cancers (8440-8499), and other based on the SEER broad grouping (SEER, 2018), and *all histology types were malignant and invasive*. Lymph node ratio (LNR) was calculated by dividing positive LN (PLN) by examined LN (ELN) number.

Resection was defined as surgical removal of the primary tumor, regardless of being curative or palliative and extents of excision and lymphadenectomy. A patient was considered to have received chemotherapy/radiotherapy if ≥1 cycle was administered, regardless of the detailed regimen, dosage, and administration method. In operated patients, neoadjuvant therapy referred to the non-surgical

treatment supplied before resection, and adjuvant treatment was that given post-operation. Chemotherapy/radiotherapy was considered palliative if resection was not conducted. Survival status was obtained from official population registers and/or valid national mortality registrations.

2.2.3 Resection of pancreatic cancer in Europe and the US

(This part has been published (Huang *et al.*, 2017).)

Data from the national population-based cancer registries of the Netherlands, Belgium, Norway, Denmark, Slovenia, and Estonia and from the US SEER-18 Program (the 2015 submission (SEER, 2016)) was used for this part of analyses (**Table 1**).

Patient age was divided into four groups (<60, 60-69, 70-79, and ≥80 years). Age-standardized resection rates were computed for each population-based registry using the age distribution of the US patients, the largest group of patients included. Trends of standardized resection rates over years were evaluated for each country and, for simplicity, rates over two-calendar year periods (2003-2004 until 2013-2014) were displayed.

Multivariable logistic regression was used to investigate the associations of resection with sex, age group, tumor location, and cTNM stage in overall patients, with female, <60 years, pancreas head tumor, and stage I-II as the reference category, respectively. Year of diagnosis was also included in the models. Sensitivity analyses were conducted by repeating association analyses after imputing missing stages using multiple imputations (Moons *et al.*, 2015) (variables applied: year of diagnosis, sex, age, tumor location, resection, chemotherapy, radiotherapy, and survival time and status; routine: PROC MI). In additional analyses, associations were investigated for tumor subgroups according to tumor stage and location, respectively, and were reassessed after adding tumor size, ECOG score, comorbidity, or hospital type one by one into the models.

2.2.4 Non-surgical therapies for resected and unresected pancreatic cancer in Europe and the US

(This part has been published (Huang *et al.*, 2018b).)

Data from the national population-based cancer registries of the Netherlands, Belgium, Norway (2003-2011, the period 2012-2014 was not included in this part of analyses due to low sensitivity of reporting), Slovenia, and Estonia and from the US SEER-18 Program (the 2015 submission (SEER, 2016)) was used for this part of analyses (**Table 1**).

A combination of cTNM and pTNM stages was used with priority given to pTNM staging. To explore the chemotherapy and radiotherapy utilization, age-standardized rates for resected and unresected PaC were computed using the age distribution in the cancer population from the US, the largest dataset in this study, as standard. Age was divided into the following groups: <60, 60-69, 70-79, and ≥80 years. Treatment rates were tested for linear trends, and rates over two-calendar year periods

(2003-2004 until 2013-2014) were depicted. Rates of chemotherapy and radiotherapy application according to age group, tumor location, and TNM stage in resected and unresected patients, and geographic disparities across the US registries during 2012-2014 were further explored. Utilization of combination therapies regarding neoadjuvant and adjuvant chemotherapy and radiotherapy in the common period 2011-2013 was assessed in the Netherlands, Belgium, and Slovenia, where information on both neoadjuvant and adjuvant treatment was available. Due to the very low rates of neoadjuvant treatment, neoadjuvant and adjuvant therapies were combined in the other analyses.

Multivariable logistic regression was used to evaluate the associations of chemotherapy and radiotherapy utilization with year of diagnosis, sex, age, tumor location, and TNM stage for resected and unresected patients in the main analyses. Additional variables (hospital type, lymph node ratio (LNR, the proportion of metastatic to harvested nodes), ECOG score, resection type, and comorbidity type and number) were included one by one into the main models in further analyses in countries with available information. Sensitivity analyses were conducted by limiting patients receiving chemotherapy or radiotherapy to those undergoing the treatment ≤90 days after diagnosis in countries with available time interval information, and by restricting the total patients to those surviving >90 days after diagnosis in all countries to control for the impact of short-term mortality on treatment reception.

2.2.5 Stratified survival of resected and overall pancreatic cancer patients in Europe and the US

(This part has been published (Huang *et al.*, 2018a).)

Data from the national population-based cancer registries of the Netherlands, Belgium, Norway, and Slovenia and from the US SEER-18 Program (the 2015 submission (SEER, 2016)) was used for this part of analyses (**Table 1**).

Patients with unknown diagnosis/follow-up date or survival status or without TNM staging information were further excluded. In stage classification, pTNM stages were prioritized over cTNM ones. Complete-case analysis was performed for patients with known TNM stages. Overall survival was defined as the months between diagnosis and death from any cause/last follow-up, and was estimated for overall and resected PaC patients stratified by TNM stage (I-II and III-IV) and age group (<60, 60-69, and ≥70 years) using the Kaplan-Meier method, with the 1-, 3-, 6-, 12-, 24-, 36-, and 60-month survival rates calculated. Cancer stage was divided into stage I-II and III-IV considering the former to be clearly-resectable and the latter mostly-unresectable, and to ensure adequate numbers for assessment in each subgroup. When describing survival for resected stage III-IV PaC, the subgroups <60 and 60-69 years were combined considering the small size of either. All categories were predefined. Sensitivity analyses were conducted by limiting the overall patients to those with microscopic confirmation. Survival trends over three calendar-year periods (2003-2005, 2006-2008, and 2009-2011) in each country were further reported. Changes in survival rates of overall and

operated patients diagnosed between 2003-2005 and 2009-2011 were examined using the log-rank test.

2.2.6 Prognostic factors and development and international validation of a benchmark population-based survival-predicting model in patients with resected stage I-II pancreatic adenocarcinoma receiving chemotherapy

Data from the national population-based cancer registries of the Netherlands, Belgium, Norway, and Slovenia and from the US SEER-18 Program (the 2017 submission (SEER, 2018)) was used for this part of analyses (**Table 1**).

2.2.6.1 Patients

Only patients with microscopically-confirmed diagnoses of primary invasive TNM stage I-II adenocarcinomas of the exocrine pancreas who underwent surgical resection in 2003 until 2014 were selected. Since chemotherapy is standard for resected PaC patients (Ducreux *et al.*, 2015b; Khorana *et al.*, 2016; Tempero *et al.*, 2017), only those receiving chemotherapy were included. Patients with unknown/obscure follow-up time or vital status were excluded. Individuals with cystic/mucinous/serous or acinar cell tumors were further excluded. To minimize the effect of the potential heterogeneity in surgery quality and perioperative care, cases surviving <3 months were excluded. Since resection is not routinely recommended for stage III or IV PaC patients (Ducreux *et al.*, 2015b; Khorana *et al.*, 2016; Tempero *et al.*, 2017), they were also excluded. Stage was a combination of pathologic and clinical stages with priority given to pathologic staging.

2.2.6.2 Prognostic factors

The Kaplan-Meier method was applied to calculate survival time and rates. To assess the independent impact of potential prognostic factors on survival, Cox proportional hazards regression was used. Variables including year of diagnosis, age, sex, tumor location, T and N stages, and differentiation were included as covariates in the main multivariable models. For complete-case analysis, patients with missing data were excluded in multivariable analyses. In the US, results for the white patients were computed for comparison with the total patients, for whom main analyses were performed. In registries with available information, resection margin, hospital type, tumor size, positive and harvested lymph node numbers, lymph node ratio, T and N stages according to the eighth edition following Kamarajah *et al.* (Kamarajah *et al.*, 2017), ECOG score, resection type, and comorbidities were incorporated one by one into the main models to examine the survival association for each of them. The proportional hazards assumption was verified for all variables by plotting the logarithm of the negative logarithm of the survival function against the logarithm of survival time (Hess, 1995).

2.2.6.3 Nomogram construction and validation

The SEER-18 dataset, the largest among the included ones, was used as the training set for nomogram construction (models based on the other cohorts did not reveal markedly better performance). Age, sex, tumor location, T and N stages, and differentiation were entered as potentially relevant prognostic factors, and the final model was selected using a backward step-down process with the Akaike information criterion (AIC) as a stopping rule (Harrell *et al.*, 1996). To permit nonlinear associations, continuous variables were modeled using restricted cubic splines where appropriate (Harrell *et al.*, 1996).

The nomogram was subjected to 1,000 bootstrap resamples for internal validation of the training US cohort, and was externally validated using the European datasets to assess the international generalizability of the model. The model performance and discrimination ability for predicting survival was numerically evaluated by computing Harrell's concordance index (C-index) (Harrell *et al.*, 1996). Comparison of C-indexes of different models followed Hanley *et al.* (Hanley and McNeil, 1983). Calibration of the nomogram for 1, 2, 3-, and 5-year survival was done by comparing the predicted with the observed survival. Bootstrapping was used for bias correction (Harrell *et al.*, 1996).

In sensitivity analyses for the training US cohort, C-indexes were re-calculated after replacing continuous age with age group, N stage with positive lymph node number or lymph node ratio, and sixth/seventh edition of cancer stages with the eighth version, after adding harvested lymph node number and/or tumor size, after limiting patients to those diagnosed after 2009 or white patients, and after stratifying patients by tumor location. The *survival* and *rms* packages in R 3.4.1 (http://www.r-project.org) were used.

2.2.7 Significance of examined lymph node number in accurate staging and long-term survival in resected stage I-II pancreatic cancer

Data from the national population-based cancer registries of the Netherlands and the US SEER-18 Program (the 2017 submission (SEER, 2018)) was used for this part of analyses.

2.2.7.1 Patients

Population-based data on PaC patients from the US SEER-18 Program (SEER, 2018) and the national Netherlands Cancer Registry (NCR) were used. The SEER Program of the National Cancer Institute is an authoritative source of information on cancer epidemiology in the US, and the NCR of the Netherlands Comprehensive Cancer Organization is the quality institute for oncological research and practice in the Netherlands. Patient-level data on patients with incident PaC were consecutively collected in both registries.

Patients undergoing resection for first TNM stage I-II primary invasive malignancy of the

exocrine pancreas during 2003-2015 were eligible. Patients with unknown follow-up period or survival status were excluded. Those with tumors originating from islets of Langerhans, with ineligible histology, or with benign or *in situ* tumors were also excluded (**Table 2**). Patients with stage III (T4) or IV (M1) disease were not eligible because resection is not routinely recommended as the standard of care for them (Ducreux *et al.*, 2015a; Ducreux *et al.*, 2015b). Patients with 0 or missing recorded ELNs were excluded, considering that lymphadenectomy is part of PaC resection and that the ELN number is required to be reported (Ducreux *et al.*, 2015a; Tol *et al.*, 2014a). The US patients diagnosed in 2003 were excluded because of the unavailability of TNM stage.

2.2.7.2 Statistical analyses

Based on the hypothesis that more ELNs confer a greater chance to identify PLNs, stage migration was evaluated by investigating the association of the ELN count with the proportion of node-positive versus node-negative status with logistic regression models, adjusting for confounders potentially associated with the ELN count and/or nodal stage before and/or during resection (year of diagnosis, sex, age, tumor location, histology, differentiation, T stage, and resection type). The association of ELN count with overall survival was investigated and visualized using multivariable Cox proportional hazards regression models, with adjustment for potential prognostic factors including year of diagnosis, sex, age, tumor location, histology, differentiation, T stage, metastatic LN number, and resection type. Interactions between ELN number and other factors were tested by adding the interaction terms one by one. Sensitivity analyses were performed by stratifying the models by demographic, clinical, and pathologic characteristics and by entering the additional variables available in only one cohort (*e.g.*, comorbidities in NCR) into the models. In the NCR, neoadjuvant and/or adjuvant chemotherapy and/or radiotherapy were included as static or time-varying covariates in the models for sensitivity analysis. Considering the low sensitivity of the non-surgical variables (Noone *et al.*, 2016) and the unavailability of the intervals between diagnosis/resection and non-surgical treatment, chemotherapy or radiotherapy was not further included in the multivariable models in SEER-18. Before performing survival analyses, the proportional hazards assumption was validated by plotting the logarithm of the negative logarithm of the survival function against the logarithm of survival time (Hess, 1995). Disease-specific survival, which was available in the US, was used as an additional endpoint for sensitivity analysis.

The associations of increasing ELN number with serial odds ratios (ORs) for stage migration and hazard ratios (HRs) for survival, the logarithms of both ratios, the mean PLN number, and LNR were depicted by curves, which were fitted using the LOWESS smoother with the default bandwidth of 2/3 (Borkowf *et al.*, 2003). The most frequent ELN counts (12 in SEER-18 and 10 in NCR) were used as the references. Structural breakpoints for the smoothed parameters in the overall and stratified US patients were then determined by the Chow test (*F*-test). Given that survival outcomes are the most

important, the breakpoint for smoothed HRs in the whole US derivation cohort was considered as the optimal threshold, and the breakpoint for smoothed ORs for stage migration as the minimal threshold. The whole US and Dutch cohorts were then used for internal and external cutoff validation, respectively, by assessing survival and stage migration associated with ≥ versus < identified threshold number of ELNs with multivariable adjustment in overall and stratified analyses.

A mathematic model involving the ELN count was additionally generated following Robinson *et al.* (Robinson *et al.*, 2016), and was used to assess the accuracy of declared node-negative disease, namely, the possibility of having ≥1 undetected PLNs in reported node-negative disease with different ELN numbers. Data were managed using the SAS (version 9.4, SAS Institute Inc.) and R 3.4.1 software (http://www.r-project.org).

2.3 Gastric cancer

2.3.1 Patients

Individual-level data of GC patients from national population-based cancer registries of the Netherlands, Belgium, Sweden, Norway, Slovenia, and Estonia, and the US SEER-18 Program were included (**Table 1**).

Only patients with microscopically-confirmed primary invasive malignancies of the stomach (C16) registered in 2003 to 2017 were selected (**Table 3**), irrespective of distant metastasis status. Both cardia and non-cardia GCs were included. Individuals with non-invasive benign/premalignant/*in situ* tumors, non-GC neoplasms involving the stomach, gastrointestinal stromal tumors/sarcomas, neuroendocrine tumors/carcinoids, lymphomas, or germ-cell neoplasms were excluded. Cases diagnosed based on DCO/autopsy were also excluded.

Table 3. Inclusion and exclusion codes for gastric cancer according to International Classification of Diseases for Oncology, Third Edition[1]

Category		Code
Topology	Inclusion	C16, C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.8, C16.9
	Exclusion	-
Morphology	Inclusion[2]	8000-8009 (unspecified neoplasms), 8010-8049 (epithelial neoplasms, NOS), 8050-8089 (squamous cell neoplasms), 8140-8389 (adenomas and adenocarcinomas), 8440-8499 (cystic, mucinous and serous neoplasms), 8500-8549 (ductal and lobular neoplasms), 8550-8559 (acinar cell neoplasms), 8560-8579 (complex epithelial neoplasms)
	Exclusion	8013, 8152, 8153, 8156, 8160, 8170, 8240-8243, 8246, 8249, 8252, 8390, 8590, 8680, 8700, 8711, 8720, 8800-8805, 8810, 8811, 8830, 8840, 8850-8852, 8858, 8890, 8891, 8895-8897, 8900, 8902, 8910, 8912, 8920, 8930, 8931, 8935, 8936, 8960, 9040, 9041, 9064, 9071, 9080, 9090, 9100, 9120, 9364, 9380, 9490, 9500, 9540, 9560, 9580
Behavior	Inclusion	3
	Exclusion	0, 2

[1]http://codes.iarc.fr/

[2]Based on Surveillance, Epidemiology, and End Results Program broad groupings.

Data on patient (year of diagnosis, sex, and age), cancer (location, differentiation, histology, and stage), treatment (resection, chemotherapy, and radiotherapy), and follow-up variables (survival time and status) (re)coded following a uniform data-request sheet were obtained. Non-surgical therapies were registered with low sensitivity in the US and Estonia. Neoadjuvant and adjuvant therapies could not be differentiated in Norway or Estonia, and adjuvant therapies were not available in Sweden. Information on hospital type (the Netherlands, Belgium, and Sweden), volume (the Netherlands and Sweden), tumor size (the US), ECOG performance status score (Belgium and Sweden), American Society of Anesthesiologists (ASA) score (Sweden), and comorbidities (Eindhoven, the Netherlands and Belgium) were only available in certain registries.

Resection was defined as removal of the primary tumor irrespective of being curative or palliative, of the type, extent, and radicality of excision and lymphadenectomy, and of the method, approach, procedure, and technique of management. Cancer topography and morphology followed the International Classification of Diseases for Oncology, Third Edition (WHO, 2018). Tumors were categorized into adenocarcinoma, signet ring cell carcinoma (SRC), and other. Tumor local invasion and lymph node metastasis were derived from the AJCC/UICC TNM staging, and were reclassified into categories consistent across the investigated period when the sixth/seventh edition was in effect.

2.3.2 Statistics

Considering the potential heterogeneity across registries, data were analyzed and presented separately in each country without pooling. Given that patients without and with distant metastasis are different clinical entities, they were analyzed separately. Patient age was categorized into four groups (<60, 60-69, 70-79, and ≥80 years). Age-standardized treatment rates were calculated using the age distribution of the US patients, the largest group of patients analyzed, as the standard. Temporal trends of the standardized rates were assessed using linear regression, and rates over two-calendar-year periods are shown graphically. Subgroup analyses according to patient age and tumor location were further conducted, and age- and location-specific rates in 2010 or later were shown.

Multivariable logistic regression models were constructed to investigate the associations of resection with patient and tumor characteristics with adjustment for year of diagnosis, patient sex, age group, tumor location, and histology in main analyses. Subgroup analyses according to age and location and in SRC and cancers invading adjacent structures were further conducted. Associations with additional variables (adjacent structure invasion, hospital type and volume, tumor size, adjacent structure invasion, ECOG and ASA scores, and comorbidities) were evaluated by adding them one by one into the main models in countries with available information. Cases with missing values were excluded from analyses.

3 RESULTS

3.1 Pancreatic cancer

3.1.1 Resection of pancreatic cancer in Europe and the US

(This part has been published (Huang *et al.*, 2017).)

3.1.1.1 Characteristics of overall patients

A total of 147,700 patients from seven population-based registries were analyzed (**Table 4**). In the US, the Netherlands, Belgium, Norway, and Slovenia, patients diagnosed between 2003/2004 and 2013/2014 were included. In Denmark and Estonia, included patients were diagnosed during 2011-2016 and 2009-2014, respectively. Patient characteristics are shown in **Table 5**. The mean ages were 70-72 years, with patients ≥70 years comprising 52.6%-59.5% of the diagnosed cases. Around half of the patients (47.2%-52.6%) were female. Most patients had pancreatic head tumors (67.8%-74.7%). Metastatic diseases were most commonly diagnosed with proportions between 54.5% (the US) and 72.8% (Slovenia), whereas stage I-II cancers only comprised 18.8% (Slovenia) to 36.2% (the US). Stage was missing for 10.5%-26.5% of patients in investigated countries except Belgium (40.1%), and the missingness was mostly associated with patient age and tumor location (**Table 6**). Overall, resection rates ranged from 13.0% (Estonia) to 21.7% (Belgium). Chemotherapy was administered to 15.0% (Estonia) to 57.3% (Belgium) of patients. Radiotherapy was less frequently used (1.9% (Slovenia) to 6.9% (Belgium)).

Table 4. General information on participating registries for Chapter 3.1.1 (Huang *et al.*, 2017)

Source	Country	Year of diagnosis	Registered primary cases[1]	Excluded cases[2]		Analyzed cases
				DCO/autopsy	TNM stage 0	
SEER-18[3]	The US	Jan. 2004-Dec. 2013	99582	2972 (3.0)	37 (0.0)	96573
NCR	The Netherlands	Jan. 2003-Dec. 2014	22579	99 (0.4)	2 (0.0)	22478
BCR	Belgium	Jan. 2004-Dec. 2013	12146	NA	1 (0.0)	12145
CRN	Norway	Jan. 2003-Dec. 2014	8022	333 (4.2)	3 (0.0)	7686
DPCD	Denmark	May 2011-May 2016	4088	NA	2 (0.0)	4086
CRS	Slovenia	Jan. 2003-Dec. 2013	3376	54 (1.6)	0 (0.0)	3322
ECR	Estonia	Jan. 2009-Dec. 2014	1509	99 (6.6)	0 (0.0)	1410

[1]A preliminary data-cleaning process had been performed to exclude cases with ineligible histology types.

[2]Shown as n (percentage [%]).

[3]Data of the year 2003 were not analyzed, as the TNM stage (version 6/7) information was unavailable.

SEER, Surveillance, Epidemiology, and End Results Program; NCR, Netherlands Cancer Registry; BCR, Belgian Cancer Registry; CRN, Cancer Registry of Norway; DPCD, Danish Pancreatic Cancer Database; CRS, Cancer Registry of Slovenia; ECR, Estonian Cancer Registry; DCO, death certificate only; NA, not applicable due to not routinely registered.

Table 5. Demographic and clinical characteristics of overall pancreatic cancer patients[1] (Huang *et al.*, 2017)

Parameter	The US	The Netherlands	Belgium	Norway	Denmark	Slovenia	Estonia
Incidence period	2004-2013	2003-2014	2004-2013	2003-2014	2011-2016	2003-2013	2009-2014
n	96573	22478	12145	7686	4086	3322	1410
Sex, female	48317 (50.0)	11184 (49.8)	5902 (48.6)	3973 (51.7)	2149 (52.6)	1691 (50.9)	665 (47.2)
Age [year]	70 ± 12	70 ± 11	70 ± 11	72 ± 12	70 ± 10	70 ± 11	71 ± 11
Age group							
< 60 years	19676 (20.4)	4199 (18.7)	2207 (18.2)	1155 (15.0)	619 (15.2)	625 (18.8)	230 (16.3)
60-69 years	24334 (25.2)	6425 (28.6)	3176 (26.2)	1956 (25.5)	1319 (32.3)	810 (24.4)	370 (26.2)
70-79 years	27073 (28.0)	7320 (32.6)	4192 (34.5)	2268 (29.5)	1490 (36.5)	1120 (33.7)	493 (35.0)
≥ 80 years	25490 (26.4)	4534 (20.2)	2570 (21.2)	2307 (30.0)	658 (16.1)	767 (23.1)	317 (22.5)
Tumor location[2]							
Pancreas head	46734 (67.8)	13997 (72.3)	4087 (68.9)	2673 (72.9)	2134 (68.8)	1445 (74.7)	754 (68.3)
Pancreas body	10769 (15.6)	2288 (11.8)	815 (13.7)	492 (13.4)	508 (16.3)	226 (11.7)	213 (19.3)
Pancreas tail	11453 (16.6)	3079 (15.9)	1034 (17.4)	490 (13.4)	462 (14.9)	264 (13.6)	137 (12.4)
Other	27617 (28.6)	3114 (13.8)	6209 (51.1)	4021 (52.4)	982 (24.0)	1387 (41.8)	306 (21.7)
cTNM stage[3]							
I-II	31313 (36.2)	5184 (27.2)	2123 (29.2)	1545 (25.0)	801 (26.7)	457 (18.8)	283 (25.2)
III	8033 (9.3)	1937 (10.1)	936 (12.9)	395 (6.4)	419 (13.9)	205 (8.4)	118 (10.5)
IV	47120 (54.5)	11993 (62.7)	4217 (58.0)	4238 (68.6)	1785 (59.4)	1773 (72.8)	721 (64.3)
Resection	15628 (16.2)	2945 (13.1)	2630 (21.7)	1005 (13.1)	690 (16.9)	602 (18.1)	183 (13.0)
Chemotherapy	NA	5061 (22.5)	6958 (57.3)	1567 (20.4)	2164 (53.0)	581 (17.5)	211 (15.0)
Radiotherapy	5282 (5.5)	510 (2.3)	836 (6.9)	319 (4.2)	149 (3.7)	64 (1.9)	34 (2.4)

[1]Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below.

[2]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of pancreas head, body, and tail; other: pancreas duct, overlapping lesion, NOS, and other specified parts.

[3]Unknown cTNM stage: the US, 10107 (10.5%); the Netherlands, 3364 (15.0%); Belgium, 4869 (40.1%); Norway, 1508 (19.6%); Denmark, 1081 (26.5%); Slovenia, 887 (26.5%); and Estonia, 288 (20.4%). For the US, Norway, and Estonia, the stage is a combination of clinical and pathological ones. The summary stage was used to help retrieve missing TNM stages.

NOS, not otherwise specified; NA, not available.

Table 6. Association of missing versus available TNM stages with demographic, clinical, and therapeutic parameters for pancreatic cancer patients estimated by multivariable logistic regression (Huang *et al.*, 2017)

Parameter	The US (n = 96573)	The Netherlands (n = 22478)	Belgium (n = 12145)	Norway (n = 7686)	Denmark (n = 4086)	Slovenia (n = 3322)	Estonia (n = 1410)
	OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Year of diagnosis	**0.94** (0.94-0.95)	**0.89** (0.88-0.90)	**0.94** (0.93-0.95)	**1.02** (1.00-1.04)	**1.26** (1.20-1.32)	**0.97** (0.95-1.00)	**0.83** (0.77-0.90)
Sex							
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	**0.91** (0.87-0.95)	1.04 (0.97-1.13)	1.01 (0.94-1.09)	1.06 (0.95-1.19)	1.06 (0.92-1.22)	0.89 (0.76-1.05)	0.79 (0.59-1.04)
Age group							
< 60 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60-69 years	**1.20** (1.10-1.31)	**1.23** (1.08-1.39)	**0.84** (0.75-0.94)	1.15 (0.94-1.42)	1.10 (0.87-1.38)	1.10 (0.86-1.41)	0.95 (0.58-1.53)
70-79 years	**1.75** (1.62-1.90)	**1.71** (1.52-1.93)	**0.89** (0.80-0.99)	**1.41** (1.16-1.72)	**1.27** (1.01-1.59)	1.01 (0.80-1.27)	**1.57** (1.01-2.43)
≥ 80 years	**4.54** (4.22-4.89)	**2.49** (2.20-2.83)	0.93 (0.83-1.05)	**2.14** (1.77-2.60)	**1.90** (1.47-2.44)	**1.46** (1.14-1.87)	**3.61** (2.29-5.71)
Tumor location							
Pancreas head	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Pancreas body	**0.54** (0.48-0.60)	**0.46** (0.39-0.54)	**0.60** (0.50-0.71)	**0.57** (0.43-0.75)	1.09 (0.87-1.36)	**0.45** (0.32-0.64)	**0.62** (0.40-0.96)
Pancreas tail	**0.35** (0.30-0.39)	**0.24** (0.20-0.28)	**0.68** (0.59-0.79)	**0.38** (0.28-0.53)	0.88 (0.69-1.12)	**0.26** (0.18-0.38)	0.58 (0.33-1.00)
Other[2]	**4.13** (3.94-4.33)	**0.70** (0.63-0.78)	**1.39** (1.28-1.51)	0.89 (0.79-1.00)	**1.30** (1.09-1.54)	**0.52** (0.44-0.62)	1.03 (0.74-1.43)

[1]Odds ratios and 95% confidence intervals for missing versus available TNM stages were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, and tumor location. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, NOS, and other specified parts.

OR, odds ratio; CI, confidence interval; NOS, not otherwise specified.

3.1.1.2 Characteristics of resected patients

Together only 16.0% (23,683/147,700) of the investigated PaC patients underwent resection (**Table 7**). Resected patients were younger (mean age, 65-67 years) than the overall patients. Only 36.9%-43.8% were ≥70 years. Most patients had stage I-II cancers (75.1% (Slovenia) to 92.4% (Denmark)). Pancreatic head cancers were more frequent among resected patients (78.7%-87.7%). Patients with pancreatic head cancers had the greatest proportion of stage I-II tumors, and those with tail cancers had the largest proportion of metastatic lesions. Neoadjuvant chemotherapy (0.3%-4.2%) and radiotherapy (0.1%-4.3%) were rarely administered in countries with available information. Pancreatoduodenectomy was the most common surgical approach (68.6% (Denmark) to 83.9% (the Netherlands)). Adjuvant chemotherapy use varied strongly with proportions between 12.0% (Estonia) and 55.7% (Denmark). Adjuvant radiotherapy was more frequently used in the US (29.5%) than in Europe, where the proportions ranged from 0.1% (Denmark) to 8.9% (Belgium).

Table 7. Demographic and clinical characteristics of resected pancreatic cancer patients[1] (Huang *et al.*, 2017)

Parameter	The US	The Netherlands	Belgium	Norway	Denmark	Slovenia	Estonia
n	15628	2945	2630	1005	690	602	183
Sex, female	7738 (49.5)	1387 (47.1)	1217 (46.3)	471 (46.9)	358 (51.9)	293 (48.7)	87 (47.5)
Age [year]	66 ± 11	65 ± 10	66 ± 10	66 ± 11	67 ± 9	65 ± 10	66 ± 10
Age group							
< 60 years	4290 (27.5)	773 (26.3)	691 (26.3)	253 (25.2)	129 (18.7)	175 (29.1)	37 (20.2)
60-69 years	4982 (31.9)	1086 (36.9)	848 (32.2)	367 (36.5)	259 (37.5)	201 (33.4)	69 (37.7)
70-79 years	4708 (30.1)	969 (32.9)	915 (34.8)	323 (32.1)	252 (36.5)	197 (32.7)	68 (37.2)
≥ 80 years	1648 (10.5)	117 (4.0)	176 (6.7)	62 (6.2)	50 (7.3)	29 (4.8)	9 (4.9)
Tumor location[2]							
Pancreas head	10730 (78.7)	2375 (87.7)	1374 (79.6)	729 (83.3)	521 (85.3)	435 (85.8)	128 (79.5)
Pancreas body	1065 (7.8)	106 (3.9)	127 (7.3)	65 (7.4)	19 (3.1)	38 (7.5)	17 (10.6)
Pancreas tail	1845 (13.5)	228 (8.4)	226 (13.1)	81 (9.3)	71 (11.6)	34 (6.7)	16 (9.9)
Other	1988 (12.7)	236 (8.0)	903 (34.3)	130 (12.9)	79 (11.5)	95 (15.8)	22 (12.0)
TNM stage[3]							
I-II	13303 (86.9)	2675 (91.9)	2155 (87.9)	526 (83.0)	635 (92.4)	406 (75.1)	159 (89.8)
III	767 (5.0)	148 (5.1)	146 (6.0)	30 (4.7)	37 (5.4)	46 (8.5)	11 (6.2)
IV	1231 (8.1)	89 (3.1)	152 (6.2)	78 (12.3)	15 (2.2)	89 (16.5)	7 (4.0)
Neoadjuvant chemotherapy	NA	65 (2.2)	82 (3.1)	NA	29 (4.2)	2 (0.3)	NA
Neoadjuvant radiotherapy	677 (4.3)	39 (1.3)	32 (1.2)	NA	6 (0.9)	1 (0.2)	NA
Resection type							
Pancreatoduodenectomy	10759 (68.8)	2472 (83.9)	NA	NA	473 (68.6)	NA	NA
Distal pancreatectomy	2208 (14.1)	298 (10.1)	NA	NA	90 (13.0)	NA	NA
Total pancreatectomy	1855 (11.9)	48 (1.6)	NA	NA	127 (18.4)	NA	NA
Other[4]	806 (5.2)	127 (4.3)	NA	NA	0 (0.0)	NA	NA
Adjuvant chemotherapy	NA	1167 (39.6)	1446 (55.0)	193 (19.2)	384 (55.7)	172 (28.6)	22 (12.0)
Adjuvant radiotherapy	4610 (29.5)	40 (1.4)	234 (8.9)	33 (3.3)	1 (0.1)	14 (2.3)	12 (6.6)

[1]Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below.

[2]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of pancreas head, body, and tail; other: pancreas duct, overlapping lesion, NOS, and other specified parts.

[3]Unkown TNM stage: the US, 327 (2.1%); the Netherlands, 33 (1.1%); Belgium, 177 (6.7%); Norway, 371 (36.9%); Denmark, 3 (0.4%); Slovenia, 61 (10.1%); and Estonia, 6 (3.3%).

[4]Pancreatectomy (NOS) and local resection.

NOS, not otherwise specified; NA, not available.

Characteristics of resected patients by cancer stage were further described (**Tables 8-11**). Operated patients with stage I-II cancers were mostly older than those with stage III-IV tumors (mean age, 65-68 *vs.* 64-66 years). There was generally a greater proportion of pancreatic head tumors in stage I-II PaCs than in stage III-IV diseases (79.4%-88.6% *vs.* 66.1%-85.3%). Compared to stage IV cancer, resected stage III PaC was more often located in pancreas head (75.4%-94.1% *vs.* 59.0%-75.8%). Accordingly, pancreatoduodenectomy was more frequently performed for stage III PaC than for stage IV disease (66.9%-80.4% *vs.* 50.9%-66.3%).

Table 8. Demographic and clinical characteristics of resected stage I-II cancer patients[1] (Huang *et al.*, 2017)

Parameter	The US	Netherlands	Belgium	Norway	Denmark	Slovenia	Estonia
n	13303	2675	2155	526	635	406	159
Sex, female	6604 (49.6)	1268 (47.4)	993 (46.1)	261 (49.6)	33.0 (52.0)	209 (51.5)	76 (47.8)
Age [year]	66 ± 11	65 ± 10	66 ± 10	65 ± 11	68 ± 9	65 ± 10	67 ± 10
Age group							
< 60 years	3574 (26.9)	693 (25.9)	546 (25.3)	134 (25.5)	112 (17.6)	122 (30.1)	32 (20.1)
60-69 years	4272 (32.1)	978 (36.6)	698 (32.4)	195 (37.1)	239 (37.6)	131 (32.3)	60 (37.7)
70-79 years	4073 (30.6)	892 (33.4)	762 (35.4)	170 (32.3)	235 (37.0)	138 (34.0)	58 (36.5)
≥ 80 years	1384 (10.4)	112 (4.2)	149 (6.9)	27 (5.1)	49 (7.7)	15 (3.7)	9 (5.7)
Tumor location[2]							
Pancreas head	9573 (80.4)	2187 (88.6)	1207 (79.6)	394 (83.3)	479 (85.4)	321 (87.2)	112 (79.4)
Pancreas body	890 (7.5)	91 (3.7)	100 (7.3)	33 (7.4)	17 (3.0)	26 (7.1)	16 (11.4)
Pancreas tail	1448 (12.2)	191 (7.7)	169 (13.1)	41 (9.3)	65 (11.6)	21 (5.7)	13 (9.2)
Other	1392 (10.5)	206 (7.7)	679 (31.5)	58 (11.0)	74 (11.7)	38 (9.4)	18 (11.3)
Neoadjuvant chemotherapy	NA	50 (1.9)	53 (2.5)	NA	26 (4.1)	2 (0.5)	NA
Neoadjuvant radiotherapy	522 (3.9)	34 (1.3)	20 (0.9)	NA	6 (0.9)	1 (0.3)	NA
Resection type							
Pancreatoduodenectomy	9479 (71.3)	2269 (84.8)	NA	NA	436 (68.7)	NA	NA
Distal pancreatectomy	1878 (14.1)	256 (9.6)	NA	NA	82 (12.9)	NA	NA
Total pancreatectomy	1629 (12.3)	42 (1.6)	NA	NA	117 (18.4)	NA	NA
Other[3]	317 (2.4)	108 (4.0)	NA	NA	0 (0.0)	NA	NA
Adjuvant chemotherapy	NA	1078 (40.3)	1200 (55.7)	127 (24.1)	355 (55.9)	120 (29.6)	18 (11.3)
Adjuvant radiotherapy	4193 (31.5)	33 (1.2)	190 (8.8)	17 (3.2)	1 (0.2)	8 (2.0)	11 (6.9)

[1]Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below.

[2]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of pancreas head, body, and tail; other: pancreas duct, overlapping lesion, NOS, and other specified parts.

[3]Pancreatectomy (NOS) and local resection.

SEER, Surveillance, Epidemiology, and End Results Program; NCR, Netherlands Cancer Registry; BCR, Belgian Cancer Registry; CRN, Cancer Registry of Norway; DPCD, Danish Pancreatic Cancer Database; CRS, Cancer Registry of Slovenia; NOS, not otherwise specified; NA, not available.

Table 9. Demographic and clinical characteristics of resected stage III-IV cancer patients[1] (Huang *et al.*, 2017)

Parameter	The US	Netherlands	Belgium	Norway	Denmark	Slovenia	Estonia
n	1998	237	298	108	52	135	18
Sex, female	969 (48.5)	106 (44.7)	154 (51.9)	47 (43.5)	28 (53.9)	56 (41.5)	9 (50.0)
Age [year]	65 ± 12	64 ± 10	64 ± 10	64 ± 10	64 ± 10	65 ± 10	66 ± 8
Age group							
< 60 years	636 (31.8)	69 (29.1)	92 (30.9)	32 (29.6)	15 (28.9)	40 (29.6)	3 (16.7)
60-69 years	622 (31.1)	96 (40.5)	103 (34.6)	43 (39.8)	19 (36.5)	45 (33.3)	8 (44.4)
70-79 years	550 (27.5)	68 (28.7)	90 (30.2)	26 (24.1)	17 (32.7)	43 (31.9)	7 (38.9)
≥ 80 years	190 (9.5)	4 (1.7)	13 (4.4)	7 (6.5)	1 (1.9)	7 (5.2)	0 (0.0)
Tumor location[2]							
Pancreas head	1069 (66.1)	166 (78.7)	126 (69.2)	57 (66.3)	42 (85.3)	80 (78.4)	12 (75.0)
Pancreas body	168 (10.4)	11 (5.2)	19 (10.4)	8 (9.3)	1 (3.1)	12 (11.8)	1 (6.3)
Pancreas tail	381 (23.5)	34 (16.1)	37 (20.3)	21 (24.4)	5 (11.6)	10 (9.8)	3 (18.8)
Other	380 (19.0)	26 (11.0)	116 (38.9)	22 (20.4)	4 (7.7)	33 (24.4)	2 (11.1)
Neoadjuvant chemotherapy	NA	15 (6.3)	24 (8.1)	NA	2 (3.9)	0 (0.0)	NA
Neoadjuvant radiotherapy	139 (7.0)	5 (2.1)	9 (3.0)	NA	0 (0.0)	0 (0.0)	NA
Resection type							
Pancreatoduodenectomy	1140 (57.1)	178 (75.1)	NA	NA	37 (71.2)	NA	NA
Distal pancreatectomy	295 (14.8)	39 (16.5)	NA	NA	7 (13.5)	NA	NA
Total pancreatectomy	211 (10.6)	5 (2.1)	NA	NA	8 (15.4)	NA	NA
Other[3]	352 (17.6)	15 (6.3)	NA	NA	0 (0.0)	NA	NA
Adjuvant chemotherapy	NA	81 (34.2)	195 (65.4)	25 (23.2)	28 (53.9)	39 (28.9)	4 (22.2)
Adjuvant radiotherapy	383 (19.2)	7 (3.0)	35 (11.7)	4 (3.7)	0 (0.0)	5 (3.7)	1 (5.6)

[1]Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below.

[2]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of pancreas head, body, and tail; other: pancreas duct, overlapping lesion, NOS, and other specified parts.

[3]Pancreatectomy (NOS) and local resection.

SEER, Surveillance, Epidemiology, and End Results Program; NCR, Netherlands Cancer Registry; BCR, Belgian Cancer Registry; CRN, Cancer Registry of Norway; DPCD, Danish Pancreatic Cancer Database; CRS, Cancer Registry of Slovenia; NOS, not otherwise specified; NA, not available.

Table 10. Demographic and clinical characteristics of resected stage III cancer patients[1] (Huang *et al.*, 2017)

Parameter	The US	Netherlands	Belgium	Norway	Denmark	Slovenia	Estonia
n	767	148	146	30	37	46	11
Sex, female	364 (47.5)	65 (43.9)	73 (50.0)	13 (43.3)	19 (51.4)	21 (45.7)	7 (63.6)
Age [year]	65 ± 11	65 ± 10	64 ± 10	66 ± 7	66 ± 9	63 ± 11	66 ± 9
Age group							
< 60 years	229 (29.9)	40 (27.0)	50 (34.3)	5 (16.7)	8 (21.6)	16 (34.8)	2 (18.2)
60-69 years	262 (34.2)	58 (39.2)	43 (29.5)	16 (53.3)	15 (40.5)	13 (28.3)	4 (36.4)
70-79 years	215 (28.0)	46 (31.1)	48 (32.9)	8 (26.7)	13 (35.1)	16 (34.8)	5 (45.5)
≥ 80 years	61 (8.0)	4 (2.7)	5 (3.4)	1 (3.3)	1 (2.7)	1 (2.2)	0 (0.0)
Tumor location[2]							
Pancreas head	487 (75.4)	112 (84.8)	70 (76.1)	21 (84.0)	32 (94.1)	33 (82.5)	8 (80.0)
Pancreas body	68 (10.5)	4 (3.0)	11 (12.0)	2 (8.0)	0 (0.0)	4 (10.0)	0 (0.0)
Pancreas tail	91 (14.1)	16 (12.1)	11 (12.0)	2 (8.0)	2 (5.9)	3 (7.5)	2 (20.0)
Other	121 (15.8)	16 (10.8)	54 (37.0)	5 (16.7)	3 (8.1)	6 (13.0)	1 (9.1)
Neoadjuvant chemotherapy	NA	12 (8.1)	17 (11.6)	NA	2 (5.4)	0 (0.0)	NA
Neoadjuvant radiotherapy	116 (15.1)	5 (3.4)	8 (5.5)	NA	0 (0.0)	0 (0.0)	NA
Resection type							
Pancreatoduodenectomy	513 (66.9)	119 (80.4)	NA	NA	28 (75.7)	NA	NA
Distal pancreatectomy	82 (10.7)	18 (12.2)	NA	NA	3 (8.1)	NA	NA
Total pancreatectomy	93 (12.1)	2 (1.4)	NA	NA	6 (16.2)	NA	NA
Other[3]	79 (10.3)	9 (6.1)	NA	NA	0 (0.0)	NA	NA
Adjuvant chemotherapy	NA	59 (39.9)	96 (65.8)	7 (23.3)	18 (48.7)	13 (28.3)	1 (9.1)
Adjuvant radiotherapy	257 (33.5)	6 (4.1)	28 (19.2)	1 (3.3)	0 (0.0)	3 (6.5)	1 (9.1)

[1]Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Results for stage IV cancers in Estonia are not presented due to limited case number (n = 7). Records are complete otherwise specified below.

[2]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of pancreas head, body, and tail; other: pancreas duct, overlapping lesion, NOS, and other specified parts.

[3]Pancreatectomy (NOS) and local resection.

SEER, Surveillance, Epidemiology, and End Results Program; NCR, Netherlands Cancer Registry; BCR, Belgian Cancer Registry; CRN, Cancer Registry of Norway; DPCD, Danish Pancreatic Cancer Database; CRS, Cancer Registry of Slovenia; NOS, not otherwise specified; NA, not available.

Table 11. Demographic and clinical characteristics of resected stage IV cancer patients[1] (Huang *et al.*, 2017)

Parameter	The US	Netherlands	Belgium	Norway	Denmark	Slovenia
n	1231	89	152	78	15	89
Sex, female	605 (49.2)	41 (46.1)	81 (53.3)	34 (43.6)	9 (60.0)	35 (39.3)
Age [year]	65 ± 12	63 ± 9	64 ± 10	64 ± 11	61 ± 11	66 ± 10
Age group						
< 60 years	407 (33.1)	29 (32.6)	42 (27.6)	27 (34.6)	7 (46.7)	24 (27.0)
60-69 years	360 (29.2)	38 (42.7)	60 (39.5)	27 (34.6)	4 (26.7)	32 (36.0)
70-79 years	335 (27.2)	22 (24.7)	42 (27.6)	18 (23.1)	4 (26.7)	27 (30.3)
≥ 80 years	129 (10.5)	0 (0.0)	8 (5.3)	6 (7.7)	0 (0.0)	6 (6.7)
Tumor location[2]						
Pancreas head	582 (59.9)	54 (68.4)	56 (62.2)	36 (59.0)	10 (71.4)	47 (75.8)
Pancreas body	100 (10.3)	7 (8.9)	8 (8.9)	6 (9.8)	1 (7.1)	8 (12.9)
Pancreas tail	290 (29.8)	18 (22.8)	26 (28.9)	19 (31.1)	3 (21.4)	7 (11.3)
Other	259 (21.0)	10 (11.2)	62 (40.8)	17 (21.8)	1 (6.7)	27 (30.3)
Neoadjuvant chemotherapy	NA	3 (3.4)	7 (4.6)	NA	0 (0.0)	0 (0.0)
Neoadjuvant radiotherapy	23 (1.9)	0 (0.0)	1 (0.7)	NA	0 (0.0)	0 (0.0)
Resection type						
Pancreatoduodenectomy	627 (50.9)	59 (66.3)	NA	NA	9 (60.0)	NA
Distal pancreatectomy	213 (17.3)	21 (23.6)	NA	NA	4 (26.7)	NA
Total pancreatectomy	118 (9.6)	3 (3.4)	NA	NA	2 (13.3)	NA
Other[3]	273 (22.2)	6 (6.7)	NA	NA	0 (0.0)	NA
Adjuvant chemotherapy	NA	22 (24.7)	99 (65.1)	18 (23.1)	10 (66.7)	26 (29.2)
Adjuvant radiotherapy	126 (10.2)	1 (1.1)	7 (4.6)	3 (3.9)	0 (0.0)	2 (2.3)

[1]Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Results for stage IV cancers in Estonia are not presented due to limited case number (n = 7). Records are complete otherwise specified below.

[2]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of pancreas head, body, and tail; other: pancreas duct, overlapping lesion, NOS, and other specified parts.

[3]Pancreatectomy (NOS) and local resection.

SEER, Surveillance, Epidemiology, and End Results Program; NCR, Netherlands Cancer Registry; BCR, Belgian Cancer Registry; CRN, Cancer Registry of Norway; DPCD, Danish Pancreatic Cancer Database; CRS, Cancer Registry of Slovenia; NOS, not otherwise specified; NA, not available.

3.1.1.3 Resection trends and rates

As shown in **Figure 1**, overall resection rates increased over time in the US (2003-2004 to 2013-2014: 14.1% to 17.0%; P_{trend}<0.001), the Netherlands (2003-2004 to 2013-2014: 8.2% to 17.9%; P_{trend}<0.001), and Denmark (2011-2012 to 2013-2014: 12.0% to 17.6%; P_{trend}=0.007), while no significant trends were observed in Belgium (P_{trend}=0.270), Norway (P_{trend}=0.102), Slovenia (P_{trend}=0.092), or Estonia (P_{trend}=0.406). Starting from as early as 1973 and 1953, respectively, trends of increasing resection rates were observed in the US (5.5%-17.8%) and Norway (5.1%-18.4%) in overall patients (results not shown). When focusing on the period 2012-2014, resection rates ranged from 13.2% (Estonia) to 21.2% (Slovenia). For the subgroup of stage I-II tumors, increasing trends

were observed in the US (2003-2004 to 2013-2014: 39.4% to 44.0%; P_{trend}<0.001), the Netherlands (2003-2004 to 2013-2014: 32.6% to 58.2%; P_{trend}<0.001), and Denmark (2011-2012 to 2013-2014: 60.5% to 70.1%; P_{trend}=0.017), while no significant trends were observed in Belgium (P_{trend}=0.726), Norway (P_{trend}=0.675), Slovenia (P_{trend}=0.596), or Estonia (P_{trend}=0.406). In 2012-2014, the proportions of resected patients ranged from 34.8% (Norway) to 68.7% (Denmark).

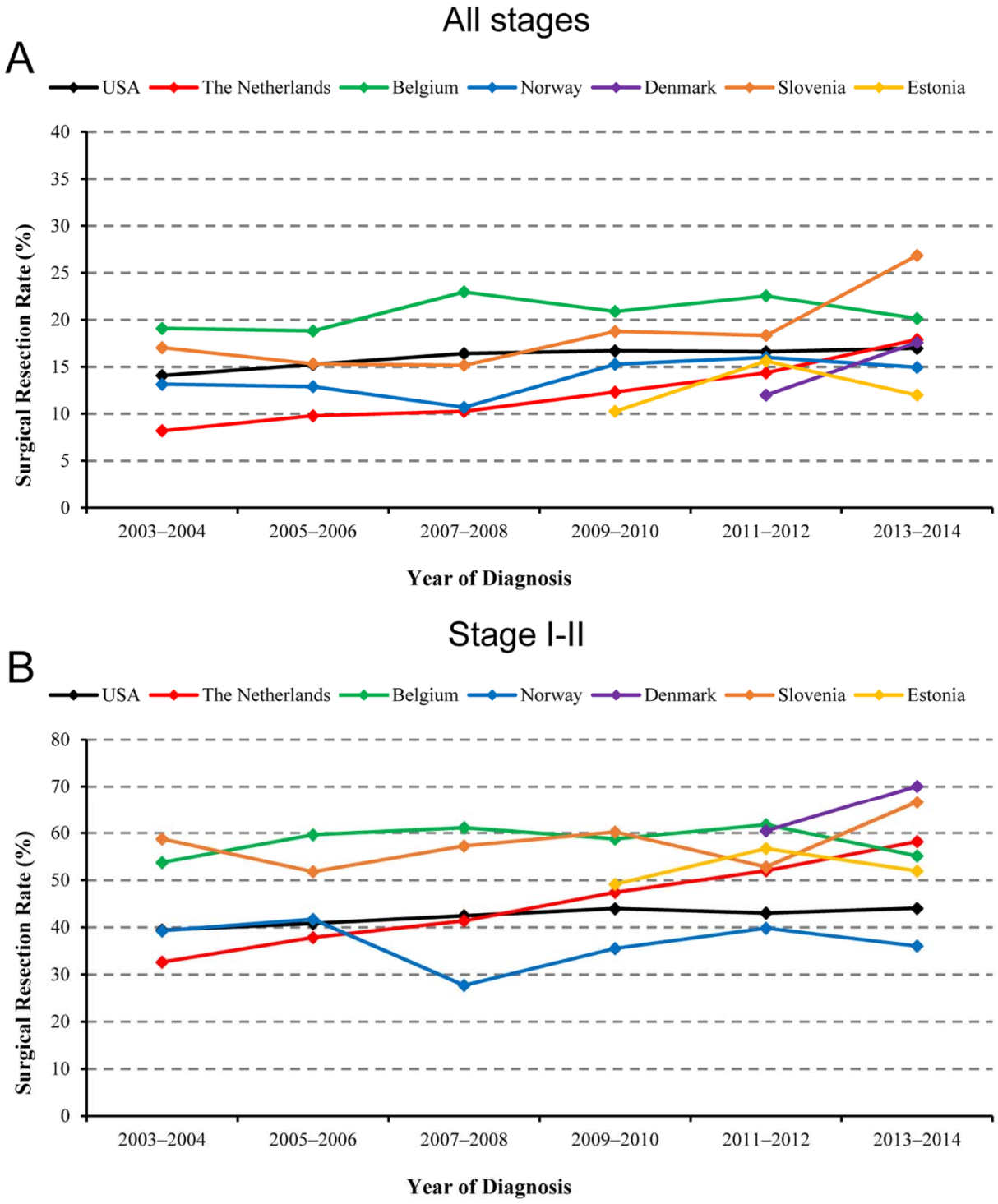

Figure 1. Age-standardized resection trends for overall pancreatic cancer patients (**A**) and those with TNM stage I-II tumors (**B**). The US cancer population was used for age standardization. (Huang *et al.*, 2017)

3.1.1.4 Association of resection with demographic and clinical parameters

Association of resection with demographic and clinical variables in each country was investigated using a multivariable model including year of diagnosis, patient sex, age, cancer location, and stage (**Table 12**). While resection was not significantly associated with sex, it was less frequently conducted with increasing age and more advanced cTNM stage. Specifically, compared to patients <60 years, the ORs for resection among patients aged 70-79 and ≥80 years ranged between 0.37 (the Netherlands) and 0.63 (Estonia) and between 0.03 (the Netherlands) and 0.16 (the US), respectively. Compared to stage I-II cancers, the ORs of stages III and IV cancers were 0.05-0.18 and 0.01-0.06, respectively. Resection was significantly less frequently conducted in pancreatic body cancers than head tumors in all countries except Slovenia and Estonia, with ORs ranging from 0.22 (Denmark) to 0.65 (the US). Pancreatic tail cancers were significantly more often resected than pancreatic head tumors in the US (OR=1.99), the Netherlands (OR=1.47), Norway (OR=1.70), Denmark (OR=2.46), and Estonia (OR=3.18), while no significant associations were observed in Belgium. In Slovenia, even an opposite pattern was detected (OR=0.49). After multiple imputations for missing stages, patterns remained unchanged (**Table 13**).

Table 12. Association of resection versus non-resection with demographic and clinical parameters for pancreatic cancer patients estimated by multivariable logistic regression (Huang *et al.*, 2017)

Parameter	The US (n = 86466)[1]	The Netherlands (n = 19114)	Belgium (n = 7276)	Norway (n = 6178)	Denmark (n = 3005)	Slovenia (n = 2435)	Estonia (n = 1122)
	OR (95% CI)[2]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Year of diagnosis	**1.01** (1.01-1.02)	**1.15** (1.13-1.17)	1.01 (0.98-1.04)	0.98 (0.95-1.01)	**1.14** (1.03-1.26)	1.04 (1.00-1.09)	1.01 (0.88-1.16)
Sex							
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	0.97 (0.93-1.01)	1.02 (0.91-1.15)	1.08 (0.91-1.27)	1.18 (0.95-1.46)	1.10 (0.82-1.47)	0.99 (0.74-1.32)	1.05 (0.65-1.68)
Age group							
< 60 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60-69 years	**0.84** (0.80-0.89)	**0.76** (0.64-0.89)	**0.72** (0.57-0.91)	0.82 (0.61-1.09)	0.71 (0.45-1.13)	0.82 (0.56-1.19)	1.14 (0.58-2.25)
70-79 years	**0.59** (0.56-0.63)	**0.37** (0.32-0.44)	**0.43** (0.34-0.54)	**0.44** (0.33-0.59)	**0.56** (0.35-0.88)	**0.46** (0.32-0.67)	0.63 (0.32-1.22)
≥ 80 years	**0.16** (0.15-0.17)	**0.03** (0.03-0.04)	**0.08** (0.06-0.12)	**0.05** (0.04-0.08)	**0.15** (0.09-0.26)	**0.05** (0.03-0.09)	**0.08** (0.03-0.19)
Tumor location							
Pancreas head	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Pancreas body	**0.65** (0.60-0.70)	**0.49** (0.38-0.64)	**0.60** (0.43-0.83)	**0.52** (0.35-0.78)	**0.22** (0.12-0.41)	0.77 (0.47-1.27)	0.92 (0.43-1.95)
Pancreas tail	**1.99** (1.85-2.14)	**1.47** (1.17-1.86)	1.07 (0.78-1.47)	**1.70** (1.16-2.50)	**2.46** (1.36-4.47)	**0.49** (0.28-0.87)	**3.18** (1.20-8.45)
Other[3]	**0.67** (0.63-0.71)	**0.63** (0.51-0.78)	**0.46** (0.38-0.56)	**0.15** (0.12-0.20)	**0.59** (0.39-0.89)	**0.29** (0.20-0.41)	0.60 (0.30-1.20)
cTNM stage[4]							
I-II	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
III	**0.12** (0.11-0.13)	**0.05** (0.04-0.06)	**0.12** (0.09-0.15)	**0.12** (0.08-0.19)	**0.05** (0.04-0.07)	**0.18** (0.12-0.29)	**0.06** (0.03-0.13)
IV	**0.03** (0.03-0.03)	**0.01** (< 0.01-0.01)	**0.02** (0.01-0.02)	**0.03** (0.02-0.04)	NE	**0.06** (0.04-0.08)	**0.01** (<0.01-0.01)

[1]Numbers in table heads indicate numbers of cases available for analyses after excluding the missing.

[2]Odds ratios and 95% confidence intervals for surgical resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and cTNM stage. ORs shown in bold are statistically significant.

[3]Other: pancreas duct, overlapping lesion, NOS, and other specified parts.

[4]For the US, Norway, and Estonia, TNM stage is a combination of clinical and pathological stages; NOS, not otherwise specified.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number.

Table 13. Association of resection versus non-resection with demographic and clinical parameters for pancreatic cancer patients estimated by multivariable logistic regression after multiple imputations for missing TNM stages[1] (Huang *et al.*, 2017)

Parameter	The US (n = 96573)	The Netherlands (n = 22478)	Norway (n = 7686)	Denmark (n = 4086)	Slovenia (n = 3322)	Estonia (n = 1410)
	OR (95% CI)[2]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Year of diagnosis	**1.01** (1.01-1.02)	**1.15** (1.13-1.17)	1.00 (0.97-1.03)	**1.12** (1.01-1.24)	**1.07** (1.03-1.12)	1.02 (0.90-1.17)
Sex						
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	0.98 (0.94-1.02)	1.08 (0.97-1.21)	1.18 (0.98-1.41)	1.08 (0.81-1.44)	0.91 (0.71-1.15)	1.11 (0.70-1.76)
Age group						
< 60 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60-69 years	**0.83** (0.78-0.88)	**0.73** (0.63-0.85)	**0.75** (0.58-0.97)	0.69 (0.44-1.08)	0.82 (0.60-1.12)	1.14 (0.58-2.21)
70-79 years	**0.57** (0.54-0.60)	**0.34** (0.29-0.40)	**0.43** (0.33-0.55)	**0.50** (0.32-0.79)	**0.40** (0.29-0.54)	0.60 (0.32-1.14)
≥ 80 years	**0.15** (0.14-0.16)	**0.03** (0.03-0.04)	**0.06** (0.04-0.08)	**0.15** (0.09-0.25)	**0.04** (0.03-0.07)	**0.06** (0.02-0.15)
Tumor location						
Pancreas head	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Pancreas body	**0.66** (0.61-0.72)	**0.47** (0.37-0.61)	**0.53** (0.38-0.76)	**0.20** (0.11-0.36)	0.68 (0.44-1.07)	0.91 (0.43-1.93)
Pancreas tail	**2.04** (1.90-2.19)	**1.44** (1.16-1.80)	**1.62** (1.14-2.30)	1.73 (0.97-3.06)	0.63 (0.39-1.00)	**2.70** (1.10-6.67)
Other[3]	**0.67** (0.63-0.71)	**0.78** (0.64-0.94)	**0.16** (0.13-0.20)	**0.25** (0.18-0.36)	**0.35** (0.26-0.46)	0.69 (0.35-1.34)
Imputed TNM stage[4]						
I-II	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
III	**0.12** (0.11-0.13)	**0.04** (0.03-0.05)	**0.08** (0.06-0.12)	**0.03** (0.02-0.04)	**0.14** (0.10-0.20)	**0.05** (0.02-0.09)
IV	**0.03** (0.03-0.03)	**0.01** (< 0.01-0.01)	**0.02** (0.02-0.03)	NE	**0.04** (0.03-0.05)	**<0.01** (<0.01-0.01)

[1]Variables applied in imputation of missing cTNM stages were: year of diagnosis, sex, age, tumor location, resection, chemotherapy, radiotherapy, and survival status and time.

[2]Odds ratios and 95% confidence intervals for surgical resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and cTNM stage. Multiple imputation was not performed for Belgium due to >30% missing TNM stages. ORs shown in bold are statistically significant.

[3]Other: pancreas duct, overlapping lesion, NOS, and other specified parts.

[4]For the US, Norway, and Estonia, TNM stage is a combination of clinical and pathological stages.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number.

Association patterns for stage I-II PaCs were mostly consistent with those for overall cancers (**Table 14**). Within stage III-IV PaCs, pancreatic tail cancers were significantly less frequently resected compared to pancreatic head tumors in the US (OR=0.83), the Netherlands (OR=0.63), and Belgium (OR=0.53); in Norway, Denmark, and Estonia, the original significant associations disappeared. Moreover, in the US male patients were significantly less often resected (OR=0.89). Resection rates were higher for stage III PaC than for stage IV disease in all countries (**Figure 2**). Resection patterns were mostly similar for stages III and IV cancers (**Table 15**). In the US (OR=2.28) and the Netherlands (OR=2.18), pancreatic tail cancers were more often resected compared to head tumors in stage III PaCs, but not in stage IV diseases. In Slovenia, pancreatic tail PaCs were less frequently resected compared to head tumors in stage IV cancers (OR=0.39), but not in stage III diseases. Association patterns were similar for pancreatic head, body, and tail cancers (data not shown).

Table 14. Association of resection versus non-resection with demographic and clinical variables for patients with cTNM stage I-II and III-IV pancreatic cancers estimated by multivariable logistic regression (Huang *et al.*, 2017)

Variable	The US	The Netherlands	Belgium	Norway	Denmark	Slovenia	Estonia
	OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
cTNM stage I-II[2]	n[3] = 31313	n = 5184	n = 2123	n = 1545	n = 801	n = 457	n = 283
Year of diagnosis	**1.02** (1.01-1.03)	**1.17** (1.15-1.19)	**1.04** (1.00-1.07)	0.98 (0.95-1.02)	**1.18** (1.05-1.32)	1.00 (0.92-1.07)	1.04 (0.89-1.23)
Sex							
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	1.00 (0.95-1.05)	1.03 (0.90-1.17)	1.12 (0.93-1.36)	1.16 (0.90-1.50)	1.09 (0.78-1.51)	0.72 (0.45-1.15)	0.97 (0.57-1.67)
Age group							
< 60 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60-69 years	**0.85** (0.80-0.91)	**0.74** (0.61-0.90)	**0.74** (0.56-0.99)	0.84 (0.58-1.21)	0.79 (0.46-1.35)	0.74 (0.37-1.47)	0.99 (0.44-2.24)
70-79 years	**0.57** (0.53-0.60)	**0.35** (0.29-0.41)	**0.43** (0.33-0.56)	**0.44** (0.31-0.63)	0.68 (0.40-1.14)	**0.29** (0.15-0.54)	0.51 (0.23-1.12)
≥ 80 years	**0.14** (0.13-0.15)	**0.03** (0.02-0.04)	**0.08** (0.06-0.12)	**0.05** (0.03-0.07)	**0.16** (0.09-0.30)	**0.01** (< 0.01-0.04)	**0.07** (0.03-0.20)
Tumor location							
Pancreas head	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Pancreas body	**0.72** (0.66-0.79)	**0.52** (0.39-0.71)	**0.57** (0.38-0.86)	**0.56** (0.34-0.91)	**0.24** (0.12-0.49)	1.44 (0.51-4.13)	1.52 (0.59-3.94)
Pancreas tail	**2.79** (2.52-3.08)	**1.62** (1.22-2.16)	1.17 (0.78-1.74)	**2.47** (1.31-4.66)	**2.65** (1.21-5.77)	0.58 (0.20-1.69)	NE
Other[4]	**0.70** (0.65-0.75)	**0.58** (0.46-0.74)	**0.46** (0.37-0.57)	**0.14** (0.10-0.19)	**0.54** (0.35-0.85)	**0.22** (0.12-0.39)	0.69 (0.32-1.50)
cTNM stage III-IV[2]	n = 55153	n = 13930	n = 5153	n = 4633	n = 2204	n = 1978	n = 839
Year of diagnosis	0.99 (0.97-1.01)	**1.06** (1.01-1.11)	**0.93** (0.88-0.98)	0.97 (0.92-1.03)	1.07 (0.88-1.30)	**1.07** (1.00-1.14)	0.99 (0.76-1.30)
Sex							
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	**0.89** (0.81-0.97)	0.92 (0.69-1.22)	0.85 (0.61-1.18)	1.20 (0.81-1.78)	1.18 (0.67-2.09)	1.18 (0.80-1.74)	1.16 (0.45-2.99)
Age group							
< 60 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60-69 years	**0.81** (0.73-0.91)	0.73 (0.52-1.03)	0.70 (0.46-1.04)	0.80 (0.50-1.28)	0.84 (0.41-1.74)	0.78 (0.48-1.25)	1.87 (0.48-7.26)
70-79 years	**0.69** (0.61-0.78)	**0.52** (0.36-0.75)	**0.49** (0.32-0.74)	**0.43** (0.26-0.74)	0.48 (0.22-1.07)	**0.56** (0.34-0.90)	1.20 (0.30-4.77)
≥ 80 years	**0.31** (0.26-0.36)	**0.02** (< 0.01-0.14)	**0.10** (0.04-0.25)	**0.13** (0.06-0.30)	**0.27** (0.08-0.98)	**0.24** (0.11-0.50)	NE
Tumor location							
Pancreas head	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Pancreas body	**0.41** (0.35-0.48)	**0.37** (0.21-0.66)	0.60 (0.33-1.08)	**0.45** (0.21-0.95)	**0.08** (0.01-0.60)	0.65 (0.35-1.21)	0.17 (0.02-1.33)
Pancreas tail	**0.83** (0.74-0.94)	**0.63** (0.42-0.94)	**0.53** (0.30-0.91)	1.08 (0.64-1.83)	0.58 (0.24-1.40)	**0.35** (0.18-0.70)	0.78 (0.22-2.84)
Other[4]	**0.44** (0.39-0.50)	**0.61** (0.39-0.95)	**0.36** (0.25-0.53)	**0.16** (0.10-0.27)	**0.37** (0.16-0.83)	**0.26** (0.17-0.41)	0.28 (0.06-1.29)

[1]Odds ratios and 95% confidence intervals for surgical resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, and tumor location. ORs shown in bold are statistically significant.

[2]For the US, Norway, and Estonia, TNM stage is a combination of clinical and pathological stages.

[3]Indicate numbers of cases available for analyses.

[4]Other: pancreas duct, overlapping lesion, NOS, and other specified parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number.

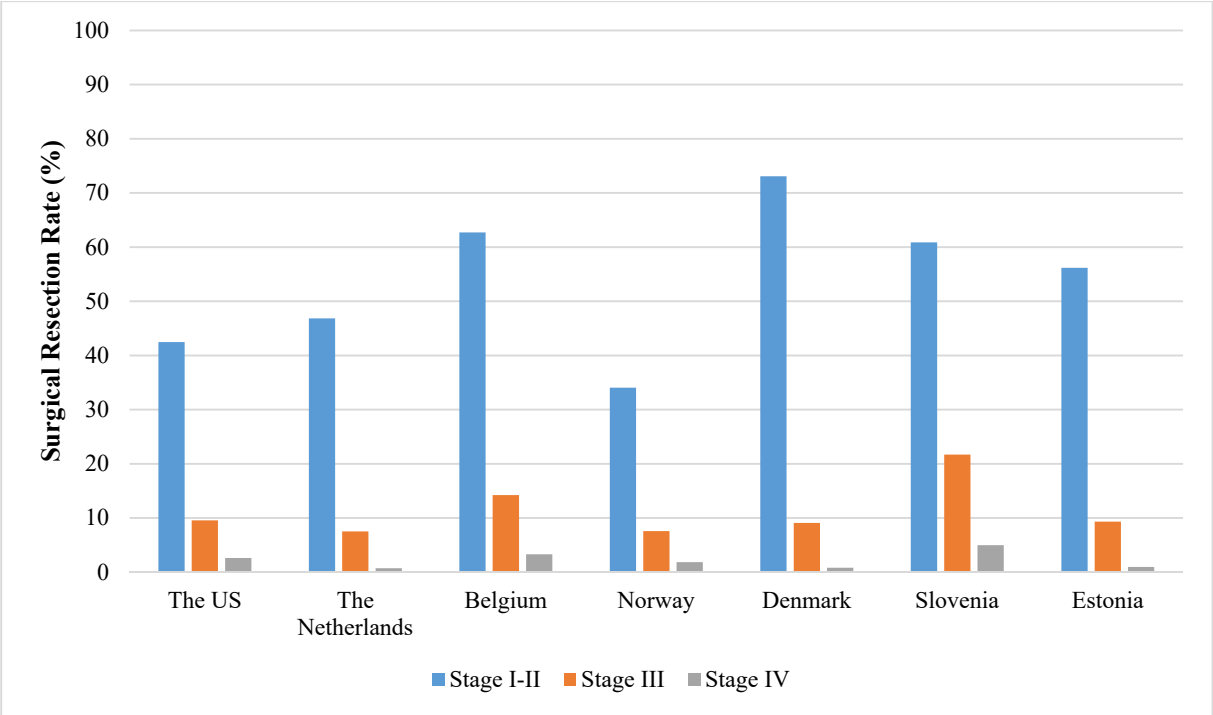

Figure 2. TNM stage-specific resection proportions for pancreatic cancer (Huang *et al.*, 2017)

Table 15. Association of resection versus non-resection with demographic and clinical variables for patients with cTNM stage III and IV pancreatic cancers estimated by multivariable logistic regression (Huang *et al.*, 2017)

Variable	Value	The US	The Netherlands	Belgium	Norway	Denmark	Slovenia
		OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
cTNM stage III[2]		N[3] = 8033	n = 1937	n = 936	n = 395	n = 419	n = 205
Year of diagnosis		**1.03** (1.00-1.06)	**1.09** (1.02-1.16)	0.95 (0.88-1.04)	0.90 (0.80-1.02)	1.03 (0.84-1.27)	**1.22** (1.05-1.41)
Sex	Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Male	1.01 (0.87-1.17)	1.17 (0.80-1.72)	1.11 (0.70-1.75)	1.73 (0.78-3.85)	1.18 (0.64-2.18)	1.25 (0.56-2.79)
Age group	< 60 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	60-69 years	0.93 (0.77-1.13)	0.79 (0.50-1.26)	0.76 (0.43-1.36)	1.87 (0.63-5.61)	0.56 (0.25-1.26)	0.41 (0.14-1.20)
	70-79 years	**0.76** (0.62-0.92)	0.73 (0.45-1.17)	**0.44** (0.24-0.81)	0.67 (0.20-2.23)	**0.31** (0.13-0.75)	0.69 (0.27-1.77)
	≥ 80 years	**0.32** (0.24-0.43)	**0.07** (0.01-0.49)	**0.10** (0.03-0.34)	**0.11** (0.01-0.96)	**0.16** (0.04-0.60)	0.22 (0.04-1.13)
Tumor location	Pancreas head	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Pancreas body	**0.44** (0.38-0.57)	**0.36** (0.16-0.78)	1.06 (0.51-2.17)	0.28 (0.06-1.27)	**0.10** (0.01-0.74)	0.54 (0.17-1.77)
	Pancreas tail	**2.28** (1.77-2.93)	**2.18** (1.16-4.10)	1.07 (0.35-3.25)	1.57 (0.29-8.64)	2.16 (0.79-5.93)	1.74 (0.21-14.41)
	Other[4]	**0.58** (0.47-0.72)	0.98 (0.54-1.77)	**0.54** (0.32-0.92)	**0.19** (0.07-0.54)	0.80 (0.33-1.95)	**0.16** (0.05-0.58)
cTNM stage IV[2]		n = 47120	n = 11993	n = 4217	n = 4238	-	n = 1773
Year of diagnosis		**0.97** (0.95-0.99)	0.99 (0.93-1.06)	0.93 (0.85-1.01)	0.99 (0.92-1.06)		1.06 (0.98-1.14)
Sex	Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-	1.00 (reference)
	Male	**0.85** (0.76-0.95)	0.81 (0.51-1.26)	0.76 (0.46-1.24)	1.16 (0.73-1.83)	-	1.24 (0.78-1.95)
Age group	< 60 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-	1.00 (reference)
	60-69 years	**0.74** (0.64-0.86)	0.77 (0.46-1.28)	0.58 (0.31-1.06)	0.59 (0.34-1.03)	-	1.01 (0.57-1.76)
	70-79 years	**0.65** (0.56-0.76)	**0.36** (0.19-0.66)	**0.47** (0.25-0.86)	**0.37** (0.20-0.68)	-	0.58 (0.32-1.05)
	≥ 80 years	**0.31** (0.26-0.38)	NE	**0.08** (0.02-0.35)	**0.13** (0.05-0.33)	-	**0.28** (0.12-0.69)
Tumor location	Pancreas head	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-	1.00 (reference)
	Pancreas body	**0.43** (0.35-0.54)	0.50 (0.21-1.19)	0.30 (0.09-1.01)	0.54 (0.22-1.29)	-	0.73 (0.34-1.54)
	Pancreas tail	0.98 (0.85-1.13)	0.92 (0.53-1.61)	0.81 (0.40-1.61)	1.38 (0.78-2.46)	-	**0.39** (0.18-0.86)
	Other[4]	**0.50** (0.43-0.57)	0.68 (0.34-1.35)	**0.39** (0.22-0.69)	**0.19** (0.10-0.33)	-	**0.35** (0.21-0.57)

[1]Odds ratios and 95% confidence intervals for surgical resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, and tumor location. For subgroups with resected cases <30 (stage IV in Denmark, 15; stage III in Estonia, 11; stage IV in Estonia, 7), results are not shown due to insufficient statistical power. ORs shown in bold are statistically significant.

[2]For the US, Norway, and Estonia, TNM stage is a combination of clinical and pathological stages.

[3]Indicate numbers of cases available for analyses.

[4]Other: pancreas duct, overlapping lesion, NOS, and other specified parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; -, not shown due to insufficient statistical power.

Associations of resection with tumor size, performance status, comorbidities, and hospital type were further explored by adding these factors one by one into the main models with the covariates of year of diagnosis, sex, age, cancer location, and stage (**Table 16**). Resection was significantly less frequently conducted with increasing tumor size in the US. In countries where performance status was available (Belgium and Denmark), tumors were less frequently resected with increasing ECOG scores. In the Netherlands (OR=2.81) and Belgium (OR=2.13), patients managed in academic hospitals underwent more often resection. Detailed information on comorbidity was available in the EiCR in the Netherlands. Cardiac, vascular, neurological, and pulmonary diseases were associated with less frequent resection. Patients with ≥2 comorbidities underwent less often resection compared to those without comorbidities (OR=0.60). Additional analyses were further performed for stage I-II and III-IV tumors, respectively. Patterns for both stage groups were mostly consistent with the overall ones.

Table 16. Association of resection versus non-resection with tumor size, performance status, comorbidities, and hospital type in pancreatic cancer patients in registries with available information estimated by multivariable logistic regression (Huang *et al.*, 2017)

Variable	The US		The Netherlands		Belgium		Denmark	
	n	OR (95% CI)[1]	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Tumor size								
< 20 mm	4648	1.00 (reference)	NA	NA	NA	NA	NA	NA
20-29 mm	13350	**0.70** (0.64-0.76)	NA	NA	NA	NA	NA	NA
30-39 mm	17743	**0.56** (0.51-0.61)	NA	NA	NA	NA	NA	NA
40-49 mm	13855	**0.48** (0.43-0.52)	NA	NA	NA	NA	NA	NA
≥ 50 mm	18386	**0.49** (0.45-0.54)	NA	NA	NA	NA	NA	NA
ECOG score								
0	NA	NA	NA	NA	756	1.00 (reference)	609	1.00 (reference)
1	NA	NA	NA	NA	5162	**0.63** (0.49-0.82)	939	**0.57** (0.37-0.89)
2	NA	NA	NA	NA	1246	**0.36** (0.26-0.52)	523	**0.25** (0.14-0.45)
3	NA	NA	NA	NA	445	**0.16** (0.07-0.36)	294	**0.18** (0.09-0.36)
4	NA	NA	NA	NA	146	**0.06** (0.01-0.47)	70	**0.17** (0.04-0.71)
Comorbidity[2]								
Cardiac disease	NA	NA	757	**0.59** (0.41-0.87)	NA	NA	NA	NA
Vascular disease	NA	NA	530	**0.59** (0.38-0.91)	NA	NA	NA	NA
Hypertension	NA	NA	935	0.99 (0.71-1.38)	NA	NA	NA	NA
Neurological disease	NA	NA	174	**0.47** (0.23-0.97)	NA	NA	NA	NA
Diabetes	NA	NA	832	0.95 (0.69-1.33)	NA	NA	NA	NA
Pulmonary disease	NA	NA	335	**0.59** (0.35-0.99)	NA	NA	NA	NA
Comorbidity number								
0	NA	NA	1332	1.00 (reference)	NA	NA	NA	NA
1	NA	NA	1122	0.91 (0.63-1.32)	NA	NA	NA	NA
≥ 2	NA	NA	1591	**0.60** (0.41-0.87)	NA	NA	NA	NA
Hospital type								
Non-academic	NA	NA	17866	1.00 (reference)	7004	1.00 (reference)	NA	NA
Academic	NA	NA	4612	**2.81** (2.46-3.20)	4767	**2.13** (1.80-2.52)	NA	NA

[1]Odds ratios and 95% confidence intervals for surgical resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and cTNM stage, with the respective variable added in the models. Results for each new model revealed consistent patterns in associations of resection with sex, age group, tumor location, and stage compared to the main analyses. ORs shown in bold are statistically significant.

[2]In the Netherlands, comorbidity information at diagnosis was available in the Eindhoven Cancer Registry. Patients without the respective comorbidities were referenced.

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Collaborative Oncology Group; NA, not available.

3.1.2 Non-surgical therapies for resected and unresected pancreatic cancer in Europe and the US

(This part has been published (Huang *et al.*, 2018b).)

3.1.2.1 Patient characteristics

Totally 145,056 PaC cases from six population-based databases during 2003-2014 were initially included (**Table 17**). After excluding DCO/autopsy-diagnosed patients (n=3483, 2.4%) and TNM stage 0 tumor patients (n=40, <0.1%), finally 141,533 (97.7%) records were analyzed. Between 12.6% (Norway) and 21.7% (Belgium) of the cancers were resected (**Table 18**). Among the resected cancer patients, the mean age was 65-67 years. Most of the resected cancers were in pancreas head (78.7%-87.7%) and stage I-II (75.1%-91.9%). Stage proportions remained stable over time. Only small minorities of the cancers (5.8%-17.0%) were well-differentiated. Compared to resected PaC patients, unresected cancer patients were older (mean age, 70-73 years; **Table 19**). Pancreatic head cancers were less common (64.5%-70.7%), and most tumors were metastatic (64.5%-79.9%).

Table 17. General information on participating registries for Chapter 3.1.2 (Huang *et al.*, 2018b)

Source	Country	Diagnosis period	Registered primary cases[1]	Excluded cases[2]		Analyzed cases
				DCO/autopsy	TNM stage 0	
SEER18[3]	the US	Jan. 2004-Dec. 2013	99582	2972 (3.0)	37 (0.0)	96573
NCR	The Netherlands	Jan. 2003-Dec. 2014	22579	99 (0.4)	2 (0.0)	22478
BCR	Belgium	Jan. 2004-Dec. 2013	12146	NA	1 (0.0)	12145
CRN	Norway	Jan. 2003-Dec. 2011	5864	259 (4.4)	0 (0.0)	5605
CRS	Slovenia	Jan. 2003-Dec. 2013	3376	54 (1.6)	0 (0.0)	3322
ECR	Estonia	Jan. 2009-Dec. 2014	1509	99 (6.6)	0 (0.0)	1410

[1]A preliminary data-cleaning process had been performed to exclude cases with ineligible histology types.

[2]Shown as n (percentage [%]).

[3]Data of the year 2003 was not analyzed, as the TNM stage (version 6/7) information was unavailable.

SEER, Surveillance, Epidemiology, and End Results Program; NCR, Netherlands Cancer Registry; BCR, Belgian Cancer Registry; CRN, Cancer Registry of Norway; CRS, Cancer Registry of Slovenia; ECR, Estonian Cancer Registry; DCO, death certificate only; NA, not available.

Table 18. Demographic and clinical characteristics of resected pancreatic cancer patients (Huang *et al.*, 2018b)

Parameter	the US	The Netherlands	Belgium	Norway	Slovenia	Estonia[5]
Diagnosis period	2004-2013	2003-2014	2004-2013	2003-2011	2003-2013	2009-2014
n[1]	15628 (16.2)	2945 (13.1)	2630 (21.7)	709 (12.6)	602 (18.1)	183 (13.0)
Sex, female	7738 (49.5)	1387 (47.1)	1217 (46.3)	326 (46.0)	293 (48.7)	87 (47.5)
Age (year)	66 ± 11	65 ± 10	66 ± 10	65 ± 11	65 ± 10	67 ± 10
Age group						
< 60 years	4290 (27.5)	773 (26.3)	691 (26.3)	193 (27.2)	175 (29.1)	37 (20.2)
60-69 years	4982 (31.9)	1086 (36.9)	848 (32.2)	251 (35.4)	201 (33.4)	69 (37.7)
70-79 years	4708 (30.1)	969 (32.9)	915 (34.8)	220 (31.0)	197 (32.7)	68 (37.2)
≥ 80 years	1648 (10.5)	117 (4.0)	176 (6.7)	45 (6.4)	29 (4.8)	9 (4.9)
Tumor location[2]						
Pancreas head	10730 (78.7)	2375 (87.7)	1374 (79.6)	532 (87.1)	435 (85.8)	128 (79.5)
Pancreas body	1065 (7.8)	106 (3.9)	127 (7.3)	31 (5.1)	38 (7.5)	17 (10.6)
Pancreas tail	1845 (13.5)	228 (8.4)	226 (13.1)	48 (7.9)	34 (6.7)	16 (9.9)
Other	1988 (12.7)	236 (8.0)	903 (34.3)	98 (13.8)	95 (15.8)	22 (12.0)
TNM stage[3]						
I-II	13303 (86.9)	2675 (91.9)	2155 (87.9)	381 (82.1)	406 (75.1)	159 (89.8)
III	767 (5.0)	148 (5.1)	146 (5.9)	23 (5.0)	46 (8.5)	11 (6.2)
IV	1231 (8.1)	89 (3.1)	152 (6.2)	60 (12.9)	89 (16.5)	7 (4.0)
Differentiation[4]						
Well	1606 (11.9)	267 (11.1)	360 (17.0)	33 (5.8)	46 (9.6)	22 (15.6)
Intermediate	6732 (49.9)	1247 (52.1)	1039 (49.1)	357 (63.0)	177 (36.8)	80 (56.7)
Poor/undifferentiated	5156 (38.2)	881 (36.8)	717 (34.9)	177 (31.2)	258 (53.6)	39 (27.7)
Neoadjuvant chemotherapy	NA	65 (2.2)	82 (3.1)	NA	2 (0.3)	NA
Neoadjuvant radiotherapy	677 (4.3)	39 (1.3)	32 (1.2)	NA	1 (0.2)	NA
Adjuvant/palliative chemotherapy	NA	1167 (39.6)	1446 (55.0)	139 (19.6)	172 (28.6)	22 (12.0)
Adjuvant/palliative radiotherapy	4610 (29.5)	40 (1.4)	234 (8.9)	31 (4.4)	14 (2.3)	12 (6.6)

Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below.

[1]Proportions in brackets are relative to the number of total incident cases in respective country.

[2]The percentages of pancreas head, body, and tail cancers are the proportions compared to the total tumor cases of the 3 locations; 'other' includes pancreas duct, overlapping lesion, NOS, and other specified parts, and its proportion is relative to the whole cases.

[3]Unkown TNM stage: the US: 327 (2.1%); The Netherlands: 33 (1.1%); Belgium: 177 (6.7%); Norway: 245 (34.6%); Slovenia: 61 (10.1%); Estonia: 6 (3.3%).

[4]Unknown differentiation: the US, 2134 (13.7%); The Netherlands, 550 (18.7%); Belgium, 514 (19.5%); Norway, 142 (20.0%); Slovenia, 121 (20.1%); Estonia, 42 (23.0%).

[5]Underreporting of non-surgical treatment data might exist in the Estonian Cancer Registry.

NOS, not otherwise specified; NA, not available.

Table 19. Demographic and clinical characteristics of unresected pancreatic cancer patients (Huang *et al.*, 2018b)

Parameter	the US	The Netherlands	Belgium	Norway	Slovenia	Estonia[4]
Diagnosis period	2004-2013	2003-2014	2004-2013	2003-2011	2003-2013	2009-2014
n[1]	80945 (83.8)	19533 (86.9)	9515 (78.3)	4896 (87.4)	2720 (81.9)	1227 (87.0)
Sex, female	40579 (50.1)	9797 (50.2)	4685 (49.2)	2576 (52.6)	1398 (51.4)	578 (47.1)
Age (year)	71 ± 12	70 ± 11	71 ± 11	73 ± 12	71 ± 11	71 ± 11
Age group						
< 60 years	15386 (19.0)	3426 (17.5)	1516 (15.9)	677 (13.8)	450 (16.5)	193 (15.7)
60-69 years	19352 (23.9)	5339 (27.3)	2328 (24.5)	1119 (22.9)	609 (22.4)	301 (24.5)
70-79 years	22365 (27.6)	6351 (32.5)	3277 (34.4)	1413 (28.9)	923 (33.9)	425 (34.6)
≥ 80 years	23842 (29.5)	4417 (22.6)	2394 (25.2)	1687 (34.5)	738 (27.1)	308 (25.1)
Tumor location[2]						
Pancreas head	36004 (65.1)	11622 (69.8)	2713 (64.5)	1417 (68.7)	1010 (70.7)	626 (66.4)
Pancreas body	9704 (17.5)	2182 (13.1)	688 (16.3)	297 (14.4)	188 (13.2)	196 (20.8)
Pancreas tail	9608 (17.4)	2851 (17.1)	808 (19.2)	291 (14.1)	230 (16.1)	121 (12.8)
Other	25629 (31.7)	2878 (14.7)	5306 (55.8)	2834 (57.9)	1292 (47.5)	284 (23.1)
TNM stage[3]						
I-II	18010 (25.3)	3035 (18.1)	1282 (19.4)	745 (18.1)	261 (12.3)	124 (13.1)
III	7266 (10.2)	1821 (10.9)	879 (13.3)	259 (6.3)	166 (7.8)	107 (11.3)
IV	45889 (64.5)	11916 (71.1)	4455 (67.3)	3103 (75.6)	1696 (79.9)	714 (75.6)
Adjuvant/palliative chemotherapy	NA	3894 (19.9)	5512 (57.9)	970 (19.8)	409 (15.0)	189 (15.4)
Adjuvant/palliative radiotherapy	953 (1.2)	470 (2.4)	602 (6.3)	248 (5.1)	50 (1.8)	22 (1.8)

Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below. Results of tumor differentiation for the unresected were not shown due to great proportions of missing values.

[1]Proportions in brackets are relative to the number of total incident cases in respective country.

[2]The percentages of pancreas head, body, and tail cancers are the proportions compared to the total tumor cases of the 3 locations; 'other' includes pancreas duct, overlapping lesion, NOS, and other specified parts, and its proportion is relative to the whole cases.

[3]Unkown TNM stage: the US: 9780 (12.1%); The Netherlands: 2761 (14.1%); Belgium: 2899 (30.5 %); Norway: 789 (16.1%); Slovenia: 597 (21.9%); Estonia: 282 (23.0%).

[4]Underreporting of non-surgical treatment data might exist in the Estonian Cancer Registry.

NOS, not otherwise specified; NA, not available.

3.1.2.2 Non-surgical therapy combinations

The Netherlands, Belgium, and Slovenia provided information on both pre- and post-surgical therapies, and were analyzed concerning the combination of non-surgical therapies (**Table 20**). Briefly, most patients did not receive any non-surgical treatment. For those receiving ≥1 non-surgical therapies, chemotherapy alone was the most common modality. Neoadjuvant treatment was rarely administered.

Table 20. Non-surgical therapy combinations for pancreatic cancer in Europe, 2011-2013 (Huang *et al.*, 2018b)

Neoadjuvant therapy	Adjuvant/palliative therapy	The Netherlands	Belgium	Slovenia
Resected		n = 1039	n = 940	n = 202
None	None	467 (45.0)	359 (38.2)	133 (65.8)
None	Chemotherapy	544 (52.4)	488 (51.9)	63 (31.2)
None	Radiotherapy	0 (0.0)	8 (0.9)	0 (0.0)
None	Chemoradiotherapy	1 (0.1)	46 (4.9)	5 (2.5)
Chemotherapy	None	3 (0.3)	5 (0.3)	1 (0.5)
Chemotherapy	Chemotherapy	2 (0.2)	19 (2.0)	0 (0.0)
Chemotherapy	Radiotherapy	0 (0.0)	2 (0.2)	0 (0.0)
Chemotherapy	Chemoradiotherapy	0 (0.0)	1 (0.1)	0 (0.0)
Radiotherapy	None	0 (0.0)	0 (0.0)	0 (0.0)
Radiotherapy	Chemotherapy	0 (0.0)	0 (0.0)	0 (0.0)
Radiotherapy	Radiotherapy	0 (0.0)	0 (0.0)	0 (0.0)
Radiotherapy	Chemoradiotherapy	0 (0.0)	0 (0.0)	0 (0.0)
Chemoradiotherapy	None	10 (1.0)	8 (0.9)	0 (0.0)
Chemoradiotherapy	Chemotherapy	12 (1.2)	2 (0.2)	0 (0.0)
Chemoradiotherapy	Radiotherapy	0 (0.0)	2 (0.2)	0 (0.0)
Chemoradiotherapy	Chemoradiotherapy	0 (0.0)	0 (0.0)	0 (0.0)
Unresected		n = 5280	n = 3358	n = 805
None	None	3907 (74.0)	1439 (42.9)	670 (83.2)
None	Chemotherapy	1261 (23.9)	1732 (51.6)	118 (14.7)
None	Radiotherapy	27 (0.5)	30 (0.9)	9 (1.1)
None	Chemoradiotherapy	85 (1.6)	157 (4.7)	8 (1.0)

Data are shown as n (percentage [%]).

Within the subgroup of resected PaC patients, significant proportions did not receive any non-surgical treatment (38.2% (Belgium) to 65.8% (Slovenia)). Among those who received ≥1 non-surgical therapy, adjuvant chemotherapy alone was the most common modality (31.2% (Slovenia) to 52.4% (the Netherlands)). Adjuvant chemoradiation was administered for 0.1%, 4.9%, and 2.5% of the patients in the Netherlands, Belgium, and Slovenia, respectively. All the other treatment combinations were used in <2.5% of the patients in all the registries.

For unresected cancer patients, the plurality or majority of patients remained untreated (42.9% (Belgium) to 83.2% (Slovenia)). Among the treated patients, most of them received chemotherapy (14.7% (Slovenia) to 51.6% (Belgium)), followed by chemoradiation (1.0% (Slovenia) to 4.7% (Belgium)) and radiotherapy alone (0.5% (the Netherlands) to 1.1% (Slovenia)).

3.1.2.3 Time between diagnosis/surgery and chemotherapy/radiotherapy use

Information on the time interval between diagnosis/resection and chemotherapy/radiotherapy administration was available in the Netherlands, Belgium, and Slovenia (**Table 21**). Among resected patients receiving chemotherapy, the mean time intervals between diagnosis and chemotherapy and between surgery and chemotherapy were 66-71 and 51-52 days, respectively. As many as 81.5%-85.5% and 93.5%-99.7% of resected patients received chemotherapy ≤90 days after diagnosis and after surgery, respectively. Compared to chemotherapy, it took longer for resected patients to receive radiotherapy after diagnosis (81-114 days) and after surgery (75-85 days), and smaller proportions of patients received radiotherapy ≤90 days after diagnosis (46.2%-62.5%) and ≤90 days after resection (58.6%-75.0%).

Table 21. Time between diagnosis/surgery and chemotherapy/radiotherapy use in resected and unresected pancreatic cancer patients receiving chemotherapy/radiotherapy in registries with available information (Huang *et al.*, 2018b)

Interval	The Netherlands				Belgium			
	n	Mean ± standard deviation	Median (interquartile range)	Administered ≤90 days	n	Mean ± standard deviation	Median (interquartile range)	Administered ≤90 days
Resected								
Diagnosis-chemotherapy	964	66 ± 33	58 (43-82)	786 (81.5)	1446	71 ± 34	64 (50-83)	1199 (82.9)
Surgery-chemotherapy	964	51 ± 18	48 (39-60)	928 (96.3)	1446	51 ± 15	50 (41-61)	1442 (99.7)
Diagnosis-radiotherapy	8	81 ± 40	70 (52-103)	5 (62.5)	234	105 ± 56	98 (62-142)	108 (46.2)
Surgery-radiotherapy	8	75 ± 33	70 (52-90)	6 (75.0)	234	85 ± 43	75 (49-115)	137 (58.6)
Unresected								
Diagnosis-chemotherapy	2882	38 ± 37	28 (17-48)	2683 (93.1)	5512	26 ± 19	20 (12-35)	5491 (99.6)
Diagnosis-radiotherapy	313	47 ± 38	40 (23-60)	279 (89.1)	602	71 ± 52	55 (25-112)	387 (64.3)

Intervals are shown in days.

Table 21. Time between diagnosis/surgery and chemotherapy/radiotherapy use in resected and unresected pancreatic cancer patients receiving chemotherapy/radiotherapy in registries with available information (Huang *et al.*, 2018b) (continued)

Interval	Slovenia			
	n	Mean ± standard deviation	Median (interquartile range)	Administered ≤90 days
Resected				
Diagnosis-chemotherapy	172	69 ± 39	63 (50-81)	147 (85.5)
Surgery-chemotherapy	168	52 ± 33	46 (38-56)	157 (93.5)
Diagnosis-radiotherapy	14	114 ± 82	89 (51-133)	7 (50.0)
Surgery-radiotherapy	13	82 ± 63	58 (33-91)	9 (69.2)
Unresected				
Diagnosis-chemotherapy	409	46 ± 52	34 (15-60)	372 (91.0)
Diagnosis-radiotherapy	50	106 ± 114	64 (32-153)	33 (66.0)

Intervals are shown in days.

In unresected patients receiving chemotherapy/radiotherapy, the time between diagnosis and chemotherapy (26-46 days) and between diagnosis and radiotherapy (47-106 days) was shorter with larger international variations. 91.0%-99.6% of unresected patients received chemotherapy ≤90 days after diagnosis, and 64.3%-89.1% of patients underwent radiotherapy within the post-diagnosis period.

3.1.2.4 Temporal trends of chemotherapy and radiotherapy use

The application trends from 2003-2004 to 2013-2014 are illustrated in **Figure 3**. For resected PaC, chemotherapy was most commonly administered in Belgium in all periods with an increasing trend (2003-2004: 29.1%, 2013-2014: 62.9%; P_{trend}=0.001). The Netherlands showed the strongest increase over the periods (2003-2004: 7.6%, 2013-2014: 56.2%; P_{trend}<0.001). Chemotherapy rates also increased in Norway (2003-2004: 2.3%, 2011-2012: 30.2%; P_{trend}<0.001) and Slovenia (2003-2004: 14.8%, 2013-2014: 33.4%; P_{trend}=0.009). Estonia showed the lowest rates with an insignificant trend (2009-2010: 8.8%, 2013-2014: 12.8%; P_{trend}=0.165). For unresected cancer, chemotherapy was again most frequently used in Belgium, where the proportions were stable (2003-2004: 53.2%, 2013-2014: 57.2%; P_{trend}=0.188). Chemotherapy use increased in the Netherlands (2003-2004: 10.7%, 2013-2014: 27.9%; P_{trend}<0.001), Norway (2003-2004: 14.3%, 2011-2012: 25.1%; P_{trend}=0.002), Slovenia (2003-2004: 11.6%, 2013-2014: 16.7%; P_{trend}=0.010), and Estonia (2009-2010: 11.6%, 2013-2014: 19.4%; P_{trend}=0.002). Rates changed most dramatically from 2003-2004 to 2009-2010 for both resected and unresected PaCs in most countries.

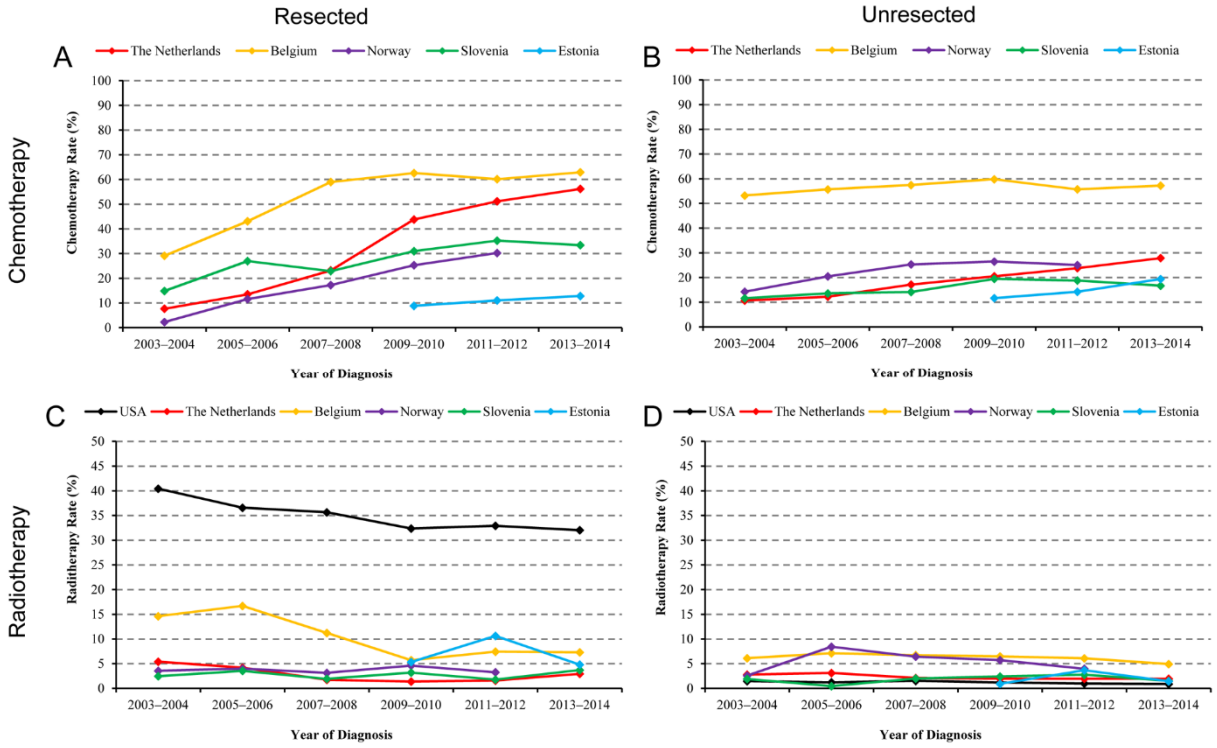

Figure 3. Age-standardized trends of chemotherapy administration for resected (**A**) and unresected (**B**) pancreatic cancer patients and of radiotherapy administration for resected (**C**) and unresected (**D**) patients. (Huang *et al.*, 2018b)

From 2003-2004 to 2013-2014 in Belgium, among patients receiving chemotherapy the utilization of combination regimens increased from 1.5% to 2.8% for resected PaC (P_{trend}=0.005), and from 2.9% to 10.5% for unresected tumor (P_{trend}<0.001). The proportion of fluorouracil-based regimens decreased from 25.0% to 7.6% (P_{trend}=0.046), with the proportion of gemcitabine-based regimens increasing from 64.6% to 89.8% (P_{trend}=0.039) for resected PaC. For unresected cancers, While with statistical insignificances, reverse, statistically insignificant trends were observed concerning the proportions of fluorouracil-based (6.8% to 11.6%, P_{trend}=0.062) and gemcitabine-based regimens (90.3% to 85.5%, P_{trend}=0.053).

For resected PaC, radiotherapy was much more frequently administered in the US compared to Europe in all study periods, with a decreasing rate (2003-2004: 40.4%, 2013-2014: 32.0%; P_{trend}<0.001). Belgium overall ranked first in radiotherapy administration in Europe, but the rate decreased from 14.6% in 2003-2004 to 7.3% in 2013-2014 (P_{trend}=0.003). In the Netherlands, a similar trend was observed (2003-2004: 5.4%, 2013-2014: 2.9%; P_{trend}=0.024). In Norway (P_{trend}=0.470) and Slovenia (P_{trend}=0.835), radiotherapy was rarely administered with stable rates <5.0%. In Estonia, no significant trends were observed (2009-2010: 5.3%, 2013-2014: 4.8%; P_{trend}=0.738). For unresected cancer, radiotherapy use was rare in all countries during 2003-2014 (<8.5% across periods; P_{trend}=0.011 (the US), 0.021 (the Netherlands), 0.124 (Belgium), 0.573 (Norway), 0.119 (Slovenia), and 0.693 (Estonia)). In 2013-2014, radiotherapy was administered in 0.9% (the US) to 4.9% (Belgium) of unresected patients.

Great variations across different geographical areas within the US were observed regarding radiotherapy use during 2012-2013 (**Figure 4**). For resected cancer patients, radiotherapy rates were generally higher in the eastern than the western US, and were markedly higher than the average level of the total SEER-18 registries (32.9%) in Iowa (43.3%), Louisiana (42.8%), Kentucky (39.3%), Atlanta (46.5%), Georgia (41.5%), and Detroit (45.5%), but markedly lower in Connecticut (18.8%) and Los Angeles (18.0%). For unresected cancer patients, radiotherapy rates were very low (0.5%-2.9%) across all the US sub-registries.

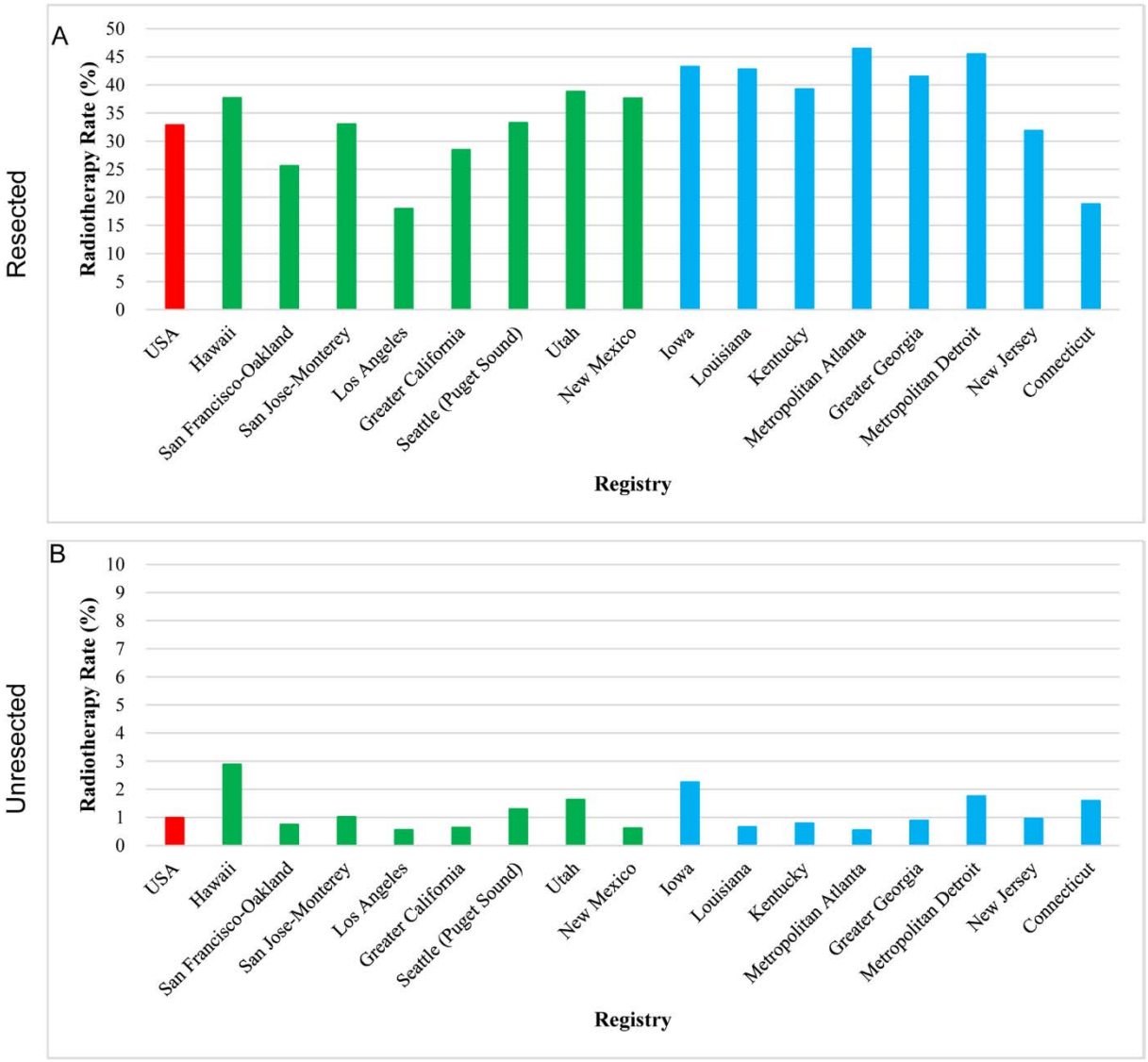

Figure 4. Age-standardized rates of radiotherapy administration for resected (A) and unresected (B) pancreatic cancer in 2012-2013 in the US. Geographical disparities of radiotherapy administration in the US are shown. The total registry is marked in red, the western US sub-registries in green, and the eastern sub-registries in blue. (Huang *et al.*, 2018b)

In 2012-2014, chemotherapy and radiotherapy use decreased with increasing age for both resected and unresected PaCs (**Figure 5**). For unresected cancers, those in pancreas body and those of stage III mostly received more frequently chemotherapy. Radiotherapy was more often used for stage III PaCs in both resected and unresected cancers.

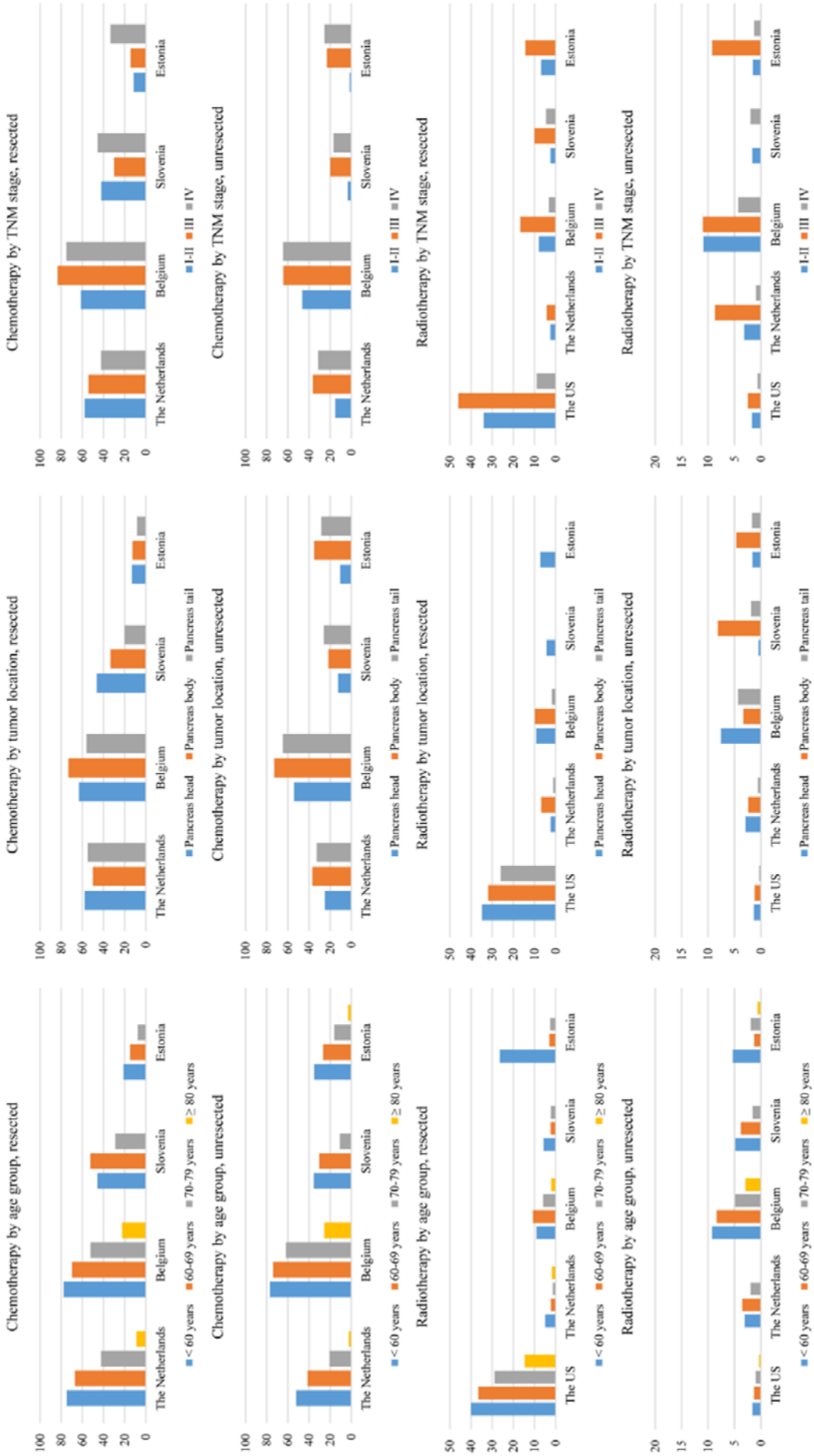

Figure 5. Rates of chemotherapy and radiotherapy administration for resected and unresected pancreatic cancer by patient age group, tumor location, and TNM stage, 2012-2014.

3.1.2.5 Factors associated with chemotherapy and radiotherapy use in resected pancreatic cancer

Using multivariable logistic regression, for resected PaC, chemotherapy was less frequently administered with increasing age, especially among patients aged 70-79 (OR=0.25-0.52 across countries) and ≥80 years (OR=0.02-0.08) compared to those <60 years (**Table 22**). Compared to stage I-II cancers, chemotherapy was less frequently administered in metastatic PaCs in the Netherlands (OR=0.50), while in Belgium, it was more often used in stage III (OR=1.94) and IV (OR=1.52) cancers. Radiotherapy was more frequently administered for male patients in the US (OR=1.08; **Table 23**). A decreasing frequency of radiotherapy administration with increasing age was observed in all countries, with ORs in patients aged 70-79 and ≥80 years versus those <60 years of 0.27-0.55 and 0.05-0.25, respectively. In the US, patients with pancreatic tail cancers received less frequently radiotherapy than those with head tumors (OR=0.72). Compared to patients with stage I-II PaCs, those with stage III tumors received more often radiotherapy (OR=1.68-3.20), while patients with metastatic cancers underwent less frequently radiotherapy (OR=0.25-0.47).

Table 22. Association of chemotherapy use with demographic and clinical variables in resected pancreatic cancer estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	The Netherlands	Belgium	Norway	Slovenia
	OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)
***Resected* (treated/total)**	1194/2912	1431/2453	108/464	161/541
Year of diagnosis	**1.34** (1.30-1.38)	**1.15** (1.11-1.19)	**1.51** (1.36-1.69)	**1.14** (1.07-1.22)
Sex (ref.: female)				
Male	0.91 (0.77-1.08)	0.90 (0.76-1.07)	1.26 (0.77-2.05)	1.29 (0.87-1.91)
Age group (ref.: < 60 years)				
60-69 years	**0.62** (0.50-0.76)	**0.63** (0.50-0.80)	1.26 (0.71-2.26)	0.73 (0.46-1.15)
70-79 years	**0.25** (0.20-0.31)	**0.29** (0.23-0.37)	0.52 (0.26-1.00)	**0.26** (0.15-0.43)
≥ 80 years	**0.02** (0.01-0.05)	**0.06** (0.04-0.10)	**0.08** (0.01-0.69)	NE
Tumor location (ref.: pancreas head)				
Pancreas body	0.84 (0.54-1.32)	1.02 (0.67-1.55)	0.22 (0.05-1.06)	0.89 (0.40-1.96)
Pancreas tail	0.74 (0.54-1.01)	1.13 (0.81-1.57)	1.39 (0.59-3.28)	0.94 (0.40-2.20)
Other[2]	**0.71** (0.52-0.97)	**0.79** (0.65-0.95)	1.29 (0.63-2.63)	1.29 (0.71-2.35)
TNM stage (ref.: I-II)				
III	1.21 (0.84-1.77)	**1.94** (1.31-2.87)	1.33 (0.44-4.08)	0.81 (0.40-1.65)
IV	**0.50** (0.30-0.84)	**1.52** (1.04-2.20)	1.50 (0.73-3.08)	0.86 (0.49-1.49)

[1]Odds ratios and 95% confidence intervals for chemotherapy versus non-chemotherapy and radiotherapy versus non-radiotherapy were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. Results for countries with number of patients receiving indicated therapy < 50 (Estonia, 22) were not reported. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

Table 23. Association of radiotherapy use with demographic and clinical variables in resected pancreatic cancer estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	**The US**	**The Netherlands**	**Belgium**
	OR (95% CI)	OR (95% CI)	OR (95% CI)
***Resected* (treated/total)**	5205/14923	78/2912	250/2453
Year of diagnosis	**0.96** (0.95-0.97)	**0.92** (0.86-0.98)	**0.87** (0.83-0.91)
Sex (ref.: female)			
Male	**1.08** (1.00-1.15)	0.82 (0.52-1.29)	1.19 (0.90-1.56)
Age group (ref.: < 60 years)			
60-69 years	**0.90** (0.83-0.98)	**0.38** (0.22-0.64)	1.00 (0.73-1.36)
70-79 years	**0.55** (0.51-0.61)	**0.27** (0.15-0.50)	**0.44** (0.30-0.63)
≥ 80 years	**0.25** (0.22-0.29)	0.17 (0.02-1.24)	**0.05** (0.01-0.35)
Tumor location (ref.: pancreas head)			
Pancreas body	0.92 (0.80-1.06)	1.64 (0.58-4.66)	1.43 (0.80-2.53)
Pancreas tail	**0.72** (0.64-0.81)	0.62 (0.22-1.74)	0.62 (0.35-1.12)
Other[2]	**0.73** (0.65-0.82)	0.85 (0.36-2.01)	0.93 (0.69-1.26)
TNM stage (ref.: I-II)			
III	**1.68** (1.45-1.96)	**3.20** (1.63-6.27)	**2.91** (1.92-4.41)
IV	**0.25** (0.21-0.30)	0.38 (0.05-2.81)	**0.47** (0.23-0.98)

[1]Odds ratios and 95% confidence intervals for chemotherapy versus non-chemotherapy and radiotherapy versus non-radiotherapy were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. Results for countries with number of patients receiving indicated therapy < 50 (Norway, 19; Slovenia, 11; Estonia, 12) were not reported. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

In countries with available information on the time interval between diagnosis and treatment, association patterns and trends remained similar after limiting patients receiving chemotherapy or radiotherapy to those undergoing the treatment ≤90 days after diagnosis (**Table 24**). After restricting the total patients to those surviving >90 days after diagnosis in all countries, association patterns and trends also remained mostly similar with only a few exceptions mostly reflected by the changes in significance (**Tables 25-26**).

Table 24. Associations of chemotherapy or radiotherapy administered ≤ 90 days after diagnosis versus not administered with demographic and clinical variables for resected pancreatic cancer estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	***Chemotherapy***			***Radiotherapy***
Country	**Netherlands**	**Belgium**	**Slovenia**	**Belgium**
	OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)
***Resected* (treated ≤ 90 days/untreated)**	781/1718	1160/1012	127/356	102/2203
Year of diagnosis	**1.48** (1.43-1.54)	**1.15** (1.11-1.18)	**1.17** (1.08-1.25)	**0.83** (0.77-0.89)
Sex (ref.: female)				
Male	0.87 (0.71-1.06)	0.89 (0.74-1.07)	1.13 (0.73-1.74)	1.22 (0.80-1.84)
Age group (ref.: < 60 years)				
60-69 years	**0.69** (0.54-0.88)	**0.63** (0.49-0.80)	0.74 (0.45-1.21)	1.32 (0.82-2.12)
70-79 years	**0.24** (0.18-0.31)	**0.27** (0.21-0.34)	**0.20** (0.11-0.37)	**0.48** (0.27-0.85)
≥ 80 years	**0.02** (0.01-0.05)	**0.06** (0.04-0.10)	NE	0.14 (0.02-1.07)
Tumor location (ref.: pancreas head)				
Pancreas body	0.67 (0.38-1.17)	0.79 (0.50-1.24)	0.78 (0.29-2.07)	1.22 (0.47-3.19)
Pancreas tail	0.84 (0.59-1.20)	1.19 (0.84-1.68)	0.77 (0.28-2.09)	0.63 (0.24-1.63)
Other[2]	**0.65** (0.45-0.95)	**0.78** (0.63-0.95)	1.59 (0.82-3.07)	1.23 (0.80-1.90)
TNM stage (ref.: I-II)				
III	1.05 (0.67-1.66)	**1.79** (1.18-2.72)	0.81 (0.37-1.73)	**3.58** (2.03-6.30)
IV	**0.27** (0.13-0.55)	**1.55** (1.05-2.29)	0.76 (0.38-1.49)	0.27 (0.07-1.13)

[1]Odds ratios and 95% confidence intervals for chemotherapy administered ≤ 90 days after diagnosis versus non-chemotherapy and radiotherapy administered ≤ 90 days after diagnosis versus non-radiotherapy were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. Results for countries with number of patients receiving indicated therapy within 90 days after diagnosis < 50 (radiotherapy: the Netherlands, 5; Slovenia, 6) were not reported. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

Table 25. Associations of chemotherapy use with demographic and clinical variables for resected pancreatic cancer patients surviving >90 days after diagnosis estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	The Netherlands	Belgium	Norway	Slovenia
	OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)
***Resected* (treated/total)**	1160/2656	1420/2275	107/437	152/456
Year of diagnosis	**1.37** (1.33-1.41)	**1.17** (1.13-1.21)	**1.52** (1.36-1.70)	**1.16** (1.08-1.24)
Sex (ref.: female)				
Male	0.93 (0.78-1.10)	0.94 (0.79-1.13)	1.34 (0.82-2.20)	1.35 (0.88-2.05)
Age group (ref.: < 60 years)				
60-69 years	**0.64** (0.52-0.80)	**0.64** (0.50-0.82)	1.33 (0.74-2.39)	0.72 (0.45-1.17)
70-79 years	**0.25** (0.20-0.32)	**0.31** (0.24-0.40)	0.56 (0.29-1.10)	**0.25** (0.15-0.44)
≥ 80 years	**0.02** (0.01-0.06)	**0.06** (0.04-0.09)	**0.11** (0.01-0.93)	NE
Tumor location (ref.: pancreas head)				
Pancreas body	0.84 (0.52-1.35)	1.02 (0.66-1.60)	0.25 (0.05-1.21)	0.92 (0.39-2.19)
Pancreas tail	**0.71** (0.51-0.98)	1.01 (0.72-1.42)	1.40 (0.58-3.34)	0.63 (0.24-1.62)
Other[2]	**0.70** (0.50-0.97)	**0.80** (0.65-0.98)	1.29 (0.62-2.66)	1.75 (0.88-3.48)
TNM stage (ref.: I-II)				
III	**1.50** (1.00-2.25)	**2.30** (1.48-3.57)	1.73 (0.54-5.54)	0.86 (0.41-1.78)
IV	**0.49** (0.28-0.85)	**1.84** (1.21-2.80)	1.51 (0.71-3.20)	1.12 (0.57-2.21)

[1]Odds ratios and 95% confidence intervals for chemotherapy versus non-chemotherapy and radiotherapy versus non-radiotherapy in pancreatic cancer patients surviving > 90 days after diagnosis were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. Results for countries with number of patients receiving indicated therapy < 50 (Estonia, 19) were not reported. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

Table 26. Associations of radiotherapy use with demographic and clinical variables for resected pancreatic cancer patients surviving >90 days after diagnosis estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	the US	The Netherlands	Belgium
	OR (95% CI)	OR (95% CI)	OR (95% CI)
***Resected* (treated/total)**	5090/13761	76/2656	249/2275
Year of diagnosis	**0.96** (0.94-0.97)	**0.92** (0.86-0.99)	**0.87** (0.83-0.91)
Sex (ref.: female)			
Male	**1.10** (1.02-1.18)	0.79 (0.49-1.25)	1.20 (0.91-1.58)
Age group (ref.: < 60 years)			
60-69 years	0.93 (0.85-1.02)	**0.39** (0.23-0.66)	1.03 (0.75-1.40)
70-79 years	**0.61** (0.55-0.66)	**0.25** (0.13-0.47)	**0.47** (0.32-0.67)
≥ 80 years	**0.29** (0.25-0.34)	0.19 (0.03-1.43)	**0.05** (0.01-0.38)
Tumor location (ref.: pancreas head)			
Pancreas body	0.92 (0.80-1.06)	1.76 (0.61-5.03)	1.43 (0.80-2.55)
Pancreas tail	**0.73** (0.65-0.82)	0.63 (0.22-1.77)	0.61 (0.34-1.10)
Other[2]	**0.74** (0.66-0.83)	0.70 (0.28-1.79)	0.95 (0.70-1.28)
TNM stage (ref.: I-II)			
III	**1.77** (1.51-2.07)	**3.46** (1.75-6.84)	**3.09** (2.02-4.72)
IV	**0.32** (0.26-0.38)	0.43 (0.06-3.15)	0.49 (0.23-1.02)

[1]Odds ratios and 95% confidence intervals for chemotherapy versus non-chemotherapy and radiotherapy versus non-radiotherapy in pancreatic cancer patients surviving > 90 days after diagnosis were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. Results for countries with number of patients receiving indicated therapy < 50 (Norway, 18; Slovenia, 11; Estonia, 11) were not reported. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

3.1.2.6 Factors associated with chemotherapy and radiotherapy use in unresected pancreatic cancer

For unresected PaC, chemotherapy was more frequently administered to male patients in Belgium (OR=1.18), but less often in Slovenia (OR=0.75; **Table 27**). Decreasing chemotherapy use rates with increasing ages were observed in all countries, with ORs in patients aged 70-79 and ≥80 years versus those <60 years of 0.19-0.44 and 0.03-0.10, respectively. Compared to pancreatic head cancers, body (OR=1.43-3.30) and tail tumors (OR=1.28-1.95) were more frequently treated with chemotherapy in all countries except Norway. Compared to patients with stage I-II PaCs, those with stage III (OR=1.90-5.70) and IV tumors (OR=1.35-5.18) received more frequently chemotherapy, and the association strengths were weaker for metastatic cancers. Radiotherapy was again less often used with increasing age (70-79 *vs.* <60 years, OR=0.24-0.46; ≥80 *vs.* <60 years, OR=0.03-0.18; **Table 28**). In the US, patients with pancreatic body (OR=0.74) and tail cancers (OR=0.42) received radiotherapy less often compared to those with head cancers. In the Netherlands, patients with pancreas tail cancers received less frequently radiation (OR=0.36). Compared to stage I-II PaCs, stage III cancers were treated with more often radiotherapy in the US (OR=1.22), the Netherlands (OR=2.93), and Belgium (OR=1.51), while patients with metastatic cancers received less often radiotherapy (OR=0.18-0.53).

Table 27. Association of chemotherapy use with demographic and clinical parameters for unresected pancreatic cancer estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	The Netherlands	Belgium	Norway	Slovenia	Estonia
	OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
***Unresected* (treated/total)**	3708/16772	4062/6616	888/4107	340/2123	175/945
Year of diagnosis	**1.13** (1.12-1.15)	1.02 (1.00-1.04)	**1.12** (1.08-1.16)	**1.08** (1.04-1.13)	**1.20** (1.09-1.33)
Sex (ref.: female)					
Male	1.02 (0.94-1.11)	**1.18** (1.05-1.32)	0.95 (0.81-1.12)	**0.75** (0.57-0.97)	1.26 (0.88-1.81)
Age group (ref.: < 60 years)					
60-69 years	**0.64** (0.58-0.70)	**0.76** (0.63-0.92)	**0.70** (0.57-0.86)	**0.62** (0.46-0.84)	0.68 (0.4.-1.09)
70-79 years	**0.23** (0.21-0.26)	**0.42** (0.35-0.50)	**0.30** (0.24-0.38)	**0.19** (0.14-0.27)	**0.44** (0.28-0.71)
≥ 80 years	**0.03** (0.02-0.03)	**0.09** (0.07-0.11)	**0.04** (0.03-0.06)	**0.03** (0.01-0.06)	**0.10** (0.04-0.22)
Tumor location (ref.: pancreas head)					
Pancreas body	**1.50** (1.33-1.69)	**1.56** (1.25-1.95)	1.22 (0.88-1.68)	1.43 (0.92-2.24)	**3.30** (2.08-5.23)
Pancreas tail	**1.28** (1.14-1.43)	**1.51** (1.23-1.86)	0.85 (0.61-1.18)	**1.95** (1.31-2.90)	**1.84** (1.04-3.25)
Other[2]	1.04 (0.92-1.17)	1.01 (0.89-1.15)	**0.71** (0.59-0.85)	0.74 (0.55-1.00)	**1.97** (1.24-3.11)
TNM stage (ref.: I-II)					
III	**2.26** (1.92-2.66)	**1.90** (1.56-2.31)	**1.91** (1.32-2.78)	**5.49** (2.64-11.41)	**5.70** (1.83-17.76)
IV	**1.35** (1.18-1.55)	**1.52** (1.32-1.75)	**1.43** (1.12-1.84)	**2.77** (1.45-5.29)	**5.18** (1.83-14.68)

[1]Odds ratios and 95% confidence intervals for chemotherapy versus non-chemotherapy and radiotherapy versus non-radiotherapy were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

Table 28. Association of radiotherapy use with demographic and clinical parameters for unresected pancreatic cancer estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	the US	The Netherlands	Belgium	Norway
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
***Unresected* (treated/total)**	908/70415	408/16772	459/6616	206/4107
Year of diagnosis	**0.96** (0.94-0.98)	**0.96** (0.93-0.99)	0.97 (0.94-1.01)	**1.06** (1.00-1.13)
Sex (ref.: female)				
Male	1.08 (0.95-1.24)	1.04 (0.85-1.28)	0.92 (0.76-1.13)	1.16 (0.87-1.55)
Age group (ref.: < 60 years)				
60-69 years	**0.79** (0.68-0.93)	**0.78** (0.61-0.99)	**0.72** (0.56-0.93)	**0.60** (0.43-0.85)
70-79 years	**0.46** (0.38-0.55)	**0.34** (0.26-0.45)	**0.39** (0.30-0.50)	**0.24** (0.16-0.36)
≥ 80 years	**0.18** (0.14-0.22)	**0.03** (0.02-0.08)	**0.13** (0.09-0.20)	**0.08** (0.04-0.14)
Tumor location (ref.: pancreas head)				
Pancreas body	**0.74** (0.60-0.92)	0.94 (0.69-1.28)	1.00 (0.69-1.45)	1.07 (0.60-1.92)
Pancreas tail	**0.42** (0.31-0.58)	**0.36** (0.21-0.62)	1.01 (0.69-1.48)	0.93 (0.49-1.76)
Other[2]	**0.79** (0.67-0.94)	0.72 (0.51-1.01)	0.95 (0.76-1.19)	1.03 (0.74-1.43)
TNM stage (ref.: I-II)				
III	**1.22** (1.03-1.45)	**2.93** (2.25-3.82)	**1.51** (1.17-1.95)	1.19 (0.70-2.05)
IV	**0.29** (0.24-0.34)	**0.18** (0.13-0.25)	**0.24** (0.19-0.31)	**0.53** (0.37-0.77)

[1]Odds ratios and 95% confidence intervals for chemotherapy versus non-chemotherapy and radiotherapy versus non-radiotherapy were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. Results for countries with number of patients receiving indicated therapy < 50 (Slovenia, 42; Estonia, 19) were not reported. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

In countries with available information on the time interval between diagnosis and treatment, association patterns and trends remained mostly similar after limiting patients to those receiving the treatment ≤90 days after diagnosis, with only a few exceptions mostly reflected by the changes in significance (**Table 29**). After limiting the total patients to those surviving >90 days after diagnosis, association patterns and trends also remained similar overall with only a few exceptions mostly reflected by the changes in significance (**Tables 30-31**).

Table 29. Associations of chemotherapy or radiotherapy administered ≤90 days after diagnosis versus not administered with demographic and clinical variables for unresected pancreatic cancer estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	***Chemotherapy***			***Radiotherapy***	
Country	**The Netherlands**	**Belgium**	**Slovenia**	**The Netherlands**	**Belgium**
Unresected	OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Treated ≤ 90 days/untreated	2593/13064	4044/2554	204/961	260/16364	292/6157
Year of diagnosis	**1.29** (1.27-1.31)	1.02 (1.00-1.04)	**1.12** (1.06-1.19)	**1.10** (1.06-1.15)	**0.91** (0.88-0.95)
Sex (ref.: female)					
Male	0.97 (0.88-1.06)	**1.17** (1.05-1.31)	0.97 (0.69-1.36)	1.20 (0.93-1.54)	1.00 (0.79-1.28)
Age group (ref.: < 60 years)					
60-69 years	**0.66** (0.58-0.73)	**0.76** (0.63-0.92)	**0.54** (0.36-0.81)	0.84 (0.63-1.12)	0.92 (0.67-1.25)
70-79 years	**0.24** (0.21-0.27)	**0.42** (0.35-0.50)	**0.22** (0.15-0.34)	**0.37** (0.26-0.52)	**0.41** (0.29-0.57)
≥ 80 years	**0.02** (0.02-0.03)	**0.09** (0.08-0.11)	**0.03** (0.01-0.08)	**0.02** (<0.01-0.07)	**0.18** (0.11-0.29)
Tumor location (ref.: pancreas head)					
Pancreas body	**1.47** (1.28-1.69)	**1.57** (1.26-1.96)	1.03 (0.57-1.88)	0.91 (0.63-1.33)	0.93 (0.57-1.52)
Pancreas tail	**1.34** (1.18-1.52)	**1.52** (1.23-1.86)	**1.83** (1.09-3.07)	**0.39** (0.21-0.73)	1.03 (0.64-1.66)
Other[2]	**1.16** (1.02-1.33)	1.01 (0.89-1.15)	0.72 (0.49-1.06)	0.77 (0.51-1.15)	1.01 (0.77-1.33)
TNM stage (ref.: I-II)					
III	**2.15** (1.76-2.63)	**1.91** (1.57-2.32)	**2.73** (1.16-6.41)	**2.56** (1.84-3.56)	**1.54** (1.13-2.11)
IV	**1.41** (1.19-1.67)	**1.53** (1.33-1.76)	1.45 (0.65-3.21)	**0.19** (0.13-0.27)	**0.26** (0.19-0.35)

[1]Odds ratios and 95% confidence intervals for chemotherapy administered ≤ 90 days after diagnosis versus non-chemotherapy and radiotherapy administered ≤ 90 days after diagnosis versus non-radiotherapy were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. Results for countries with number of patients receiving indicated therapy within 90 days after diagnosis < 50 (radiotherapy: Slovenia, 14) were not reported. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

Table 30. Associations of chemotherapy use with demographic and clinical parameters for unresected pancreatic cancer patients surviving >90 days after diagnosis estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	**The Netherlands**	**Belgium**	**Norway**	**Slovenia**	**Estonia**
	OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Unresected **(treated/total)**	3006/8079	3239/4304	714/2022	191/534	118/447
Year of diagnosis	**1.14** (1.12-1.16)	**1.04** (1.01-1.07)	**1.13** (1.09-1.18)	**1.16** (1.07-1.25)	**1.22** (1.06-1.40)
Sex (ref.: female)					
Male	**1.18** (1.06-1.31)	**1.38** (1.18-1.62)	1.02 (0.83-1.25)	1.25 (0.83-1.87)	1.31 (0.82-2.08)
Age group (ref.: < 60 years)					
60-69 years	**0.67** (0.59-0.76)	1.00 (0.77-1.31)	0.84 (0.65-1.10)	**0.58** (0.35-0.95)	0.82 (0.45-1.51)
70-79 years	**0.26** (0.23-0.30)	**0.55** (0.43-0.70)	**0.39** (0.30-0.52)	**0.18** (0.11-0.31)	**0.51** (0.28-0.93)
≥ 80 years	**0.03** (0.02-0.04)	**0.11** (0.09-0.15)	**0.07** (0.04-0.10)	**0.04** (0.01-0.13)	**0.12** (0.04-0.38)
Tumor location (ref.: pancreas head)					
Pancreas body	**1.68** (1.44-1.96)	**1.65** (1.20-2.26)	1.25 (0.84-1.85)	0.98 (0.49-1.93)	**3.08** (1.68-5.67)
Pancreas tail	**1.83** (1.56-2.15)	**1.41** (1.04-1.91)	0.95 (0.61-1.47)	**2.33** (1.17-4.62)	1.69 (0.78-3.63)
Other[2]	**1.32** (1.13-1.54)	1.11 (0.93-1.33)	**0.73** (0.58-0.91)	0.88 (0.56-1.39)	**2.50** (1.39-4.49)
TNM stage (ref.: I-II)					
III	**2.16** (1.81-2.59)	**2.29** (1.81-2.90)	**2.29** (1.52-3.45)	**2.81** (1.15-6.86)	**3.76** (1.14-12.38)
IV	**2.38** (2.04-2.77)	**3.07** (2.57-3.67)	**2.29** (1.74-3.02)	**2.52** (1.08-5.89)	**4.92** (1.68-14.39)

[1]Odds ratios and 95% confidence intervals for chemotherapy versus non-chemotherapy and radiotherapy versus non-radiotherapy in pancreatic cancer patients surviving > 90 days after diagnosis were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

Table 31. Associations of radiotherapy use with demographic and clinical parameters for unresected pancreatic cancer patients surviving >90 days after diagnosis estimated by multivariable logistic regression (Huang *et al.*, 2018b)

Variable	the US	The Netherlands	Belgium	Norway
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Unresected **(treated/total)**	825/37825	368/8079	413/4304	161/2022
Year of diagnosis	**0.95** (0.93-0.98)	**0.95** (0.92-0.98)	0.97 (0.93-1.01)	1.04 (0.98-1.12)
Sex (ref.: female)				
Male	1.12 (0.97-1.29)	1.12 (0.90-1.39)	0.95 (0.77-1.17)	1.28 (0.92-1.78)
Age group (ref.: < 60 years)				
60-69 years	**0.82** (0.69-0.98)	**0.77** (0.60-1.00)	**0.72** (0.55-0.94)	**0.62** (0.42-0.90)
70-79 years	**0.55** (0.45-0.66)	**0.39** (0.29-0.52)	**0.46** (0.35-0.61)	**0.28** (0.18-0.44)
≥ 80 years	**0.27** (0.21-0.35)	**0.03** (0.01-0.09)	**0.15** (0.10-0.24)	**0.07** (0.03-0.16)
Tumor location (ref.: pancreas head)				
Pancreas body	**0.69** (0.55-0.87)	1.01 (0.73-1.40)	1.01 (0.68-1.49)	1.01 (0.53-1.95)
Pancreas tail	**0.44** (0.31-0.63)	**0.38** (0.20-0.70)	1.09 (0.73-1.64)	0.86 (0.39-1.91)
Other[2]	**0.82** (0.68-0.98)	0.75 (0.51-1.10)	0.96 (0.76-1.22)	1.16 (0.80-1.68)
TNM stage (ref.: I-II)				
III	1.15 (0.96-1.37)	**2.81** (2.13-3.71)	**1.57** (1.21-2.05)	1.21 (0.69-2.13)
IV	**0.38** (0.32-0.45)	**0.21** (0.15-0.30)	**0.25** (0.19-0.33)	**0.55** (0.37-0.82)

[1]Odds ratios and 95% confidence intervals for chemotherapy versus non-chemotherapy and radiotherapy versus non-radiotherapy in pancreatic cancer patients surviving > 90 days after diagnosis were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and TNM stage. Results for countries with number of patients receiving indicated therapy < 50 (Slovenia, 20; Estonia, 16) were not reported. ORs shown in bold are statistically significant.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified (NOS) parts.

OR, odds ratio; CI, confidence interval; NE, not estimable due to small case number; NA, not available.

3.1.2.7 Associations of chemotherapy and radiotherapy use with additional variables

For resected cancer patients (**Tables 32-33**), those treated in academic hospitals were more likely to receive chemotherapy (OR=1.39) and radiotherapy (OR=2.05). Increasing ECOG scores were associated with less frequent use of radiotherapy in Belgium. Patients received less often radiotherapy after total pancreatectomy versus pancreatoduodenectomy (OR=0.88). For unresected PaC (**Tables 34-35**), patients managed in academic hospitals received more frequently chemotherapy (OR=1.51) and radiotherapy (OR=7.94) in the Netherlands, and more often radiotherapy in Belgium (OR=1.54). In Belgium, chemotherapy and radiotherapy were less commonly used with increasing ECOG scores. Cardiac (OR=0.74), vascular (OR=0.64), and neurological diseases (OR=0.45) and multiple comorbidities (OR=0.65) were associated with less frequent chemotherapy administration in Eindhoven, the Netherlands.

Table 32. Associations of chemotherapy use with hospital type, lymph node ratio, performance status, resection type, and comorbidities for resected pancreatic cancer in countries with available information estimated by adjusted multivariable logistic regression (Huang *et al.*, 2018b)

Variable	The Netherlands		Belgium	
	n	OR (95% CI)	n	OR (95% CI)
Hospital type				
Non-academic	1633	1.00 (reference)	1127	1.00 (reference)
Academic	1312	**1.39** (1.17-1.64)	1502	0.84 (0.70-1.00)
Lymph node ratio (as continuous)	2725	1.31 (0.91-1.88)	-	-
ECOG score				
0	-	-	302	1.00 (references)
1	-	-	1434	0.98 (0.74-1.29)
≥ 2	-	-	182	0.78 (0.52-1.18)
Resection type				
Pancreatoduodenectomy	2472	1.00 (reference)	-	-
Distal pancreatectomy	298	0.92 (0.56-1.52)	-	-
Total pancreatectomy	48	0.60 (0.30-1.21)	-	-
Other	127	**0.39** (0.18-0.85)		
Comorbidity type				
Cardiac disease (yes *vs.* no)	74	1.21 (0.67-2.17)	-	-
Vascular disease (yes *vs.* no)	46	0.99 (0.48-2.06)	-	-
Hypertension (yes *vs.* no)	127	0.91 (0.56-1.49)	-	-
Neurological disease (yes *vs.* no)	11	0.35 (0.06-1.98)	-	-
Diabetes (yes *vs.* no)	107	0.72 (0.43-1.21)	-	-
Pulmonary disease (yes *vs.* no)	38	0.77 (0.35-1.70)	-	-
Comorbidity number				
0	168	1.00 (reference)	-	-
1	140	0.90 (0.51-1.57)	-	-
≥ 2	158	0.88 (0.49-1.57)	-	-

The main logistic regression models adjusted for year of diagnosis, age, sex, tumor location, and TNM stage. ORs were calculated after the additionally investigated variables were included one by one into the main models. Statistically significant ORs are shown in bold.
OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; -, not available; NE, not estimable.

Table 33. Associations of radiotherapy use with hospital type, lymph node ratio, performance status, resection type, and comorbidities for resected pancreatic cancer in countries with available information estimated by adjusted multivariable logistic regression (Huang *et al.*, 2018b)

Variable	the US		The Netherlands		Belgium	
	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Hospital type						
Non-academic	-	-	1633	1.00 (reference)	1127	1.00 (reference)
Academic	-	-	1312	**2.05** (1.28-3.27)	1502	1.13 (0.86-1.50)
Lymph node ratio (as continuous)	14086	1.04 (0.87-1.24)	2725	0.46 (0.15-1.41)	-	-
ECOG score						
0	-	-	-	-	302	1.00 (references)
1	-	-	-	-	1434	**0.65** (0.44-0.97)
≥ 2	-	-	-	-	182	0.64 (0.34-1.20)
Resection type						
Pancreatoduodenectomy	10759	1.00 (reference)	2472	1.00 (reference)	-	-
Distal pancreatectomy	2208	0.95 (0.83-1.09)	298	0.46 (0.11-1.88)	-	-
Total pancreatectomy	1855	**0.88** (0.79-0.98)	48	0.63 (0.08-4.95)	-	-
Other	806	0.83 (0.68-1.02)	127	0.40 (0.11-1.40)		
Comorbidity type						
Cardiac disease (yes *vs.* no)	-	-	74	0.57 (0.07-4.99)	-	-
Vascular disease (yes *vs.* no)	-	-	46	NE	-	-
Hypertension (yes *vs.* no)	-	-	127	0.61 (0.12-3.05)	-	-
Neurological disease (yes *vs.* no)	-	-	11	NE	-	-
Diabetes (yes *vs.* no)	-	-	107	1.10 (0.27-4.44)	-	-
Pulmonary disease (yes *vs.* no)	-	-	38	NE	-	-
Comorbidity number						
0	-	-	168	1.00 (reference)	-	-
1	-	-	140	2.26 (0.65-7.81)	-	-
≥ 2	-	-	158	0.81 (0.13-4.96)	-	-

The main logistic regression models adjusted for year of diagnosis, age, sex, tumor location, and TNM stage. ORs were calculated after the additionally investigated variables were included one by one into the main models. Statistically significant ORs are shown in bold.
OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; -, not available; NE, not estimable.

Table 34. Associations of chemotherapy use with hospital type, lymph node ratio, performance status, resection type, and comorbidities for unresected pancreatic cancer in countries with available information estimated by adjusted multivariable logistic regression (Huang *et al.*, 2018b)

Variable	The Netherlands		Belgium	
	n	OR (95% CI)	n	OR (95% CI)
Hospital type				
Non-academic	16233	1.00 (reference)	5877	1.00 (reference)
Academic	3300	**1.51** (1.37-1.66)	3265	0.98 (0.87-1.11)
ECOG score				
0	-	-	537	1.00 (reference)
1	-	-	4415	0.80 (0.63-1.01)
2	-	-	1295	**0.42** (0.32-0.55)
≥ 3	-	-	569	**0.11** (0.08-0.16)
Comorbidity type				
Cardiac disease (yes *vs.* no)	807	**0.74** (0.57-0.96)	-	-
Vascular disease (yes *vs.* no)	559	**0.64** (0.48-0.85)	-	-
Hypertension (yes *vs.* no)	942	1.00 (0.80-1.25)	-	-
Neurological disease (yes *vs.* no)	198	**0.45** (0.26-0.79)	-	-
Diabetes (yes *vs.* no)	846	0.91 (0.73-1.14)	-	-
Pulmonary disease (yes *vs.* no)	361	0.74 (0.53-1.05)	-	-
Comorbidity number				
0	1164	1.00 (reference)	-	-
1	982	0.97 (0.76-1.23)	-	-
≥ 2	1433	**0.65** (0.51-0.83)	-	-

The main logistic regression models adjusted for year of diagnosis, age, sex, tumor location, and TNM stage. ORs were calculated after the additionally investigated variables were included one by one into the main models. Statistically significant ORs are shown in bold.
OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; -, not available; NE, not estimable.

Table 35. Associations of radiotherapy use with hospital type, lymph node ratio, performance status, resection type, and comorbidities for unresected pancreatic cancer in countries with available information estimated by adjusted multivariable logistic regression (Huang *et al.*, 2018b)

Variable	The Netherlands		Belgium	
	n	OR (95% CI)	n	OR (95% CI)
Hospital type				
Non-academic	16233	1.00 (reference)	5877	1.00 (reference)
Academic	3300	**7.94** (6.27-10.05)	3265	**1.54** (1.26-1.88)
ECOG score				
0	-	-	537	1.00 (reference)
1	-	-	4415	**0.52** (0.38-0.70)
2	-	-	1295	**0.38** (0.26-0.57)
≥ 3	-	-	569	**0.29** (0.16-0.55)
Comorbidity type				
Cardiac disease (yes *vs.* no)	807	1.46 (0.72-2.95)	-	-
Vascular disease (yes *vs.* no)	559	1.51 (0.70-3.28)	-	-
Hypertension (yes *vs.* no)	942	1.17 (0.60-2.29)	-	-
Neurological disease (yes *vs.* no)	198	0.77 (0.18-3.32)	-	-
Diabetes (yes *vs.* no)	846	1.61 (0.87-2.99)	-	-
Pulmonary disease (yes *vs.* no)	361	0.79 (0.21-3.32)	-	-
Comorbidity number				
0	1164	1.00 (reference)	-	-
1	982	1.75 (0.85-3.59)	-	-
≥ 2	1433	1.17 (0.54-2.56)	-	-

The main logistic regression models adjusted for year of diagnosis, age, sex, tumor location, and TNM stage. ORs were calculated after the additionally investigated variables were included one by one into the main models. Statistically significant ORs are shown in bold.
OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; -, not available; NE, not estimable.

3.1.3 Stratified survival of resected and overall pancreatic cancer patients in Europe and the US

(This part has been published (Huang *et al.*, 2018a).)

3.1.3.1 Patient characteristics

Data on a total of 125,183 PaC patients (stage I-II, 42,955 (34%); stage III-IV, 82,228 (66%)) were analyzed (**Table 36**). Patients were diagnosed in comparable periods across all countries (2003/2004 through 2013/2014). Demographic and clinical characteristics for the overall and resected cancer patients with stages I-II and III-IV PaCs are shown in **Tables 37-38**. Within overall PaCs, 66% (Norway) to 91% (Belgium) of stage I-II cancers and 53% (Slovenia) to 86% (Belgium) of stage III-IV tumors were microscopically confirmed. Nearly all resected PaCs were microscopically confirmed (stage I-II, 99%->99%; stage III-IV, 92%-100%).

Table 36. General information on participating registries for Chapter 3.1.3 (Huang *et al.*, 2018a)

Source	Country	Diagnosis period	Censoring date	Registered malignant cases[1]	Excluded cases[2]			Analyzed cases	
					DCO /autopsy	Unknown stage /stage 0	Unknown survival[3]	Stage I-II	Stage III-IV
SEER18[4]	The US	Jan. 2004-Dec. 2013	Dec. 31, 2013	99582	2972 (3)	10144 (10)	0 (0)	31313	55153
NCR	The Netherlands	Jan. 2003-Dec. 2014	Feb 1, 2015	22579	99 (<1)	2796 (12)	0 (0)	5710	13974
BCR	Belgium	Jan. 2004-Dec. 2013	Jul. 1, 2015	12146	-[5]	3077 (25)	0 (0)	3437	5632
CRN	Norway	Jan. 2003-Dec. 2014	Jun. 30, 2015	8022	333 (4)	1509 (19)	2 (<1)	1545	4633
CRS	Slovenia	Jan. 2003-Dec. 2013	May 25, 2016	3376	54 (2)	658 (20)	0 (0)	667	1997

[1]A preliminary data-cleaning process had been performed to exclude cases with ineligible histology types.
[2]Shown as n (percentage [%]).
[3]Unknown survival time and/or vital status.
[4]Data of the year 2003 was not analyzed, as the TNM stage (version 6/7) information was unavailable.
[5]Not routinely registered.
SEER, Surveillance, Epidemiology, and End Results Program; NCR, The Netherlands Cancer Registry; BCR, Belgian Cancer Registry; CRN, Cancer Registry of Norway; CRS, Cancer Registry of Slovenia; DCO, death certificate only.

In stage I-II PaCs (**Table 37**), 49%-55% of the overall patients were female. The mean age was 69-72 years. Most cancers were located in pancreas head (81%-89%). Only 10%-18% of the tumors were well-differentiated. Chemotherapy was administered for 17% (Norway) to 52% (Belgium) of the European patients. Radiotherapy was more frequently applied in the US (14%) than in Europe (1% (Slovenia) to 10% (Belgium)). Resection rates were 34% (Norway) to 63% (Belgium). Compared to overall patients, resected cancer patients were less frequently female and mostly younger. Tumor location was comparable, but slightly fewer cancers were well-differentiated (6%-17%). Neoadjuvant chemotherapy (1%-3%) and radiotherapy (0%-4%) were rarely used. Resected cancer patients received more frequently adjuvant chemotherapy (24%-56%), but less often radiotherapy (1%-9%) compared to the overall patient groups in Europe. In the US, resected patients received markedly more often radiotherapy (32%) compared to the overall US or the resected European patients.

Table 37. Demographic and clinical characteristics of stage I-II pancreatic cancer patients (Huang *et al.*, 2018a)

Parameter	**The US** (2004-2013)		**Netherlands** (2003-2014)		**Belgium** (2004-2013)	
Group	*Overall*	*Resected*	*Overall*	*Resected*	*Overall*	*Resected*
n	31313	13303 (43)	5710	2675 (47)	3437	2155 (63)
Microscopically confirmed[1]	27290 (87)	13290 (>99)	4046 (71)	2673 (>99)	3127 (91)	2148 (>99)
Gender, female	16193 (52)	6604 (50)	2951 (52)	1268 (47)	1684 (49)	993 (46)
Age [year]	70 ± 12	66 ± 11	71 ± 11	65 ± 10	69 ± 11	66 ± 10
Age group						
< 60 years	6100 (20)	3574 (27)	981 (17)	693 (26)	686 (20)	546 (25)
60-69 years	7817 (25)	4272 (32)	1477 (26)	978 (37)	937 (27)	698 (32)
≥ 70 years	17396 (56)	5457 (41)	3252 (57)	1004 (38)	1814 (53)	911 (42)
Tumor location[1]						
Pancreas head	22412 (83)	9573 (80)	4666 (89)	2187 (89)	1807 (81)	1207 (82)
Pancreas body	2502 (9)	890 (8)	255 (5)	91 (4)	179 (8)	100 (7)
Pancreas tail	2196 (8)	1448 (12)	296 (6)	191 (8)	244 (11)	169 (11)
Other	4203 (13)	1392 (11)	493 (9)	206 (8)	1207 (35)	679 (32)
Differentiation[2]						
Well	2145 (13)	1428 (12)	283 (12)	244 (11)	389 (18)	302 (17)
Intermediate	7574 (47)	6026 (51)	1225 (51)	1138 (52)	1072 (48)	901 (50)
Poor/undifferentiated	6264 (39)	4464 (38)	920 (38)	802 (37)	762 (34)	608 (34)
Neoadjuvant chemotherapy	-	NA	-	50 (2)	-	53 (3)
Neoadjuvant radiotherapy	-	522 (4)	-	34 (1)	-	20 (1)
Resection type						
Pancreatoduodenectomy	-	9479 (71)	-	2269 (85)	-	NA
Distal pancreatectomy	-	1878 (14)	-	256 (10)	-	NA
Total pancreatectomy	-	1629 (12)	-	42 (2)	-	NA
Other[3]	-	314 (2)	-	108 (4)	-	NA
Adjuvant/palliative chemotherapy	NA	NA	1392 (24)	1078 (40)	1796 (52)	1200 (56)
Adjuvant/palliative radiotherapy	4460 (14)	4193 (32)	120 (2)	33 (1)	326 (10)	190 (9)

Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below.

[1]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of the 3 locations; 'other' includes pancreas duct, overlapping lesion, NOS, and other specified parts, and its proportion is relative to the whole cases.

[2]Unknown differentiation: the US, overall: 15330 (49%), resected: 1385 (10%); The Netherlands, overall: 3282 (58%), resected: 491 (18%); Belgium, overall: 1214 (35%), resected: 344 (16%); Norway, overall: 909 (59%), resected: 100 (19%); Slovenia, overall: 252 (38%), resected: 35 (9%); Estonia, overall: 134 (47%), resected: 32 (20%).

[3]Pancreatectomy (NOS) and local resection.

NOS, not otherwise specified; NA, not available; -, not applicable.

Table 37. Demographic and clinical characteristics of stage I-II pancreatic cancer patients (Huang *et al.*, 2018a) (continued)

Parameter	**Norway** (2003-2014)		**Slovenia** (2003-2013)	
Group	*Overall*	*Resected*	*Overall*	*Resected*
n	1545	526 (34)	667	406 (61)
Microscopically confirmed[1]	1017 (66)	520 (99)	475 (71)	401 (99)
Gender, female	853 (55)	261 (50)	361 (54)	209 (52)
Age [year]	72 ± 12	65 ± 11	69 ± 11	65 ± 10
Age group				
< 60 years	234 (15)	134 (26)	144 (22)	122 (30)
60-69 years	375 (24)	195 (37)	166 (25)	131 (32)
≥ 70 years	936 (61)	197 (37)	357 (54)	153 (38)
Tumor location[1]				
Pancreas head	851 (85)	394 (84)	471 (88)	321 (87)
Pancreas body	87 (9)	33 (7)	35 (7)	26 (7)
Pancreas tail	62 (6)	41 (9)	32 (6)	21 (6)
Other	545 (35)	58 (11)	129 (19)	38 (9)
Differentiation[2]				
Well	61 (10)	27 (6)	41 (10)	37 (10)
Intermediate	352 (55)	259 (61)	153 (37)	142 (38)
Poor/undifferentiated	223 (35)	135 (32)	221 (53)	192 (52)
Neoadjuvant chemotherapy	-	NA	-	2 (1)
Neoadjuvant radiotherapy	-	0 (0)	-	1 (<1)
Resection type				
Pancreatoduodenectomy	-	NA	-	NA
Distal pancreatectomy	-	NA	-	NA
Total pancreatectomy	-	NA	-	NA
Other[3]	-	NA	-	NA
Adjuvant/palliative chemotherapy	265 (17)	127 (24)	131 (20)	120 (30)
Adjuvant/palliative radiotherapy	64 (4)	17 (3)	9 (1)	8 (2)

Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below.

[1]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of the 3 locations; 'other' includes pancreas duct, overlapping lesion, NOS, and other specified parts, and its proportion is relative to the whole cases.

[2]Unknown differentiation in stage I-II cancer: the US, overall: 15330 (49%), resected: 1385 (10%); The Netherlands, overall: 3282 (58%), resected: 491 (18%); Belgium, overall: 1214 (35%), resected: 344 (16%); Norway, overall: 909 (59%), resected: 100 (19%); Slovenia, overall: 252 (38%), resected: 35 (9%); Estonia, overall: 134 (47%), resected: 32 (20%).

[3]Pancreatectomy (NOS) and local resection.

NOS, not otherwise specified; NA, not available; -, not applicable.

Compared to patients with stage I-II PaCs, overall patients with stage III-IV cancers were less frequently women (48%-50%), and were younger (mean age, 68-71 years; **Table 38**). Pancreatic head cancers comprised smaller proportions (56%-64%), and well-differentiated tumors were rarer (8%-17%). Chemotherapy was more often used (18% (Slovenia) to 65% (Belgium)), while radiotherapy was less frequently administered (1% (the US) to 6% (Belgium)). Resection rates ranged from 2% (the Netherlands) to 7% (Slovenia). The comparison patterns of resected versus overall cancer patients with stage III-IV PaCs were similar to those with stage I-II tumors regarding patient sex, age, tumor differentiation, and chemotherapy application. However, the proportions of pancreatic head cancers among resected tumor patients were greater (66%-79%). Neoadjuvant chemotherapy (0%-8%) and radiotherapy rates (0%-7%) remained low. Radiotherapy was used for 3%-19% of resected cancer patients, and was again more frequently administered in the US.

Table 38. Demographic and clinical characteristics of stage III-IV pancreatic cancer patients (Huang *et al.*, 2018a)

Parameter	**The US** (2004-2013)		**Netherlands** (2003-2014)		**Belgium** (2004-2013)	
Group	*Overall*	*Resected*	*Overall*	*Resected*	*Overall*	*Resected*
n	55153	1998 (4)	13974	237 (2)	5632	298 (5)
Microscopically confirmed[1]	46973 (85)	1994 (>99)	10375 (74)	237 (100)	4837 (86)	297 (>99)
Gender, female	26427 (48)	969 (49)	6755 (48)	106 (45)	2700 (48)	154 (52)
Age [year]	69 ± 12	65 ± 12	68 ± 11	64 ± 10	69 ± 11	64 ± 10
Age group						
< 60 years	12582 (23)	636 (32)	2938 (21)	69 (29)	1043 (19)	92 (31)
60-69 years	15081 (27)	622 (31)	4412 (32)	96 (41)	1608 (29)	103 (35)
≥ 70 years	27490 (50)	740 (37)	6624 (47)	72 (30)	2981 (53)	103 (35)
Tumor location[1]						
Pancreas head	21244 (56)	1069 (66)	7202 (62)	166 (79)	1585 (58)	126 (69)
Pancreas body	7893 (21)	168 (10)	1844 (16)	11 (5)	508 (19)	19 (10)
Pancreas tail	9003 (24)	381 (24)	2666 (23)	34 (16)	649 (24)	37 (20)
Other	17013 (31)	380 (19)	2262 (16)	26 (11)	2890 (51)	116 (39)
Differentiation[2]						
Well	1213 (10)	173 (11)	222 (9)	20 (11)	425 (17)	42 (17)
Intermediate	4518 (35)	680 (45)	833 (35)	98 (51)	962 (39)	113 (47)
Poor/undifferentiated	6795 (56)	670 (44)	1340 (56)	73 (38)	1082 (44)	88 (36)
Neoadjuvant chemotherapy	-	NA	-	15 (6)	-	24 (8)
Neoadjuvant radiotherapy	-	139 (7)	-	5 (2)	-	9 (3)
Resection type						
Pancreatoduodenectomy	-	1140 (57)	-	178 (75)	-	NA
Distal pancreatectomy	-	295 (15)	-	39 (17)	-	NA
Total pancreatectomy	-	211 (11)	-	5 (2)	-	NA
Other[3]	-	352 (18)	-	15 (6)	-	NA
Adjuvant/palliative chemotherapy	NA	NA	3475 (25)	81 (34)	3661 (65)	195 (65)
Adjuvant/palliative radiotherapy	770 (1)	383 (19)	328 (2)	7 (3)	358 (6)	35 (12)

Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below.

[1]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of the 3 locations; 'other' includes pancreas duct, overlapping lesion, NOS, and other specified parts, and its proportion is relative to the whole cases.

[2]Unknown differentiation: the US, overall: 42627 (77%), resected: 475 (24%); The Netherlands, overall: 11579 (83%), resected: 46 (19%); Belgium, overall: 3163 (56%), resected:55 (19%); Norway, overall: 3150 (68%), resected: 26 (24%); Slovenia, overall: 1555 (78%), resected: 47 (35%); Estonia, overall: 718 (86%), resected: 5 (28%).

[3]Pancreatectomy (NOS) and local resection.

NOS, not otherwise specified; NA, not available; -, not applicable.

Table 38. Demographic and clinical characteristics of stage III-IV pancreatic cancer patients (Huang *et al.*, 2018a) (continued)

Parameter	**Norway** (2003-2014)		**Slovenia** (2003-2013)	
Group	*Overall*	*Resected*	*Overall*	*Resected*
n	4633	108 (2)	1997	135 (7)
Microscopically confirmed[1]	3224 (70)	105 (97)	1056 (53)	124 (92)
Gender, female	2332 (50)	47 (44)	967 (48)	56 (42)
Age [year]	71 ± 12	64 ± 10	69 ± 11	65 ± 10
Age group				
< 60 years	759 (16)	32 (30)	393 (20)	40 (30)
60-69 years	1268 (27)	43 (40)	513 (26)	45 (33)
≥ 70 years	2606 (56)	26 (24)	1091 (55)	43 (32)
Tumor location[1]				
Pancreas head	1245 (63)	57 (66)	653 (64)	80 (78)
Pancreas body	340 (17)	8 (9)	160 (16)	12 (12)
Pancreas tail	382 (19)	21 (24)	215 (21)	10 (10)
Other	2666 (58)	22 (20)	969 (49)	33 (24)
Differentiation[3]				
Well	122 (8)	6 (7)	33 (8)	6 (7)
Intermediate	596 (40)	50 (61)	112 (25)	30 (34)
Poor/undifferentiated	765 (52)	26 (32)	297 (67)	52 (59)
Neoadjuvant chemotherapy	-	NA	-	0 (0)
Neoadjuvant radiotherapy	-	0 (0)	-	0 (0)
Resection type				
Pancreatoduodenectomy	-	NA	-	NA
Distal pancreatectomy	-	NA	-	NA
Total pancreatectomy	-	NA	-	NA
Other[3]	-	NA	-	NA
Adjuvant/palliative chemotherapy	1159 (25)	25 (23)	368 (18)	39 (29)
Adjuvant/palliative radiotherapy	198 (4)	4 (4)	46 (2)	5 (4)

Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation. Records are complete otherwise specified below.

[1]The percentages of pancreas head, body, and tail are the proportions compared to the total tumor cases of the 3 locations; 'other' includes pancreas duct, overlapping lesion, NOS, and other specified parts, and its proportion is relative to the whole cases.

[2] Unknown differentiation: the US, overall: 42627 (77%), resected: 475 (24%); The Netherlands, overall: 11579 (83%), resected: 46 (19%); Belgium, overall: 3163 (56%), resected:55 (19%); Norway, overall: 3150 (68%), resected: 26 (24%); Slovenia, overall: 1555 (78%), resected: 47 (35%); Estonia, overall: 718 (86%), resected: 5 (28%).

[3]Pancreatectomy (NOS) and local resection.

NOS, not otherwise specified; NA, not available; -, not applicable.

3.1.3.2 Survival of overall and resected stage I-II pancreatic cancer patients

Survival of overall and resected stage I-II cancer patients is shown in **Figures 6-7**, and the corresponding 1-month to 5-year survival rates are detailed in **Table 39**. For overall cancer patients, survival was lower in older patients and decreased strongly after diagnosis, with 3-year survival rates of 20%-34% (<60 years), 14%-25% (60-69 years), and 9%-13% (≥70 years), respectively. The subgroup of resected cancer patients of all age groups in all countries had higher survival estimates, with 1-month (perioperative) survival rates of 98%-100% (<60 years), 97%-99% (60-69 years) and 94%-99% (≥70 years), and 3-year survival rates of 23%-39% (<60 years), 16%-31% (60-69 years) and 17%-30% (≥70 years), respectively. Again, younger patients had better survival than older ones. However, age-specific differences were smaller, especially between those aged 60-69 and ≥70 years.

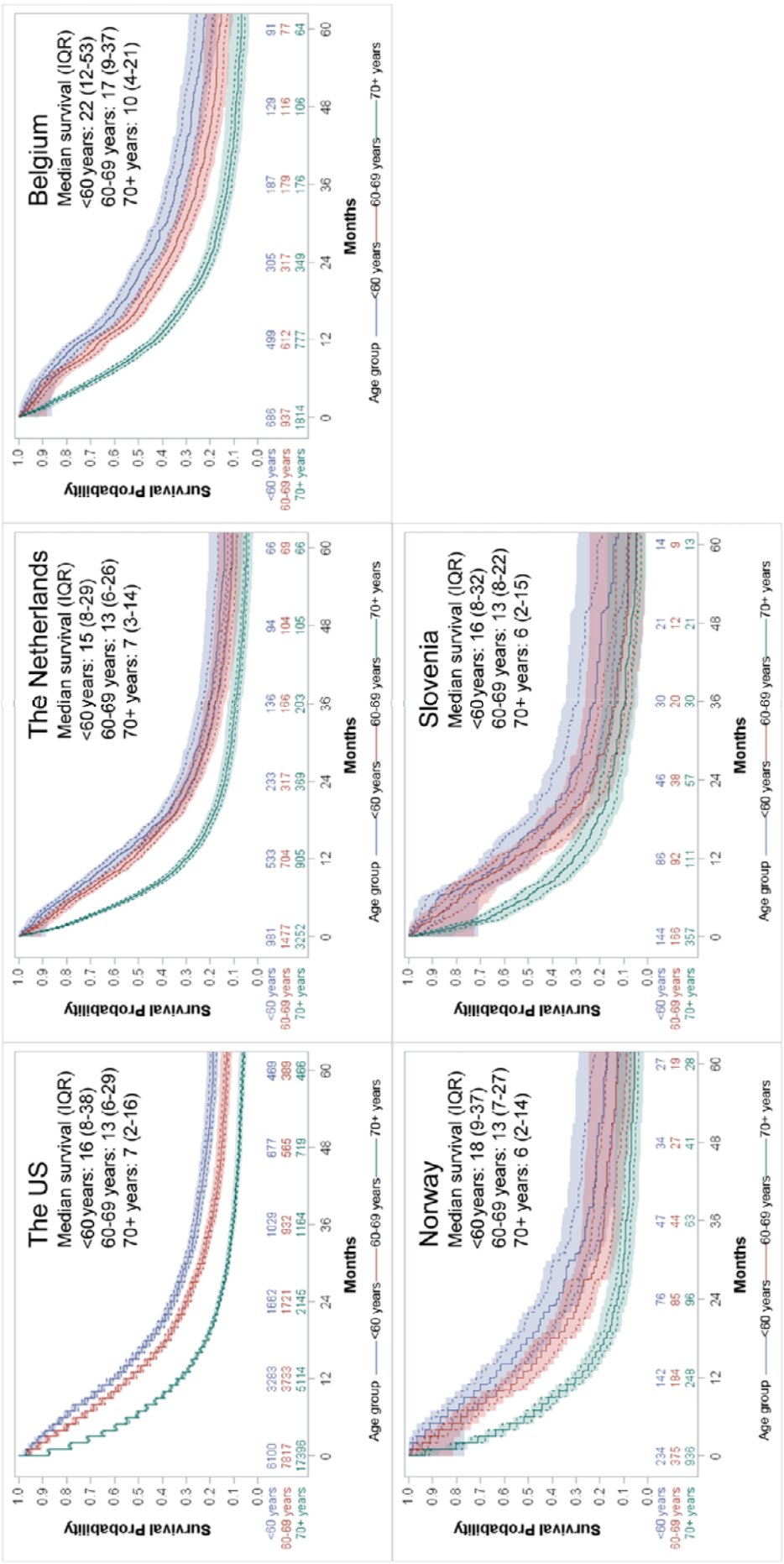

Figure 6. Kaplan-Meier curves (solid lines) of age group-specific survival in overall cancer patients with TNM stage I-II pancreatic cancers. The dashed lines indicate the 95% confidence limits and the shadows represent the Hall-Wellner confidence bands. Numbers of patients at risk are also shown. Median survival is in months. IQR, interquartile range. (Huang *et al.*, 2018a)

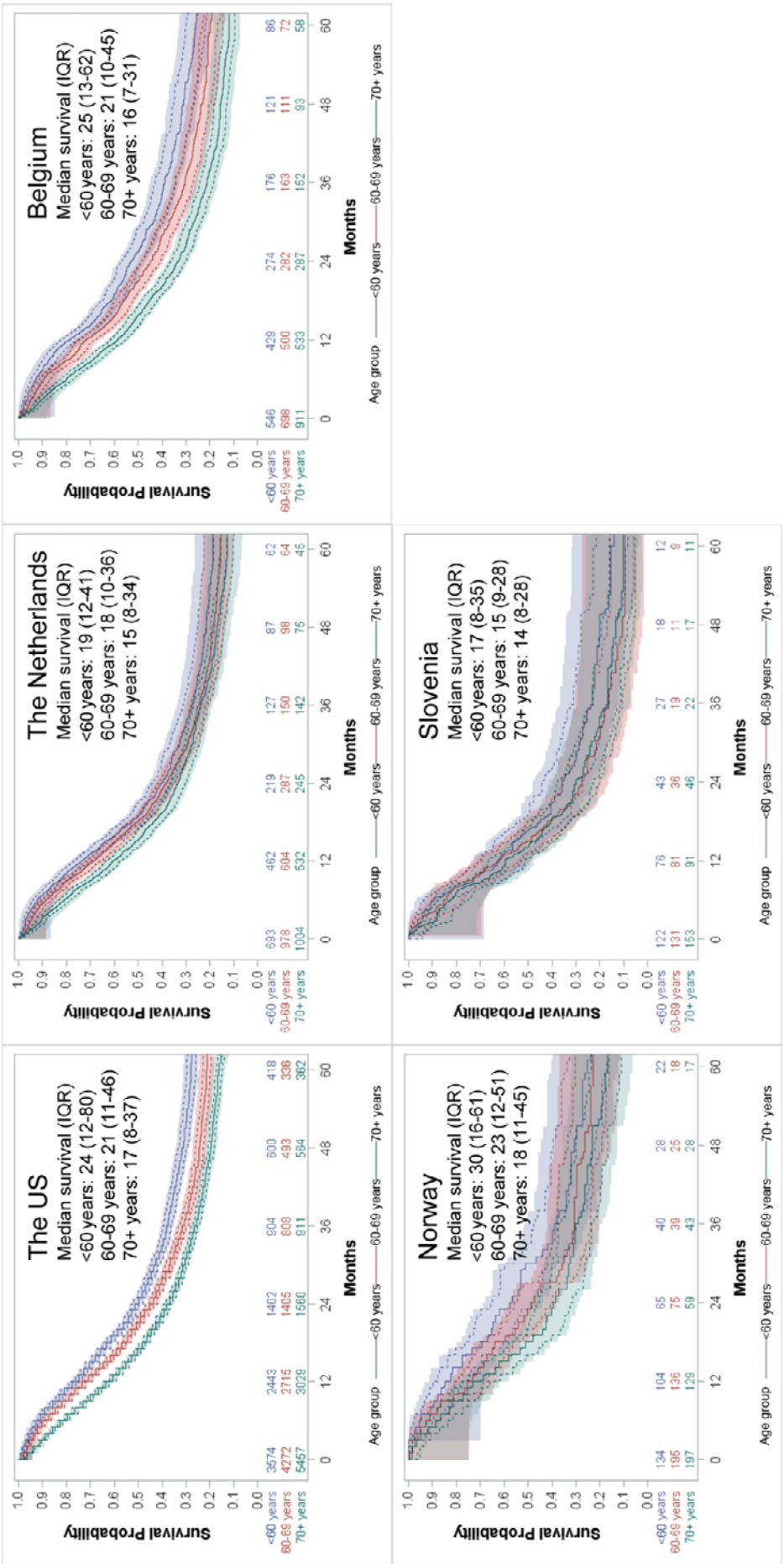

Figure 7. Kaplan-Meier curves (solid lines) of age group-specific survival in resected cancer patients with TNM stage I-II pancreatic cancers. The dashed lines indicate the 95% confidence limits and the shadows represent the Hall-Wellner confidence bands. Numbers of patients at risk are also shown. Median survival is in months. IQR, interquartile range. (Huang *et al.*, 2018a)

Table 39. Unadjusted survival proportions of overall and resected stage I-II pancreatic cancer patients (Huang *et al.*, 2018a)

Time	The US		The Netherlands		Belgium	
	Overall	***Resected***	***Overall***	***Resected***	***Overall***	***Resected***
	OS (95% CI)[1]	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)
1 month						
< 60 years	95 (94-95)	98 (98-99)	97 (96-98)	98 (97-99)	98 (97-99)	99 (97-99)
60-69 years	92 (91-93)	97 (96-97)	95 (94-96)	97 (96-98)	97 (96-98)	98 (97-99)
≥ 70 years	79 (78-79)	94 (93-94)	88 (87-89)	96 (95-97)	93 (92-94)	96 (94-97)
3 months						
< 60 years	89 (88-90)	96 (95-97)	92 (90-94)	97 (95-98)	95 (93-96)	96 (94-98)
60-69 years	84 (84-85)	94 (93-95)	87 (85-89)	94 (93-96)	93 (91-94)	94 (92-96)
≥ 70 years	65 (64-66)	89 (88-90)	72 (70-73)	91 (89-92)	83 (81-84)	90 (88-92)
6 months						
< 60 years	80 (79-81)	91 (90-92)	81 (78-83)	92 (90-94)	90 (87-92)	93 (90-95)
60-69 years	73 (72-74)	88 (86-89)	76 (74-78)	89 (86-91)	86 (83-88)	89 (87-91)
≥ 70 years	51 (50-51)	80 (79-81)	53 (51-55)	81 (78-83)	67 (65-69)	80 (77-83)
12 months						
< 60 years	59 (57-60)	75 (73-76)	60 (56-63)	74 (70-77)	73 (70-76)	78 (75-82)
60-69 years	52 (51-53)	71 (69-72)	53 (50-55)	68 (65-71)	65 (62-68)	72 (68-75)
≥ 70 years	31 (31-32)	61 (59-62)	30 (29-32)	61 (57-64)	43 (40-45)	58 (55-62)
24 months						
< 60 years	35 (34-37)	50 (48-52)	30 (27-33)	40 (36-44)	47 (43-51)	53 (49-57)
60-69 years	29 (28-30)	44 (42-45)	28 (25-30)	38 (35-42)	38 (35-41)	45 (41-48)
≥ 70 years	16 (15-16)	37 (35-38)	14 (13-15)	33 (30-37)	21 (19-23)	33 (30-36)
36 months						
< 60 years	26 (24-27)	37 (36-39)	20 (18-23)	27 (24-31)	34 (30-37)	39 (35-43)
60-69 years	20 (19-21)	31 (29-32)	18 (16-20)	25 (22-28)	25 (22-28)	30 (27-34)
≥ 70 years	10 (10-11)	26 (24-27)	9 (8-11)	24 (21-27)	13 (11-14)	21 (19-24)
60 months						
< 60 years	19 (18-20)	28 (26-30)	14 (12-17)	19 (16-23)	23 (19-26)	26 (22-30)
60-69 years	13 (12-14)	21 (20-23)	11 (9-13)	16 (13-19)	16 (14-19)	20 (17-23)
≥ 70 years	6 (6-7)	16 (15-17)	5 (4-6)	13 (10-16)	7 (6-8)	12 (10-15)

[1]Data are shown as survival proportion (95% confidence interval) [%].

OS, overall survival; CI, confidence interval.

Table 39. Unadjusted survival proportions of overall and resected stage I-II pancreatic cancer patients (Huang *et al.*, 2018a) (continued)

Time	Norway		Slovenia	
	Overall	***Resected***	***Overall***	***Resected***
	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)
1 month				
< 60 years	98 (96-99)	100 (100-100)	97 (93-99)	98 (93-99)
60-69 years	97 (94-98)	99 (95-100)	96 (92-98)	99 (94-100)
≥ 70 years	89 (86-90)	99 (95-100)	85 (81-89)	99 (95-100)
3 months				
< 60 years	95 (92-97)	99 (95-100)	92 (86-95)	94 (88-97)
60-69 years	90 (86-93)	97 (93-99)	90 (84-94)	96 (91-98)
≥ 70 years	68 (65-71)	95 (91-98)	66 (61-71)	88 (82-92)
6 months				
< 60 years	86 (81-90)	96 (90-98)	88 (81-92)	89 (82-94)
60-69 years	77 (72-81)	91 (86-95)	78 (71-84)	85 (77-90)
≥ 70 years	50 (47-53)	88 (83-92)	50 (45-55)	82 (75-88)
12 months				
< 60 years	64 (57-70)	82 (75-88)	60 (52-68)	63 (54-71)
60-69 years	52 (47-57)	73 (66-79)	55 (48-63)	62 (53-70)
≥ 70 years	28 (25-31)	70 (63-76)	31 (26-36)	60 (51-67)
24 months				
< 60 years	38 (32-45)	58 (48-66)	33 (25-41)	36 (27-44)
60-69 years	29 (24-34)	48 (40-55)	23 (17-30)	28 (20-35)
≥ 70 years	13 (10-15)	38 (31-45)	16 (12-20)	30 (23-37)
36 months				
< 60 years	26 (20-32)	39 (30-48)	22 (16-29)	23 (16-31)
60-69 years	18 (14-23)	31 (24-38)	14 (9-19)	16 (11-23)
≥ 70 years	9 (7-11)	30 (23-37)	9 (7-13)	17 (11-23)
60 months				
< 60 years	17 (12-23)	25 (17-34)	15 (9-21)	15 (9-23)
60-69 years	13 (9-17)	23 (16-30)	8 (5-13)	10 (5-16)
≥ 70 years	6 (4-7)	17 (11-24)	5 (3-8)	10 (6-16)

[1]Data are shown as survival proportion (95% confidence interval) [%].

OS, overall survival; CI, confidence interval.

3.1.3.3 Survival of overall and resected stage III-IV pancreatic cancer patients

Considering the potential varying proportions of underreporting of advanced-stage cancers, survival results for stage III-IV PaC patients should be interpreted with caution. The survival of the overall and resected stage III-IV cancer patients is shown in **Figures 8-9**, and the corresponding 1-month to 5-year survival rates are detailed in **Table 40**. Generally, patients with stage III-IV cancers had much lower survival than those with stage I-II tumors, and already had high mortality shortly after diagnosis. In the overall patient group, survival decreased with increasing age, with 3-year survival rates of 2%-5% (<60 years), 1%-2% (60-69 years), and 1%-1% (≥70 years), respectively. The resected cancer patient subgroups showed higher survival estimates than the overall in all countries and all age groups (perioperative survival rates: <70 years, 94%-99%; ≥70 years, 81%-96%; 3-year survival rates: <70 years, 5%-19%; ≥70 years, 2%-14%). The differences between age groups were smaller in the resected cancer patient subgroups than the overall patient population.

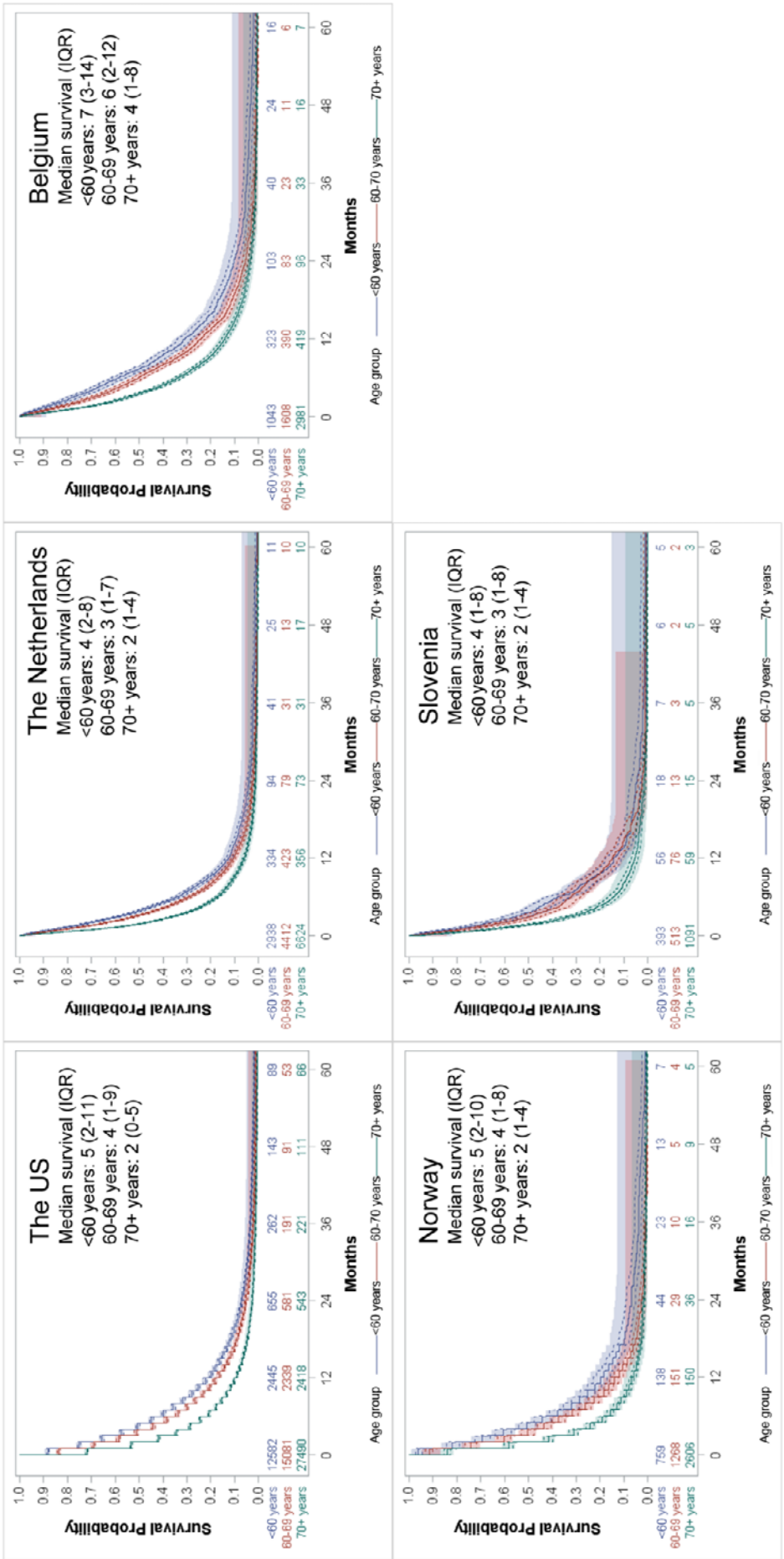

Figure 8. Kaplan-Meier curves (solid lines) of age group-specific survival of overall cancer patients with TNM stage III-IV pancreatic cancers. The dashed lines indicate the 95% confidence limits and the shadows represent the Hall-Wellner confidence bands. The numbers of patients at risk are also shown. Median survival is in months. IQR, interquartile range. (Huang *et al.*, 2018a)

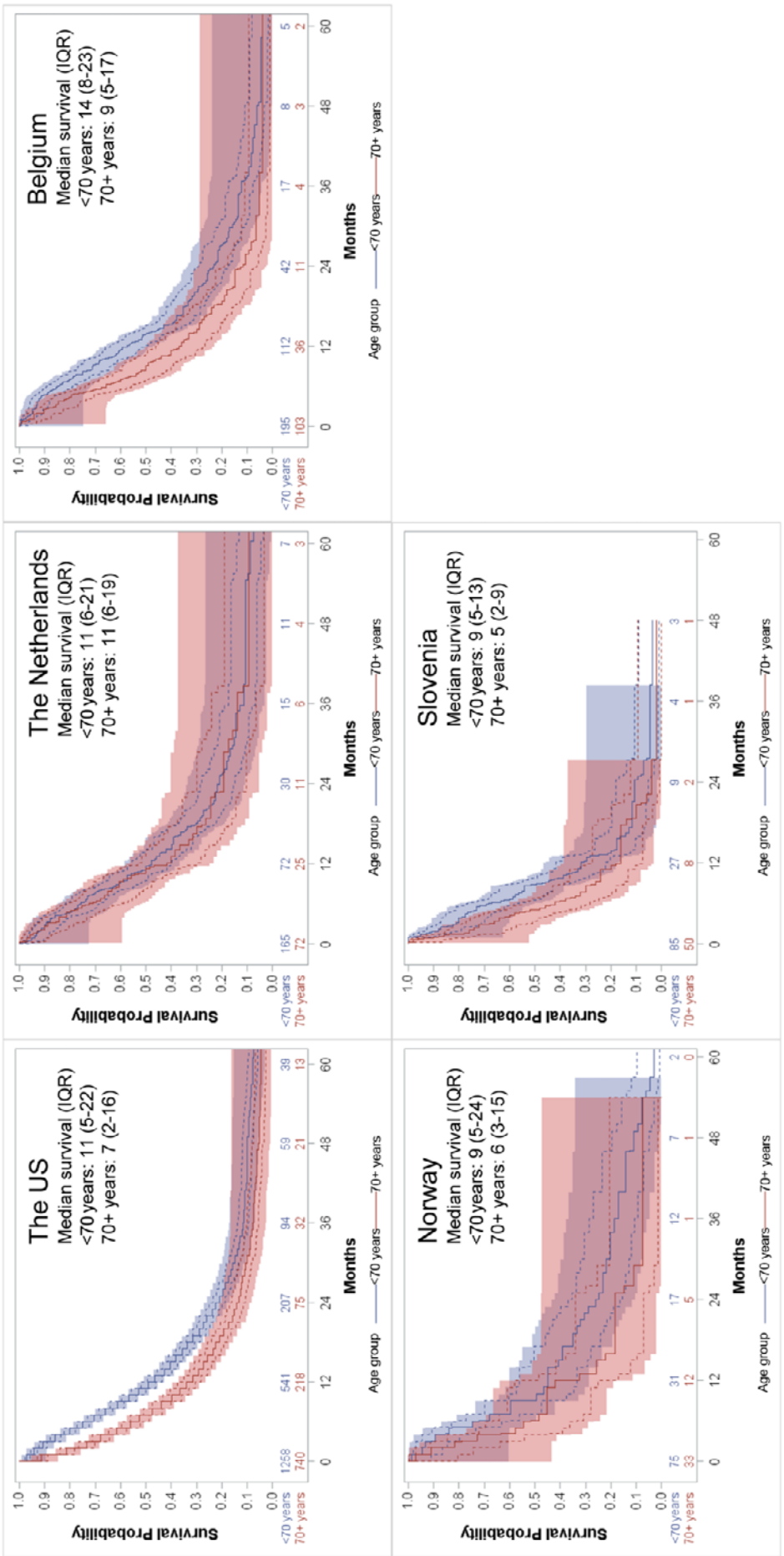

Figure 9. Kaplan-Meier curves (solid lines) of age group-specific survival of resected cancer patients with TNM stage III-IV pancreatic cancers. The dashed lines indicate the 95% confidence limits and the shadows represent the Hall-Wellner confidence bands. The numbers of patients at risk are also shown. Median survival is in months. IQR, interquartile range. (Huang *et al.*, 2018a)

Table 40. Unadjusted survival proportions of overall and resected stage III-IV pancreatic cancer patients (Huang *et al.*, 2018a)

Time	The US		The Netherlands		Belgium	
	Overall	***Resected***[2]	***Overall***	***Resected***	***Overall***	***Resected***
	OS (95% CI)[1]	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)
1 month						
< 60 years	75 (74-76)	94 (93-96)	86 (85-87)	94 (89-97)	93 (92-95)	99 (95-100)
60-69 years	69 (68-70)		81 (80-82)		89 (88-91)	
≥ 70 years	53 (53-54)	81 (78-84)	69 (68-70)	96 (88-99)	81 (80-83)	96 (90-99)
3 months						
< 60 years	58 (57-58)	86 (84-88)	59 (57-61)	90 (84-93)	78 (75-80)	93 (89-96)
60-69 years	51 (50-52)		52 (50-53)		69 (67-71)	
≥ 70 years	34 (34-35)	68 (64-71)	36 (35-37)	89 (79-94)	55 (53-56)	85 (77-91)
6 months						
< 60 years	40 (39-41)	71 (68-73)	34 (32-36)	76 (68-82)	59 (56-62)	85 (79-89)
60-69 years	34 (33-35)		29 (28-31)		50 (48-53)	
≥ 70 years	21 (20-21)	53 (49-56)	18 (17-18)	72 (60-82)	34 (32-35)	66 (56-74)
12 months						
< 60 years	20 (19-21)	47 (44-50)	13 (11-14)	48 (40-56)	31 (28-34)	57 (50-64)
60-69 years	16 (16-17)		11 (10-12)		24 (22-26)	
≥ 70 years	9 (9-9)	32 (28-35)	6 (5-7)	42 (30-53)	14 (13-15)	36 (27-45)
24 months						
< 60 years	7 (6-7)	21 (19-24)	4 (3-5)	21 (15-28)	10 (9-12)	23 (17-29)
60-69 years	5 (5-6)		2 (2-3)		6 (5-7)	
≥ 70 years	3 (2-3)	13 (11-16)	1 (1-2)	19 (10-30)	4 (3-4)	12 (6-19)
36 months						
< 60 years	3 (3-4)	11 (9-13)	2 (2-3)	11 (7-17)	5 (4-7)	12 (8-17)
60-69 years	2 (2-2)		1 (1-1)		2 (1-3)	
≥ 70 years	1 (1-1)	8 (5-10)	1 (1-1)	14 (7-24)	1 (1-2)	5 (2-11)
60 months						
< 60 years	2 (2-2)	8 (6-10)	1 (1-1)	9 (5-14)	2 (1-4)	4 (2-8)
60-69 years	1 (1-1)		1 (<1-1)		1 (<1-1)	
≥ 70 years	1 (1-1)	5 (3-7)	<1 (<1-1)	9 (3-19)	1 (<1-1)	4 (1-10)

[1]Data are shown as survival proportion (95% confidence interval) [%].

[2]For the resected group in each center, the age groups '< 60 years' and '60-69 years' were combined to the group '< 70 years' due to limited case numbers.

OS, overall survival; CI, confidence interval; NA, not available.

Table 40. Unadjusted survival proportions of overall and resected stage III-IV pancreatic cancer patients (Huang *et al.*, 2018a) (continued)

Time	Norway		Slovenia	
	Overall	***Resected***	***Overall***	***Resected***
	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)
1 month				
< 60 years	91 (89-93)	97 (90-99)	83 (79-86)	99 (92-100)
60-69 years	84 (82-86)		79 (75-82)	
≥ 70 years	73 (71-74)	91 (74-97)	67 (64-70)	90 (78-96)
3 months				
< 60 years	65 (62-68)	89 (80-95)	55 (50-60)	81 (71-88)
60-69 years	57 (54-59)		49 (44-53)	
≥ 70 years	37 (35-39)	76 (57-87)	33 (30-35)	68 (53-79)
6 months				
< 60 years	41 (38-45)	72 (60-81)	38 (33-42)	68 (57-77)
60-69 years	35 (32-38)		32 (28-36)	
≥ 70 years	18 (16-19)	49 (31-64)	14 (12-16)	42 (28-55)
12 months				
< 60 years	19 (16-22)	45 (33-56)	14 (11-18)	32 (22-42)
60-69 years	13 (11-14)		15 (12-18)	
≥ 70 years	6 (5-7)	39 (22-55)	5 (4-7)	16 (8-27)
24 months				
< 60 years	7 (5-9)	25 (15-35)	5 (3-7)	11 (5-18)
60-69 years	3 (2-4)		3 (1-4)	
≥ 70 years	2 (1-2)	19 (7-34)	1 (1-2)	4 (1-12)
36 months				
< 60 years	4 (3-6)	19 (11-29)	2 (1-4)	5 (2-11)
60-69 years	1 (1-2)		1 (<1-2)	
≥ 70 years	1 (1-1)	7 (1-21)	1 (<1-1)	2 (<1-9)
60 months				
< 60 years	1 (1-3)	3 (1-10)	1 (1-3)	4 (1-9)
60-69 years	1 (<1-1)		1 (<1-2)	
≥ 70 years	<1 (<1-1)	NA	<1 (<1-1)	NA

[1]Data are shown as survival proportion (95% confidence interval) [%].

[2]For the resected group in each center, the age groups '< 60 years' and '60-69 years' were combined to the group '< 70 years' due to limited case numbers.

OS, overall survival; CI, confidence interval; NA, not available.

3.1.3.4 Survival of overall stage I-II and III-IV pancreatic cancer patients with microscopic confirmation

Considering the relatively high proportions of overall PaC patients without microscopic confirmation, sensitivity analyses were conducted by limiting the overall stage I-II and III-IV cancer patients to those with microscopically confirmed cancers (**Figures 10-11** and **Table 41**). Patients with microscopically confirmed stage I-II and III-IV cancers generally had higher survival especially in those ≥70 years and within 24 months after diagnosis, in all participating countries except Belgium, where microscopic confirmation rates were high and where survival remained very similar. The 3-year survival rates remained mostly similar to the results of the main analyses, and were 21%-34% (<60 years), 14%-25% (60-69 years), and 12%-14% (≥70 years) for stage I-II PaC, and 2%-5% (<60 years), 1%-2% (60-69 years), and 1%-1% (≥70 years) for stage III-IV tumor.

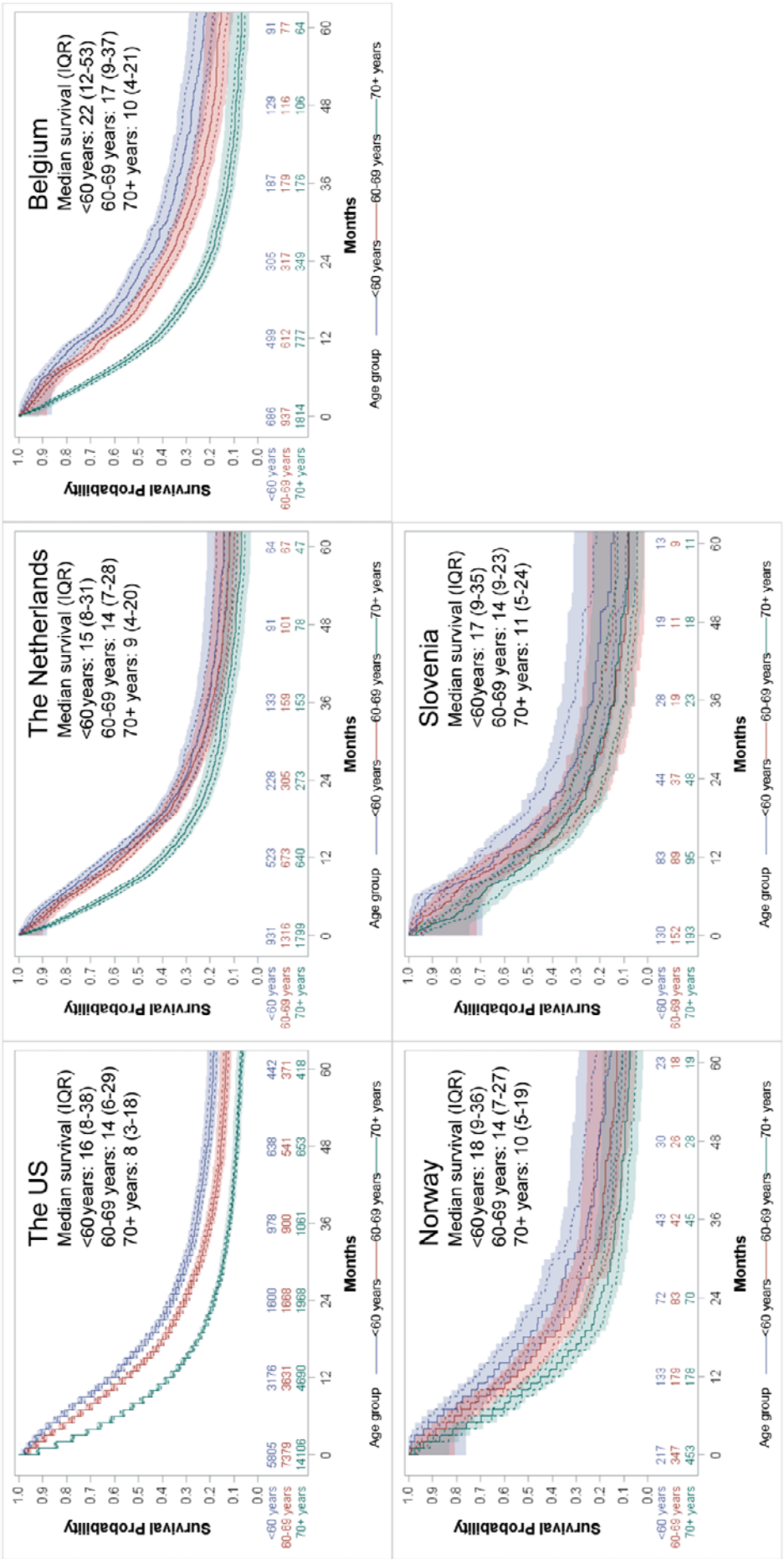

Figure 10. Kaplan-Meier curves (solid lines) of age group-specific survival in microscopically confirmed overall TNM stage I-II pancreatic cancer patients. The dashed lines indicate the 95% confidence limits and the shadows represent the Hall-Wellner confidence bands. Numbers of patients at risk are also reported. Median survival is in months. IQR, interquartile range. (Huang *et al.*, 2018a)

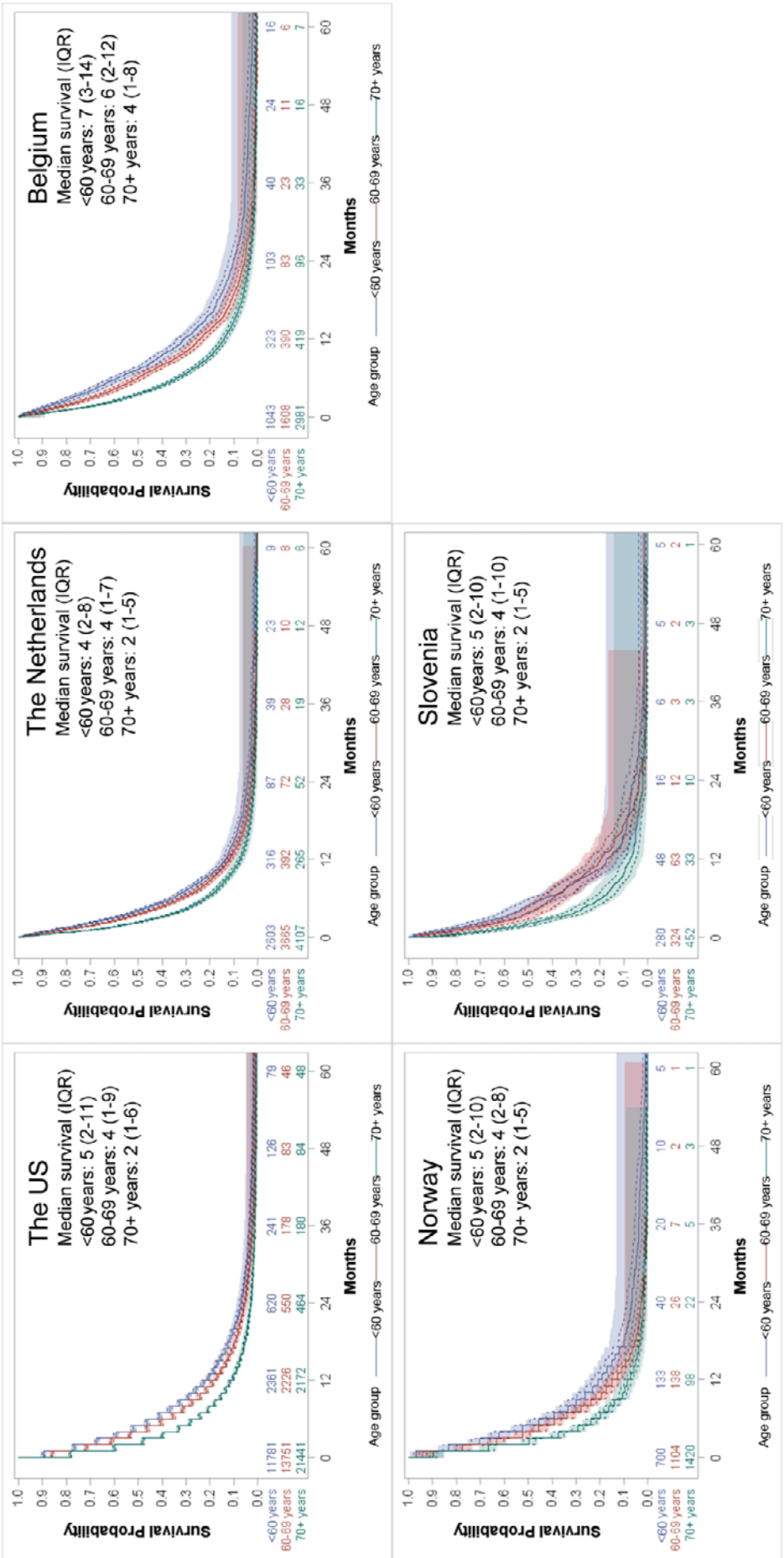

Figure 11. Kaplan-Meier curves (solid lines) of age group-specific survival in microscopically confirmed overall TNM stage III-IV pancreatic cancer patients. The dashed lines indicate the 95% confidence limits and the shadows represent the Hall-Wellner confidence bands. Numbers of patients at risk are also reported. Median survival is in months. IQR, interquartile range. (Huang *et al.*, 2018a)

Table 41. Unadjusted survival proportions of overall patients with microscopically confirmed stages I-II and III-IV pancreatic cancers (Huang *et al.*, 2018a)

Time	The US		The Netherlands		Belgium	
	Stage I-II	***Stage III-IV***	***Stage I-II***	***Stage III-IV***	***Stage I-II***	***Stage III-IV***
	OS (95% CI)[1]	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)
1 month						
< 60 years	96 (95-96)	77 (76-78)	98 (97-99)	87 (86-89)	98 (97-99)	93 (91-95)
60-69 years	93 (92-93)	72 (71-72)	96 (95-97)	83 (82-84)	97 (96-98)	89 (87-91)
≥ 70 years	84 (84-85)	60 (59-61)	92 (90-93)	74 (72-75)	93 (92-94)	81 (80-83)
3 months						
< 60 years	90 (90-91)	59 (58-60)	93 (91-94)	61 (59-63)	95 (93-96)	78 (75-80)
60-69 years	86 (85-87)	53 (53-54)	89 (87-91)	55 (53-57)	92 (91-94)	69 (67-71)
≥ 70 years	71 (71-72)	40 (39-40)	79 (77-81)	42 (41-44)	83 (81-84)	55 (53-56)
6 months						
< 60 years	81 (80-82)	41 (40-42)	83 (81-86)	36 (34-37)	90 (87-92)	59 (56-62)
60-69 years	74 (73-75)	35 (35-36)	79 (77-81)	32 (31-34)	86 (83-88)	50 (48-53)
≥ 70 years	57 (56-57)	24 (24-25)	63 (61-66)	22 (21-23)	67 (65-69)	34 (32-35)
12 months						
< 60 years	60 (58-61)	20 (20-21)	62 (59-65)	13 (12-15)	72 (69-76)	31 (28-34)
60-69 years	54 (52-55)	17 (17-18)	57 (54-59)	12 (11-13)	65 (62-68)	24 (22-26)
≥ 70 years	36 (35-36)	10 (10-11)	40 (38-42)	7 (7-8)	43 (40-45)	14 (13-15)
24 months						
< 60 years	36 (34-37)	7 (6-7)	31 (28-34)	4 (4-5)	47 (43-51)	10 (9-12)
60-69 years	30 (29-31)	5 (5-6)	30 (27-33)	3 (2-3)	38 (35-41)	6 (4-7)
≥ 70 years	18 (17-19)	3 (3-3)	20 (18-22)	2 (1-2)	21 (19-22)	3 (3-4)
36 months						
< 60 years	26 (24-27)	3 (3-4)	21 (18-24)	2 (2-3)	34 (30-37)	5 (4-7)
60-69 years	20 (19-21)	2 (2-3)	19 (17-22)	1 (1-2)	25 (22-28)	2 (1-3)
≥ 70 years	12 (11-12)	1 (1-2)	14 (12-16)	1 (<1-1)	13 (11-14)	1 (1-2)
60 months						
< 60 years	19 (18-20)	2 (1-2)	14 (12-17)	1 (1-1)	23 (19-26)	2 (1-3)
60-69 years	13 (12-14)	1 (1-1)	12 (10-14)	<1 (<1-1)	16 (14-19)	1 (<1-1)
≥ 70 years	7 (7-8)	1 (<1-1)	7 (6-9)	<1 (<1-1)	7 (6-8)	1 (<1-1)

[1]Data are shown as survival proportion (95% confidence interval) [%].

OS, overall survival; CI, confidence interval; NA, not available.

Table 41. Unadjusted survival proportions of overall patients with microscopically confirmed stages I-II and III-IV pancreatic cancers (Huang *et al.*, 2018a) (continued)

Time	Norway		Slovenia	
	Stage I-II	***Stage III-IV***	***Stage I-II***	***Stage III-IV***
	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)
1 month				
< 60 years	99 (96-100)	92 (90-94)	98 (93-99)	87 (82-90)
60-69 years	97 (94-98)	87 (85-89)	97 (92-99)	82 (77-86)
≥ 70 years	96 (94-98)	80 (78-82)	94 (90-97)	67 (63-72)
3 months				
< 60 years	96 (93-98)	67 (63-70)	95 (90-98)	61 (55-67)
60-69 years	91 (88-94)	59 (56-62)	93 (88-96)	54 (48-59)
≥ 70 years	85 (82-88)	44 (42-47)	81 (75-86)	39 (35-44)
6 months				
< 60 years	88 (82-91)	43 (39-46)	92 (85-95)	44 (38-49)
60-69 years	79 (74-83)	37 (34-40)	82 (74-87)	40 (34-45)
≥ 70 years	67 (63-71)	22 (20-24)	70 (63-76)	19 (16-23)
12 months				
< 60 years	65 (58-71)	20 (17-23)	65 (56-72)	17 (13-22)
60-69 years	55 (49-60)	13 (11-15)	59 (50-66)	19 (15-24)
≥ 70 years	42 (37-46)	7 (6-9)	49 (42-56)	7 (5-10)
24 months				
< 60 years	39 (32-46)	7 (5-9)	35 (27-43)	6 (3-9)
60-69 years	30 (25-35)	3 (2-4)	24 (18-31)	4 (2-6)
≥ 70 years	19 (16-23)	2 (1-3)	25 (19-31)	2 (1-4)
36 months				
< 60 years	25 (19-32)	4 (2-6)	23 (16-30)	2 (1-4)
60-69 years	19 (14-24)	1 (<1-2)	14 (9-20)	2 (1-3)
≥ 70 years	13 (10-17)	1 (<1-1)	14 (9-19)	1 (<1-2)
60 months				
< 60 years	16 (11-22)	1 (<1-2)	15 (9-23)	2 (1-4)
60-69 years	13 (9-18)	<1 (<1-1)	8 (4-14)	1 (<1-3)
≥ 70 years	8 (5-11)	<1 (<1-1)	8 (5-13)	<1 (<1-1)

[1]Data are shown as survival proportion (95% confidence interval) [%].

OS, overall survival; CI, confidence interval; NA, not available.

3.1.3.5 Temporal trends of survival in overall and resected pancreatic cancers by TNM stage

The trends of the 1-month to 5-year survival of PaC patients diagnosed in 2003-2005, 2006-2008, and 2009-2011 are shown in **Table 42** and **Figures 12-16**. Significant survival changes between 2003-2005 and 2009-2011 are described in detail as follows.

Short-term survival

Significant increases in 1-month survival for overall PaC patients were observed in the US and the Netherlands, with 3 and 3% units increase for stage I-II cancers and 2 and 3% units increase for stage III-IV tumors. In Slovenia, an increase by 6% units in 1-month survival was observed among overall stage III-IV cancer patients. For the subgroup of resected cancer patients, a significant survival increase was only observed for stage I-II cancer patients in the US (by 2% units). Improvements in 3-month survival were mostly larger and also significant among overall cancer patients in the US and the Netherlands, with 4 and 6% units increase in stage I-II cancers and 3 and 3% units increase in stage III-IV tumors, respectively. In Norway, an increase by 6% units was observed for stage I-II cancer patients. In Slovenia, a significant increase by 8% units persisted for patients with stage III-IV cancers. Within the resected cancer patient subgroup, significant increasing trends were observed in both stage I-II (by 2% units) and III-IV cancer patients (by 7% units) in the US, and in patients with stage III-IV cancers in Slovenia (by 10% units).

Longer-term survival

While in all countries 1-year survival increased for patients with stage I-II PaCs, the increases were only significant in the US (by 6% units), the Netherlands (by 12% units), and Norway (by 10% units). For the subgroup of resected cancer patients, again 1-year survival increased in all countries, but the changes were only significant in the US (by 5% units) and Norway (by 11% units). For overall patients with stage III-IV cancers, 1-year survival increased significantly in the US (by 3% units), the Netherlands (by 1% unit), Norway (by 2% units), and Slovenia (by 6% units). For patients with resected stage III-IV PaCs, significant increases were only observed in the US (by 13% units). Improvements in 3-year survival for overall patients with stage I-II cancers were mostly smaller and were significant in the US (by 4% units), the Netherlands (by 8% units), and Norway (by 2% units). For the subgroup of patients with resected stage I-II tumors, significant increases were observed in the US (by 5% units), the Netherlands (by 11% units), and Belgium (by 5% units). Changes in 3-year survival of patients with stage III-IV PaCs were minor and significant only in the US (by <1% unit increase) and the Netherlands (by <1% unit increase). Significant changes for the subgroup of patients with resected stage III-IV cancers were observed only in the US (by 5% unit increase). Regarding 5-year survival, significant increases were observed only in patients with stage I-II tumors. Survival rates increased by 6 and 1% unit in the Netherlands and Norway respectively for overall cancer patients, and by 8% units in the Netherlands for the resected tumor patients.

Table 42. Unadjusted survival rates of overall and resected pancreatic cancer patients diagnosed in 2003-2005, 2006-2008, and 2009-2011 (Huang *et al.*, 2018a)

Survival	Period	Stage	The US		The Netherlands		Belgium	
			Overall	***Resected***	***Overall***	***Resected***	***Overall***	***Resected***
			OS (95% CI)[1]	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)
1-month	*2003-2005*	I-II	83 (82-84)	95 (94-96)	89 (87-91)	96 (93-97)	94 (92-96)	97 (94-98)
		III-IV	61 (60-62)	86 (82-89)	73 (71-75)	88 (74-95)	88 (85-90)	96 (86-99)
	2006-2008	I-II	84 (84-85)	96 (95-96)	92 (91-94)	97 (95-98)	95 (94-97)	97 (95-98)
		III-IV	62 (61-63)	89 (86-91)	77 (75-78)	100 (100-100)	86 (85-88)	98 (91-99)
	2009-2011	I-II	86 (85-87)	96 (96-97)	92 (90-93)	97 (96-98)	96 (95-97)	98 (97-99)
		III-IV	63 (62-64)	90 (88-92)	76 (75-78)	91 (81-96)	85 (84-87)	100 (100-100)
	%unit change[2], *P*	I-II	**+3**, **0.006**	**+2**, **0.004**	**+3**, **0.021**	+1, 0.257	+2, 0.116	+1, 0.577
		III-IV	**+2**, **0.002**	+4, 0.989	**+3**, **0.001**	+3, 0.635	-2, 0.086	+4, 0.189
3-month	*2003-2005*	I-II	72 (71-73)	91 (90-92)	74 (71-76)	92 (89-94)	86 (83-89)	93 (90-96)
		III-IV	42 (41-43)	74 (69-78)	42 (40-43)	84 (69-92)	66 (62-69)	93 (82-97)
	2006-2008	I-II	73 (72-74)	92 (91-92)	78 (76-81)	93 (91-95)	87 (85-89)	92 (90-94)
		III-IV	44 (43-44)	79 (76-82)	46 (44-47)	98 (88-100)	63 (61-65)	85 (95-91)
	2009-2011	I-II	76 (75-77)	93 (92-94)	80 (78-82)	93 (91-95)	89 (87-91)	94 (92-96)
		III-IV	45 (44-46)	81 (78-84)	45 (43-46)	85 (74-92)	63 (60-65)	93 (85-96)
	%unit change[2], *P*	I-II	**+4**, **<0.001**	**+2**, <**0.001**	**+6**, **0.001**	+1, 0.546	+3, 0.118	+1, 0.508
		III-IV	**+3**, **<0.001**	**+7**, **0.017**	**+3**, **0.001**	+1, 0.831	-3, 0.087	-<1, 0.972
12-month	*2003-2005*	I-II	38 (36-39)	64 (62-66)	33 (30-36)	64 (59-68)	52 (48-57)	62 (56-67)
		III-IV	11 (11-12)	34 (29-39)	8 (7-9)	49 (33-63)	19 (17-22)	45 (31-57)
	2006-2008	I-II	40 (39-41)	65 (64-67)	36 (33-38)	64 (60-68)	56 (53-60)	69 (65-73)
		III-IV	12 (12-13)	35 (31-39)	8 (7-9)	53 (38-64)	19 (17-21)	47 (36-57)
	2009-2011	I-II	44 (43-45)	70 (68-71)	45 (43-48)	69 (65-72)	55 (52-57)	68 (65-71)
		III-IV	14 (14-15)	47 (42-51)	9 (8-10)	41 (29-52)	20 (18-22)	53 (42-62)
	%unit change[2], *P*	I-II	**+6**, **< 0.001**	**+5**, **<0.001**	**+12**, **<0.001**	+5, 0.066	+3, 0.297	+6, 0.057
		III-IV	**+3**, **< 0.001**	**+13**, **<0.001**	**+1**, **0.001**	-8, 0.496	+1, 0.476	+8, 0.548
36-month	*2003-2005*	I-II	13 (13-14)	27 (25-29)	8 (7-10)	18 (14-22)	17 (14-21)	24 (19-29)
		III-IV	2 (2-2)	7 (5-10)	1 (1-2)	14 (6-26)	2 (2-4)	8 (2-16)
	2006-2008	I-II	14 (14-15)	29 (27-30)	12 (10-13)	24 (20-28)	21 (18-23)	28 (25-32)
		III-IV	2 (2-2)	9 (7-11)	1 (1-1)	11 (5-21)	2 (2-3)	7 (3-14)
	2009-2011	I-II	17 (16-18)	33 (31-34)	16 (15-18)	29 (26-32)	20 (18-22)	30 (26-33)
		III-IV	2 (2-2)	11 (9-14)	1 (1-1)	12 (6-21)	2 (1-3)	10 (5-16)
	%unit change[2], *P*	I-II	**+4**, **<0.001**	**+5**, **<0.001**	**+8**, **<0.001**	**+11**, **<0.001**	+3, 0.076	**+5**, **0.035**
		III-IV	**+<1**, **<0.001**	**+5**, **<0.001**	**+<1**, **0.005**	-2, 0.886	-1, 0.285	+2, 0.317
60-month	*2003-2005*	I-II	9 (8-10)	18 (17-20)	4 (3-5)	10 (7-13)	11 (8-14)	16 (12-21)
		III-IV	1 (1-1)	4 (2-6)	1 (<1-1)	9 (3-20)	1 (<1-2)	4 (1-11)
	2006-2008	I-II	10 (9-11)	20 (19-21)	7 (6-9)	15 (12-19)	13 (11-15)	18 (15-21)
		III-IV	1 (1-1)	6 (5-9)	<1 (<1-1)	6 (2-14)	1 (1-2)	5 (2-11)
	2009-2011	I-II	NA	NA	10 (8-12)	18 (15-21)	12 (10-14)	18 (15-21)
		III-IV	NA	NA	1 (<1-1)	12 (6-21)	1 (<1-1)	2 (<1-7)
	%unit change[2], *P*	I-II	NA, NA	NA, NA	**+6**, **<0.001**	**+8**, **<0.001**	+1, 0.109	+2, 0.090
		III-IV	NA, NA	NA, NA	**+<1**, **0.004**	+3, 0.935	-<1, 0.290	-2, 0.409

[1]Data are shown as survival rate (95% confidence interval) [%].

[2]%changes are shown by comparing average survival of patients diagnosed in 2009-2011 to those in 2003-2005. Significant changes according to *P* values calculated using the log-rank test are highlighted in bold.

OS, overall survival; NA, not available as follow-up was not long enough.

Table 42. Unadjusted survival rates of overall and resected pancreatic cancer patients diagnosed in 2003-2005, 2006-2008, and 2009-2011 (Huang *et al.*, 2018a) (continued)

Survival	Period	Stage	Norway		Slovenia	
			Overall	***Resected***	***Overall***	***Resected***
			OS (95% CI)	OS (95% CI)	OS (95% CI)	OS (95% CI)
1-month	*2003-2005*	I-II	91 (88-94)	99 (94-100)	89 (84-93)	96 (90-98)
		III-IV	78 (75-80)	100 (100-100)	69 (65-74)	92 (71-98)
	2006-2008	I-II	90 (83-96)	99 (93-100)	93 (88-96)	99 (93-100)
		III-IV	79 (76-81)	96 (75-99)	75 (71-78)	97 (80-100)
	2009-2011	I-II	94 (91-96)	98 (95-99)	90 (85-94)	99 (94-100)
		III-IV	78 (75-80)	96 (77-100)	75 (72-79)	98 (86-100)
	%unit change[2], *P*	I-II	+3, 0.175	-1, 0.473	+1, 0.851	+4, 0.083
		III-IV	+<1, 0.972	-4, 0.301	**+6**, **0.024**	+6, 0.229
3-month	*2003-2005*	I-II	76 (71-80)	98 (93-99)	76 (69-82)	87 (79-92)
		III-IV	44 (41-47)	87 (68-95)	36 (31-40)	58 (36-75)
	2006-2008	I-II	72 (67-76)	94 (86-97)	80 (73-86)	92 (85-96)
		III-IV	48 (46-51)	84 (63-94)	43 (39-47)	85 (67-93)
	2009-2011	I-II	82 (78-85)	96 (92-98)	76 (70-82)	97 (91-99)
		III-IV	47 (44-49)	86 (66-94)	44 (40-48)	76 (61-86)
	%unit change[2], *P*	I-II	**+6**, **0.035**	-1, 0.562	+<1, 0.909	**+10**, **0.005**
		III-IV	+3, 0.225	-1, 0.890	**+8**, **0.007**	+18, 0.085
12-month	*2003-2005*	I-II	34 (29-39)	66 (57-74)	38 (30-45)	51 (41-60)
		III-IV	8 (6-10)	37 (20-53)	5 (3-8)	13 (3-29)
	2006-2008	I-II	33 (29-38)	71 (60-79)	51 (43-59)	67 (57-76)
		III-IV	11 (10-13)	56 (35-73)	12 (10-15)	39 (23-55)
	2009-2011	I-II	44 (39-49)	77 (70-83)	42 (35-48)	60 (50-68)
		III-IV	10 (8-11)	46 (28-63)	11 (9-14)	17 (8-30)
	%unit change[2], *P*	I-II	**+10**, **0.003**	**+11 0.025**	+4, 0.577	+9, 0.101
		III-IV	**+2**, **0.027**	+100.689	**+6**, <**0.001**	+5, 0.238
36-month	*2003-2005*	I-II	12 (9-16)	28 (20-36)	9 (6-14)	11 (6-17)
		III-IV	1 (1-2)	10 (3-24)	1 (<1-2)	NA
	2006-2008	I-II	10 (7-14)	32 (22-41)	19 (14-26)	27 (19-37)
		III-IV	2 (1-2)	24 (10-42)	2 (1-3)	12 (4-26)
	2009-2011	I-II	15 (12-18)	30 (23-37)	12 (8-16)	17 (11-24)
		III-IV	1 (1-2)	14 (5-30)	1 (<1-1)	NA
	%unit change[2], *P*	I-II	**+2**, **0.025**	+2, 0.205	+2, 0.468	+6, 0.069
		III-IV	-<1, 0.062	+4, 0.785	**+<1**, **0.002**	NA, NA
60-month	*2003-2005*	I-II	9 (6-12)	18 (12-25)	7 (3-11)	9 (5-15)
		III-IV	1 (<1-1)	3 (<1-15)	<1 (<1-1)	NA
	2006-2008	I-II	7 (4-9)	20 (12-28)	9 (5-14)	13 (7-21)
		III-IV	1 (<1-1)	4 (<1-17)	2 (1-3)	12 (4-26)
	2009-2011	I-II	10 (7-13)	20 (14-27)	8 (5-12)	11 (6-17)
		III-IV	<1 (<1-1)	NA	<1 (<1-1)	NA
	%unit change[2], *P*	I-II	**+1**, **0.043**	+2, 0.262	+2, 0.469	+2, 0.113
		III-IV	-<1, 0.069	NA, NA	**+<1**, **0.002**	NA, NA

[1]Data are shown as survival rate (95% confidence interval) [%].

[2]%changes are shown by comparing average survival of patients diagnosed in 2009-2011 to those in 2003-2005. Significant changes according to *P* values calculated using the log-rank test are highlighted in bold.

OS, overall survival; NA, not available as follow-up was not long enough.

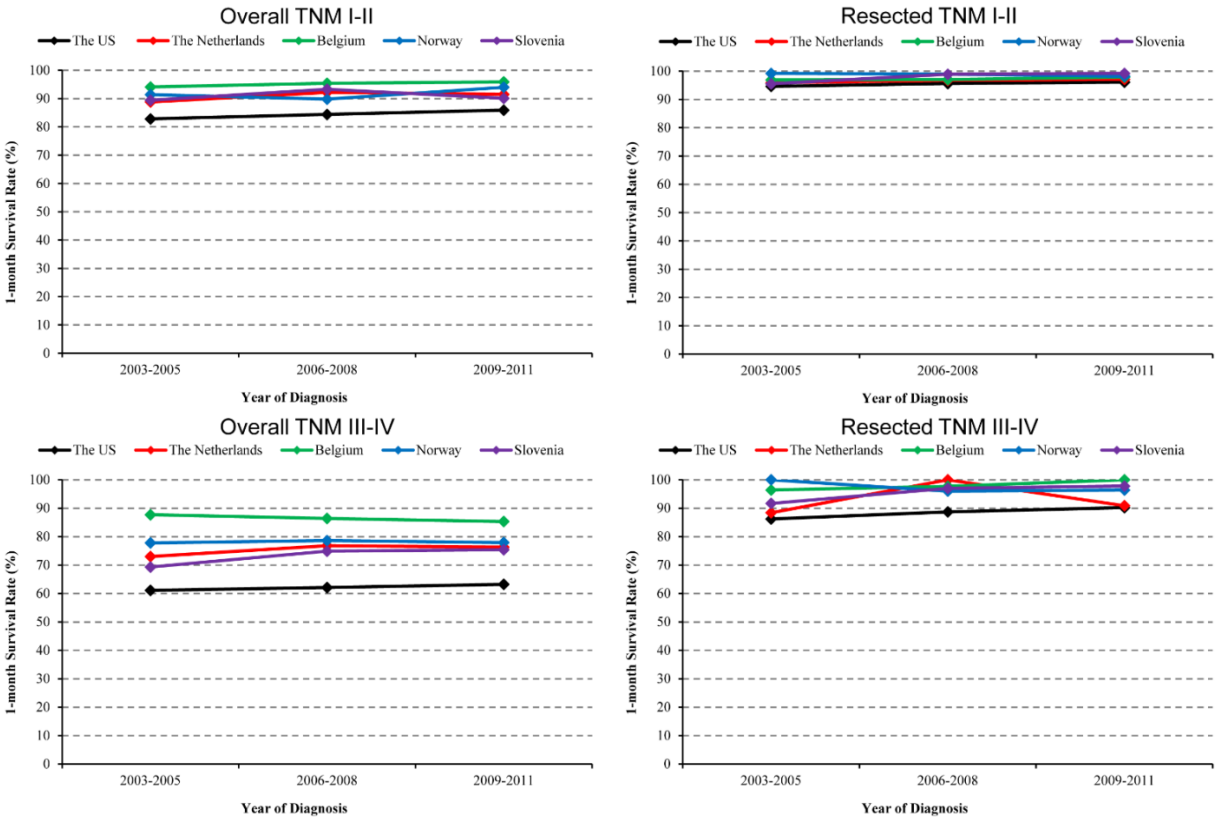

Figure 12. Changes in 1-month survival over calendar periods among overall and resected patients with stages I-II and III-IV pancreatic cancers (Huang *et al.*, 2018a)

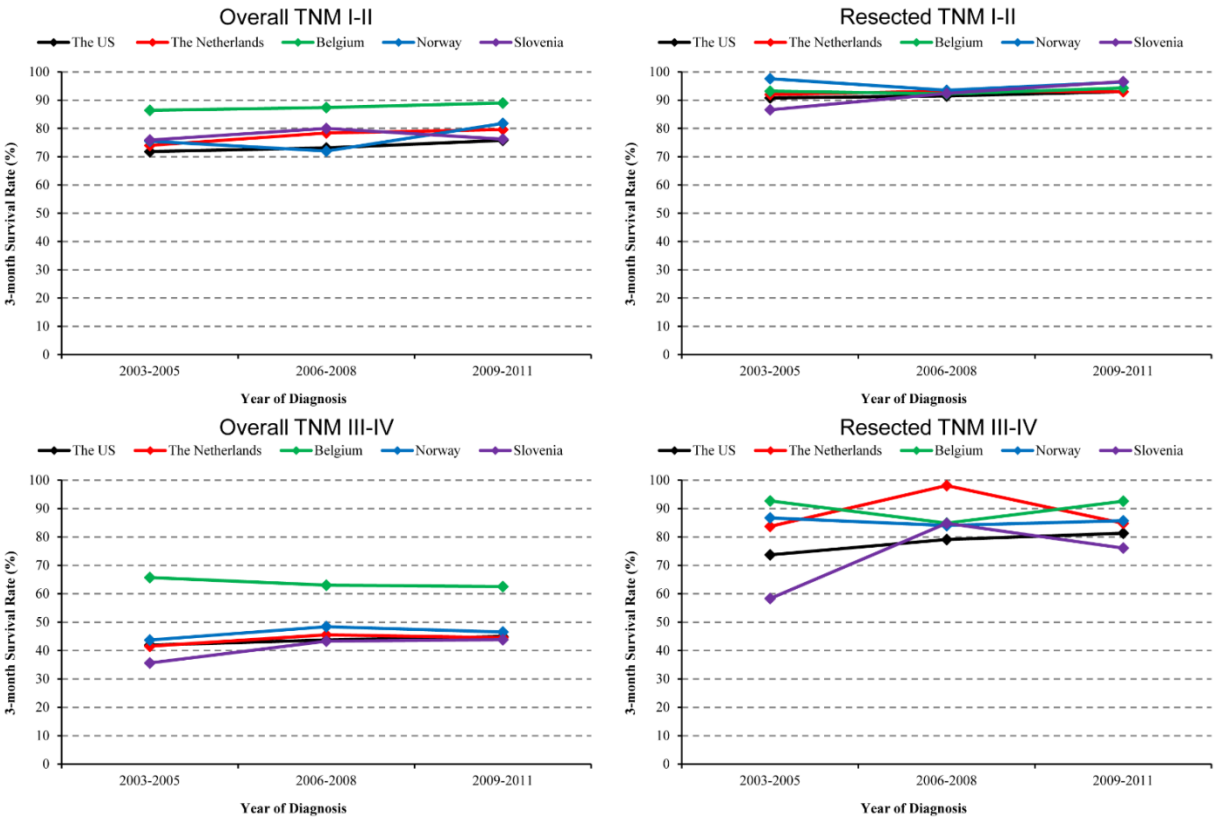

Figure 13. Changes in 3-month survival over calendar periods among overall and resected patients with stages I-II and III-IV pancreatic cancers (Huang *et al.*, 2018a)

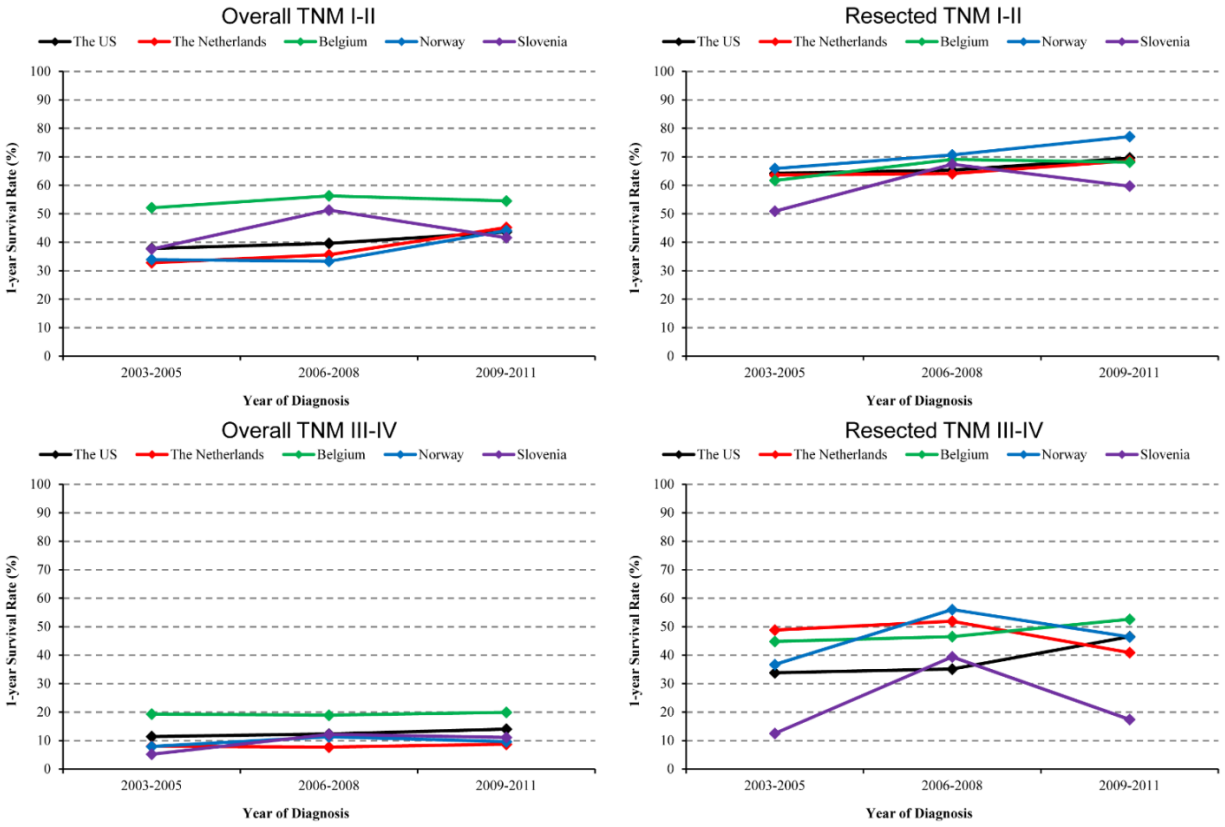

Figure 14. Changes in 12-month survival over calendar periods among overall and resected patients with stages I-II and III-IV pancreatic cancers (Huang *et al.*, 2018a)

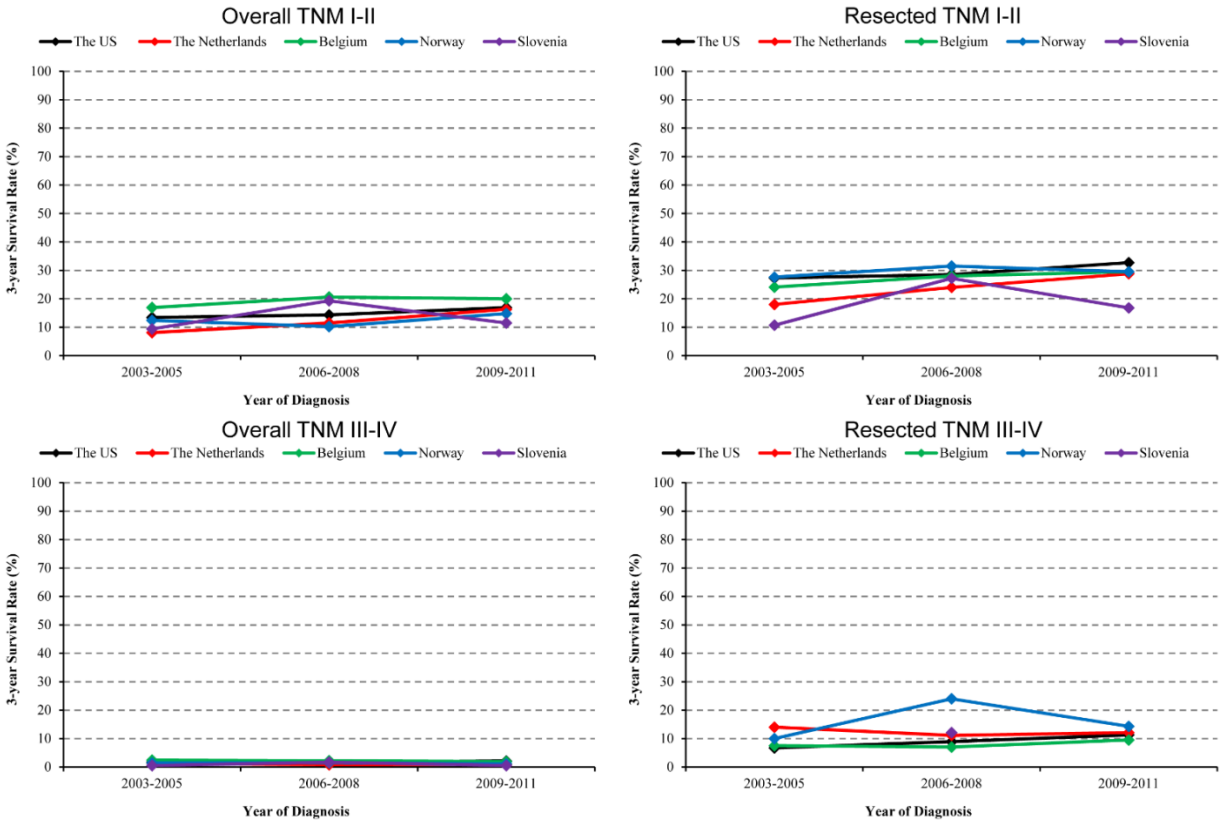

Figure 15. Changes in 36-month survival over calendar periods among overall and resected patients with stages I-II and III-IV pancreatic cancers (Huang *et al.*, 2018a)

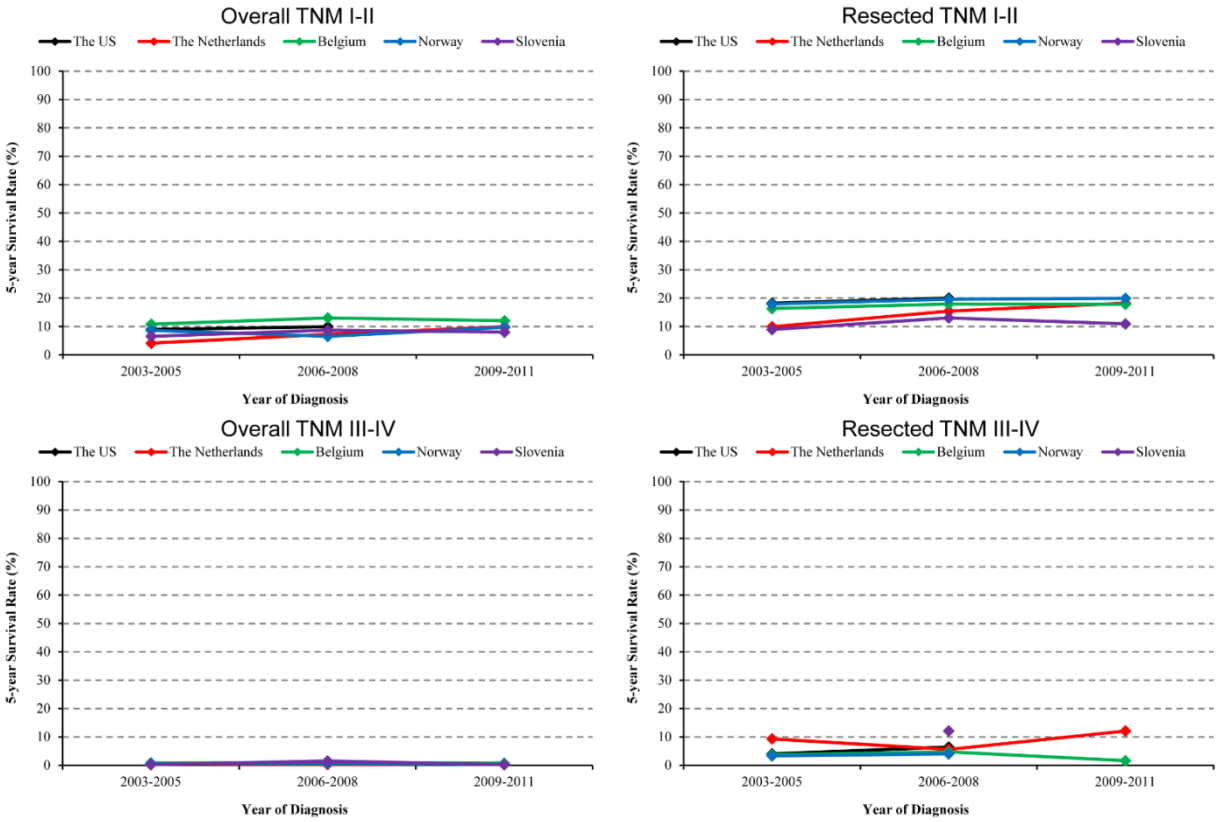

Figure 16. Changes in 60-month survival over calendar periods among overall and resected patients with stages I-II and III-IV pancreatic cancers (Huang *et al.*, 2018a)

3.1.4 Prognostic factors and development and international validation of a benchmark population-based survival-predicting model in patients with resected stage I-II pancreatic adenocarcinoma receiving chemotherapy

3.1.4.1 Patient characteristics

A total of 168,949 PaC patients were registered in the population-based registries during 2003/2004-2013/2014 with follow-up until 2014-2016. After excluding patients diagnosed based on DCO/autopsy (n=4,403), unresected (n=137,605), receiving no/unknown chemotherapy (n=11,465), without microscopically-confirmed tumors or with tumors of ineligible pathology (n=1,418), with stage 0/III/IV/unknown tumors (n=1,856), and with survival <3 months or unknown (n=365), finally 11,837 patients were eligible for analysis (**Table 43**). Of the analyzed patients (**Table 44**), 52%-76% were diagnosed in 2010 or later. The proportion of women was 42%-51%, and the mean age was 61-65 years. Most patients were 50-69 years (58%-71%). Tumors were most commonly located at pancreas head (82%-92%). A minority of patients had T1 (0%-8%) or T2 cancers (7%-26%) compared to T3 tumors (66%-93%). N1 tumors comprised 55%-84%. Most patients had either moderately- (40%-63%) or poorly-differentiated/undifferentiated tumors (34%-50%).

Table 43. General information on participating registries for Chapter 3.1.4

Source	Diagnosis period	Censoring date	Registered primary cases[2]	Excluded cases[1]					Analyzed cases	Follow-up months[3]
				DCO/ autopsy	Not resected/ no/unknown chemotherapy	Not microscopically confirmed/ineligible pathology	Stage 0/III/IV/ unknown	Survival <3 months/ unknown		
SEER-18[4]	Jan. 2004-Dec. 2015	Dec. 31, 2015	122826	3917	106524	1102	1436	328	9519	56 (28-89)
BCR	Jan. 2004-Dec. 2013	Jul. 1, 2015	12146	NA	10658	142	233	8	1105	64 (40-89)
NCR	Jan. 2003-Dec. 2014	Feb. 1, 2015	22579	99	21277	106	86	29	982	36 (20-59)
CRS	Jan. 2003-Dec. 2013	May 25, 2016	3376	54	3140	22	42	0	118	75 (51-87)
CRN	Jan. 2003-Dec. 2014	Jun. 30, 2015	8022	333	7471	46	59	0	113	40 (32-65)

[1]Data exclusion followed this sequence: DCO/autopsy, not resected, no/unknown chemotherapy, stage 0/III/IV, not microscopically-confirmed/ineligible pathology, and survival <3 months/unknown (from left to right).
[2]A preliminary data-cleaning process had been performed to exclude cases with ineligible histology types except cystic, mucinous, and serous malignancies.
[3]Shown as median (interquartile range), and computed using the reverse Kaplan-Meier method.
[4]Data of the year 2003 was not analyzed, as the TNM stage (version 6/7) information was unavailable.
SEER, Surveillance, Epidemiology, and End Results Program; NCR, Netherlands Cancer Registry; BCR, Belgian Cancer Registry; CRN, Cancer Registry of Norway; CRS, Cancer Registry of Slovenia; DCO, death certificate only; NA, not available.

Table 44. Demographic and clinical characteristics of resected pancreas cancer patients receiving chemotherapy[1]

Variable	The US	Belgium	The Netherlands	Slovenia	Norway
n	9519	1105	982	118	113
Incidence period	2004-2015	2004-2013	2003-2014	2003-2013	2003-2014
Diagnosis in 2010 or later	5635 (59)	579 (52)	747 (76)	67 (57)	79 (70)
Sex, female	4671 (49)	522 (47)	483 (49)	50 (42)	58 (51)
Age (years)					
Mean ± standard deviation	65 ± 10	64 ± 10	62 ± 9	61 ± 9	64 ± 8
Median (interquartile range)	65 (58-72)	65 (58-71)	64 (57-69)	61 (54-68)	63 (59-70)
< 50	706 (7)	90 (8)	92 (9)	11 (9)	4 (4)
50-59	2101 (22)	264 (24)	235 (24)	38 (32)	29 (26)
60-69	3464 (36)	406 (37)	417 (42)	46 (39)	50 (44)
≥ 70	3248 (34)	345 (31)	238 (24)	23 (19)	30 (27)
Tumor location[2]					
Pancreas head	7314 (83)	658 (82)	820 (90)	97 (92)	91 (88)
Pancreas body	622 (7)	58 (7)	31 (3)	5 (5)	4 (4)
Pancreas tail	845 (10)	86 (11)	63 (7)	3 (3)	8 (8)
Other	738 (8)	303 (27)	68 (7)	13 (11)	10 (9)
T stage[3]					
T1	494 (5)	56 (5)	72 (7)	0 (0)	8 (8)
T2	1192 (13)	185 (17)	182 (19)	8 (7)	28 (26)
T3	7815 (82)	860 (78)	727 (74)	108 (93)	70 (66)
N stage, N1[4]	6339 (67)	805 (73)	703 (72)	97 (84)	60 (55)
Differentiation[5]					
Well	858 (10)	149 (15)	91 (11)	12 (11)	3 (3)
Intermediate	4540 (52)	511 (52)	423 (51)	44 (40)	64 (63)
Poor/undifferentiated	3266 (38)	326 (33)	319 (38)	55 (50)	35 (34)

[1]Categorical data are shown as count (percentage [%]). For brevity, results for the counterparts in dichotomous variables are omitted. Records are complete otherwise specified below.
[2]The percentages of pancreas head, body, tail, and overlapping cancers are the proportions compared to the total cases of the four locations; 'other' includes overlapping lesion, pancreas duct, and not otherwise specified location, and its proportion is relative to the whole cases.
[3]Missing T stage: the US: 18 (<1%); Belgium: 4 (<1%); the Netherlands: 1 (<1%); Slovenia: 2 (2%); Norway: 7 (6%).
[4]Missing N stage: the US: 0 (0%); Belgium: 7 (1%); the Netherlands: 0 (0%); Slovenia: 2 (2%); Norway: 3 (3%).
[5]Missing differentiation: the US: 855 (9%); Belgium: 119 (11%); the Netherlands: 149 (15%); Slovenia: 7 (6%); Norway: 11 (10%).

3.1.4.2 Survival-associated factors

The median overall survival time was 18 (Slovenia) to 23 months (the US), and the 3-year survival rate was 21% (Slovenia) to 31% (the US; **Figure 17**). Results from multivariable Cox regression are shown in **Table 45**, and only significant results are described. Increasing age was associated with worse survival in the US (HR per year=1.01), Belgium (HR=1.02), and Norway (HR=1.04). Survival was significantly worse in men only in the US (HR=1.10) and in pancreas body compared to head tumors in Norway (HR=2.67). Compared to T3 cancers, T1 cancers were associated with higher survival in all investigated countries (HR=0.17-0.70), while T2 cancers were associated with better survival only in the US (HR=0.86). Negative nodal status was associated with significantly higher survival in the US (HR=0.65), Belgium (HR=0.78), and the Netherlands (HR=0.51). Better differentiation was significantly associated with higher survival in all countries except Slovenia and Norway, and the HRs for well- and intermediately- versus poorly-/un-differentiated tumors were 0.48-0.68 and 0.61-0.81, respectively. Association patterns and strengths were similar between white and overall US patients.

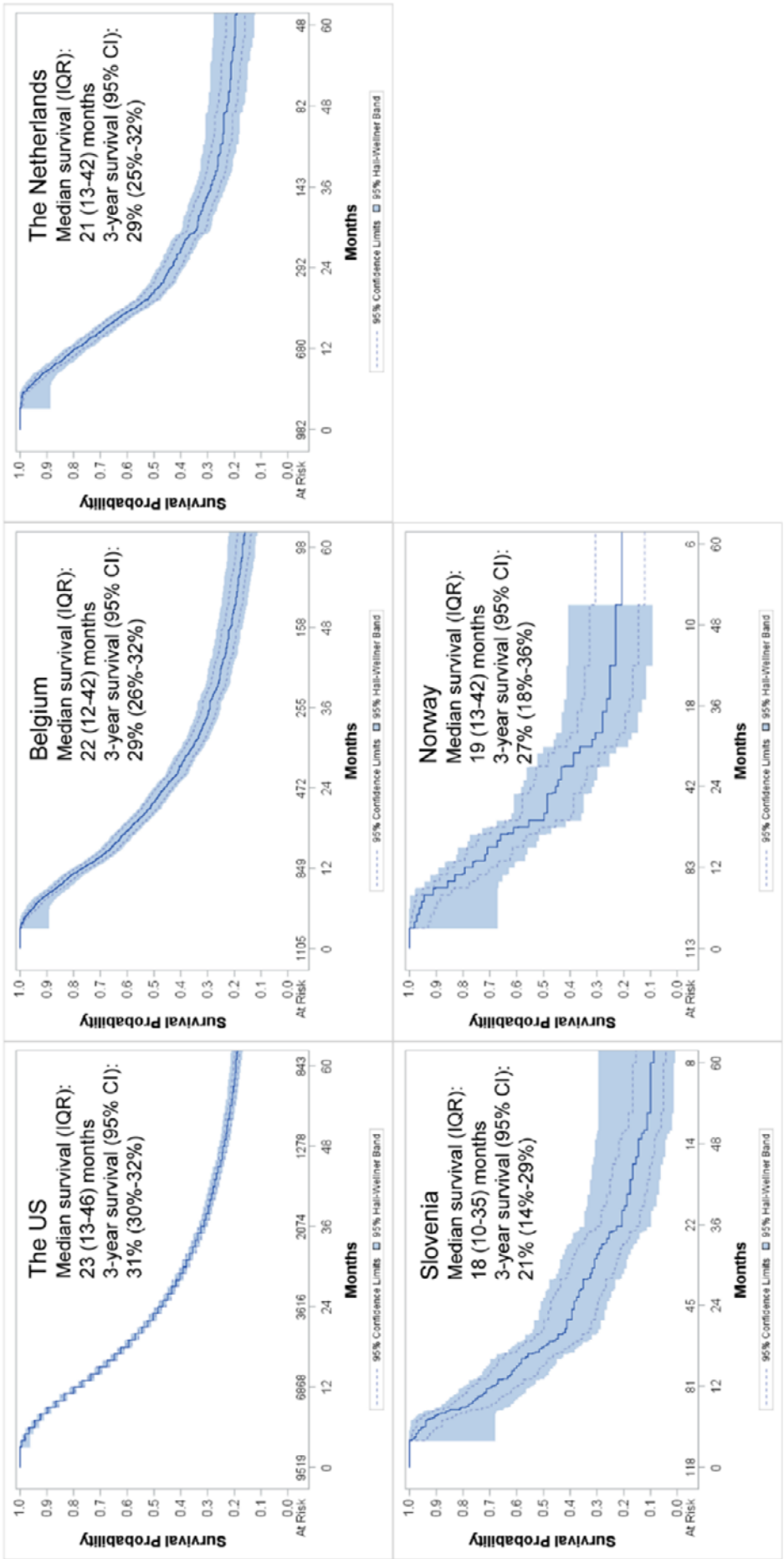

Figure 17. Kaplan-Meier overall survival curves for patients with resected stage I-II pancreatic cancer receiving chemotherapy in each country. The 95% confidence limits curves and the 95% Hall-Wellner bands are additionally shown. Median survival time (interquartile range) in months and 3-year survival rates (95% confidence interval) are calculated and provided. IQR, interquartile range; CI, confidence interval.

Table 45. Association of demographic and clinical variables with overall survival for resected pancreatic cancer patients estimated by adjusted multivariable Cox proportional hazards regression

Variable	The US	The US (white)	Belgium	The Netherlands	Slovenia	Norway
Used no.	8657	7170	979	833	109	96
	HR (95% CI)[1]	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Year of diagnosis (per year; continuous)	**0.97** (0.96-0.98)	**0.97** (0.96-0.98)	0.98 (0.95-1.01)	0.99 (0.95-1.03)	0.96 (0.89-1.03)	**0.80** (0.69-0.93)
Age (per year; continuous)	**1.01** (1.01-1.01)	**1.01** (1.01-1.01)	**1.02** (1.01-1.02)	1.00 (0.99-1.01)	1.01 (0.99-1.04)	**1.04** (1.00-1.08)
Sex						
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	**1.10** (1.05-1.16)	**1.12** (1.06-1.18)	0.93 (0.80-1.07)	1.08 (0.91-1.29)	1.49 (0.96-2.32)	1.14 (0.67-1.95)
Tumor location						
Pancreas head	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Pancreas body	1.03 (0.92-1.15)	1.04 (0.92-1.17)	1.34 (0.99-1.82)	1.19 (0.69-2.04)	1.33 (0.47-3.81)	0.40 (0.05-2.98)
Pancreas tail	1.02 (0.93-1.12)	1.03 (0.93-1.14)	1.00 (0.76-1.30)	0.85 (0.57-1.26)	0.39 (0.09-1.66)	**2.67** (1.09-6.53)
Other[2]	1.02 (0.93-1.13)	1.03 (0.93-1.15)	0.95 (0.80-1.12)	0.92 (0.65-1.38)	0.83 (0.37-1.84)	0.89 (0.30-2.65)
T stage						
T1	**0.66** (0.57-0.75)	**0.70** (0.61-0.81)	**0.68** (0.47-0.97)	**0.48** (0.33-0.71)	-	**0.17** (0.04-0.72)
T2	**0.86** (0.79-0.93)	**0.88** (0.81-0.97)	0.89 (0.74-1.08)	1.02 (0.82-1.26)	0.70 (0.29-1.67)	0.89 (0.49-1.61)
T3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
N stage						
N0	**0.65** (0.61-0.69)	**0.65** (0.61-0.69)	**0.78** (0.66-0.92)	**0.51** (0.41-0.64)	0.77 (0.40-1.51)	0.71 (0.39-1.29)
N1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Differentiation						
Well	**0.60** (0.55-0.66)	**0.59** (0.53-0.65)	**0.68** (0.55-0.85)	**0.48** (0.35-0.67)	0.57 (0.27-1.22)	0.31 (0.04-2.58)
Intermediate	**0.77** (0.73-0.81)	**0.78** (0.73-0.82)	**0.81** (0.69-0.94)	**0.61** (0.50-0.73)	0.82 (0.51-1.32)	0.93 (0.54-1.61)
Poor/undifferentiated	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

[1]HRs were calculated by Cox proportional hazard regression with adjustment for year of diagnosis, age, sex, tumor location, T, N, and M stages, histology, and differentiation. In stratified analyses, the stratification factor was omitted from the model. Statistically significant HRs are shown in bold.

[2]Other: pancreas duct, overlapping lesion, and not otherwise specified location.

HR, hazard ratio; CI, confidence interval; -, not available.

Associations with further variables were explored in countries with available relevant information (**Table 46**). In the Netherlands, positive resection margin was associated with worse survival in (HR=1.36), and resection in academic hospital was associated with better survival (HR=0.79). In the US, larger tumor size was associated with inferior survival, and replacing T stage according to the sixth/seventh edition with the eighth edition revealed similar association patterns and strengths. In the US and the Netherlands, while increasing metastatic node number (HR per positive lymph node=1.05 and 1.07) and lymph node ratio (HR=2.60 and 3.15) were associated with inferior survival, more harvested nodes suggested better survival (both HR per harvested node=0.99). Following the eighth version of TNM staging, N1 (HR=1.42 and 1.68) and N2 stages (HR=1.84 and 2.43) were associated with worse survival compared to N0 stage in the US and the Netherlands. In Eindhoven, the Netherlands, more comorbidities were associated with inferior survival (*e.g.*, $HR_{\geq 2 \text{ vs. } 0 \text{ comorbidities}}$=1.86).

Table 46. Association of survival with potential prognostic factors available in at least one registry for resected pancreatic cancer estimated by adjusted Cox proportional hazard regression

Variable	The US		Belgium		The Netherlands		Slovenia	
	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
Resection margin								
Negative	-	-	-	-	637	1.00 (reference)	51	1.00 (reference)
Positive	-	-	-	-	291	**1.36** (1.12-1.65)	34	1.54 (0.82-2.88)
Hospital type								
Non-academic	-	-	497	1.00 (reference)	510	1.00 (reference)	-	-
Academic	-	-	608	0.89 (0.77-1.03)	472	**0.79** (0.66-0.94)	-	-
Tumor size								
≤2 cm	1490	1.00 (reference)	-	-	-	-	-	-
2-3 cm	3146	**1.23** (1.12-1.35)	-	-	-	-	-	-
3-4 cm	2487	**1.38** (1.25-1.52)	-	-	-	-	-	-
4-5 cm	1229	**1.60** (1.44-1.78)	-	-	-	-	-	-
>5 cm	938	**1.56** (1.39-1.75)	-	-	-	-	-	-
T stage (8th version)								
T1	1490	**0.62** (0.57-0.68)	-	-	-	-	-	-
T2	5633	**0.81** (0.76-0.87)	-	-	-	-	-	-
T3	2167	1.00 (reference)	-	-	-	-	-	-
Positive LN number[2]	9426	**1.05** (1.04-1.06)	-	-	974	**1.07** (1.04-1.10)	-	-
N stage (8th version)								
N0 (0 positive LNs)	3180	1.00 (reference)	-	-	280	1.00 (reference)	-	-
N1 (1-3 positive LNs)	3885	**1.42** (1.33-1.51)	-	-	416	**1.68** (1.33-2.13)	-	-
N2 (≥4 positive LNs)	2244	**1.84** (1.72-1.98)	-	-	278	**2.43** (1.89-3.12)	-	-
Harvested LN number[2]	9484	**0.99** (0.99-0.99)	-	-	959	0.99 (0.98-1.00)	-	-
LN ratio[2]	9138	**2.60** (2.26-3.00)	-	-	945	**3.15** (2.05-4.84)	-	-
ECOG score								
0	-	-	140	1.00 (reference)	-	-	-	-
1	-	-	662	0.96 (0.76-1.20)	-	-	-	-
≥2	-	-	63	1.04 (0.73-1.47)	-	-	-	-
Resection type								
Pancreatoduodenectomy	7108	1.00 (reference)	-	-	877	1.00 (reference)	-	-
Distal pancreatectomy	1142	1.02 (0.92-1.14)	-	-	88	1.33 (0.61-2.91)	-	-
Total pancreatectomy	1102	1.07 (0.99-1.15)	-	-	10	0.98 (0.36-2.65)	-	-
Comorbidity (yes *v* no)								
Cardiovascular disease	-	-	-	-	30/119	1.33 (0.69-2.57)	-	-
Hypertension	-	-	-	-	39/110	1.01 (0.59-1.75)	-	-
Diabetes	-	-	-	-	33/116	1.34 (0.76-2.38)	-	-
Pulmonary disease	-	-	-	-	14/135	1.96 (0.88-4.36)	-	-
Number of comorbidities								
0	-	-	-	-	52	1.00 (reference)	-	-
1	-	-	-	-	48	1.48 (0.84-2.62)	-	-
≥ 2	-	-	-	-	49	**1.86** (1.00-3.46)	-	-

[1]The main Cox proportional hazard regression models adjusted for year of diagnosis, age, sex, tumor location, T, N, and M stages, histology, and differentiation. HRs were calculated after N stage was replaced by metastatic node number (group) or lymph node ratio, or after the other investigated variables were included one by one into the main models. Statistically significant HRs are shown in bold.

[2]As continuous.

HR, hazard ratio; CI, confidence interval; LN, lymph node; ECOG, Eastern Cooperative Oncology Group; -, not available.

Sensitivity analyses of the main models by incorporation of the further prognostic covariates did not change the association patterns or markedly alter the association strengths for the variables included in the main models (data not shown).

3.1.4.3 Prognostic nomogram

Construction

A nomogram incorporating prognostic factors remaining after backward selection in the US (sex, age, T and N stages, and differentiation) was established (**Figure 18**). The nomogram illustrated age and differentiation to have the largest contributions to prognosis. T and N stages showed moderate impacts on survival. Each number/category of these variables is assigned a score on the *Points* scale. After summing up the total score and locating it on the *Total Points* scale, a line drawn straight down to the *Median Survival* or *1-/2-/3-/5-Year Survival Probability* scale shows the estimated survival time or probability at each time point. Score assignment for specific categories of the variables and survival for different accumulated scores are shown in **Table 47**. The layout of an online version of the model is shown in **Figure 19**.

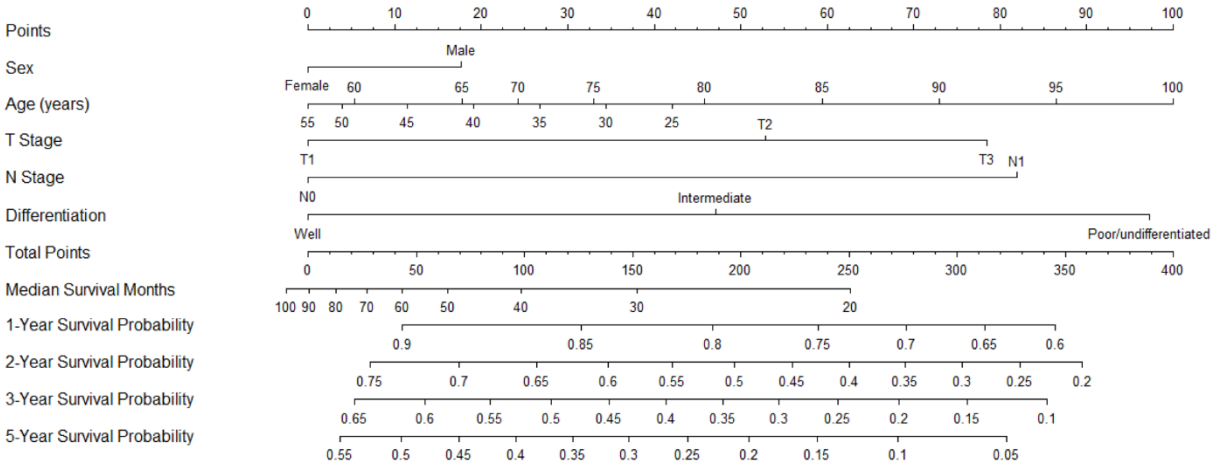

Figure 18. Prognostic nomogram for patients with resected stage I-II pancreatic cancer receiving chemotherapy derived from the US cohort. Each number/category of the prognostic variables is assigned a score on the *Points* scale. After summing up the total score and locating it on the *Total Points* scale, a line drawn straight down to the *Median Survival* or *1-/2-/3-/5-Year Survival* scale shows the median survival time and estimated survival probability at each time point. Age is in years.

Table 47. Score assignment for specific categories of the variables included in the nomogram

Prognostic factors		
Variable	**Category**	**Score**
Sex	Female	0
	Male	18
Age (years)	25	42
	30	34
	35	27
	40	19
	45	11
	50	4
	55	0
	60	5
	65	18
	70	24
	75	33
	80	46
	85	59
	90	73
	95	86
	100	100
T stage	T1	0
	T2	53
	T3	78
N stage	N0	0
	N1	82
Differentiation	Well	0
	Intermediate	47
	Poor/undifferentiated	97

Median survival	
Total score	**Median survival** (months)
251	20
152	30
99	40
64	50
43	60
27	70
13	80
0	90

1-year survival	
Total score	**1-year survival probability**
345	0.60
313	0.65
277	0.70
236	0.75
187	0.80
126	0.85
44	0.90

2-year survival	
Total score	**2-year survival probability**
358	0.20
329	0.25
302	0.30
276	0.35
250	0.40
224	0.45
197	0.50
169	0.55
138	0.60
106	0.65
70	0.70
29	0.75

3-year survival	
Total score	**3-year survival probability**
342	0.10
305	0.15
273	0.20
245	0.25
218	0.30
192	0.35
166	0.40
139	0.45
112	0.50
84	0.55
54	0.60
21	0.65

5-year survival	
Total score	**5-year survival probability**
323	0.05
272	0.10
235	0.15
204	0.20
175	0.25
148	0.30
122	0.35
96	0.40
70	0.45
43	0.50
15	0.55

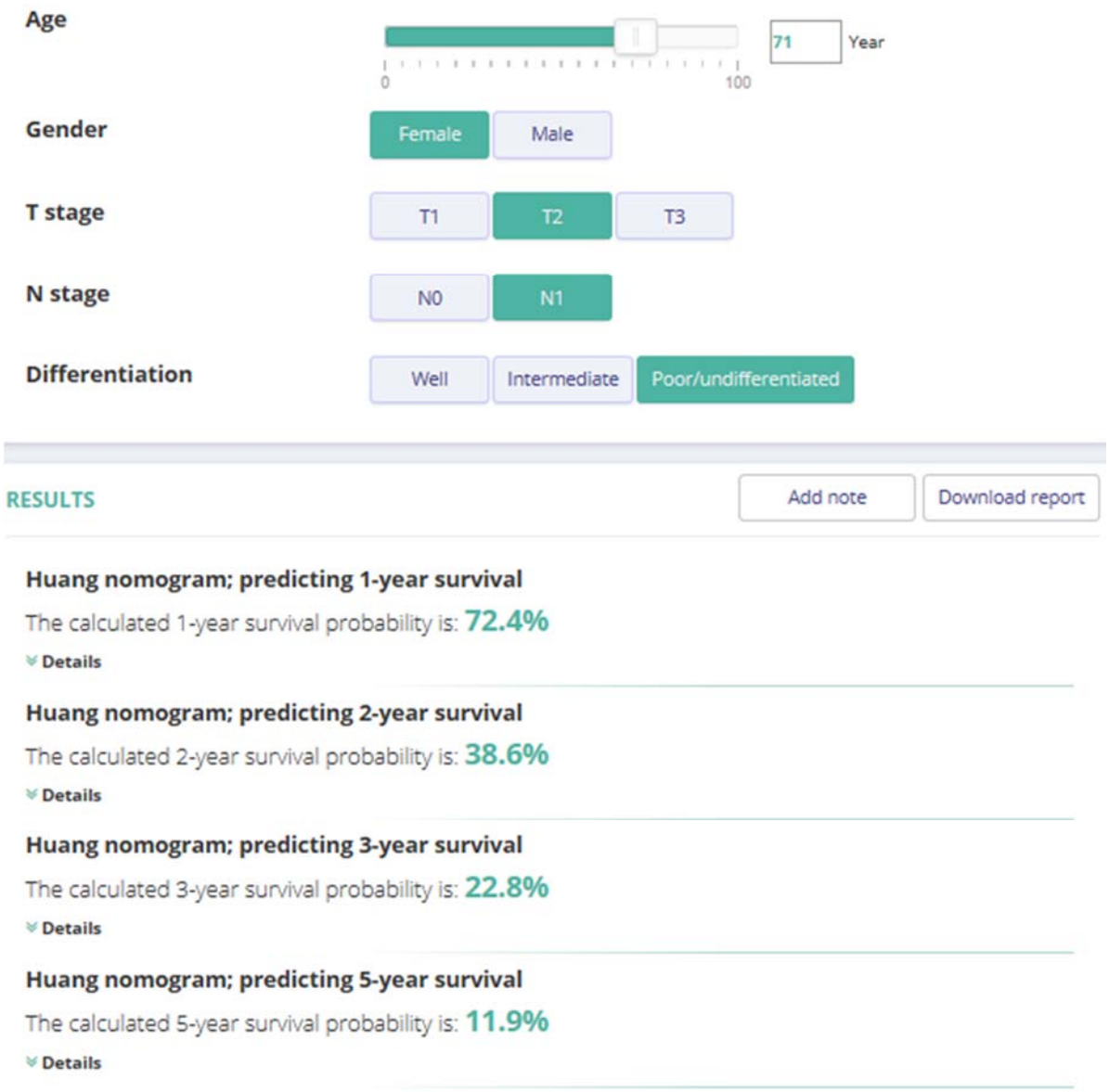

Figure 19. Layout of a potential online version of the developed nomogram with Evidencio (www.evidencio.com; not public yet)

Model function

Reference values: sex="Female", t="T1", n="N0", dgrade="Well" (the variable names “age”, “sex”, “t”, “n”, and “dgrade” are for “Age”, “Sex”, “T Stage”, “N Stage”, and “Differentiation” in the nomogram (**Figure 18**), respectively)

Function:-0.71148656+0.09222951*(sex=="Male")-0.0080361358*age+4.0504221e-05*pmax(age-47,0)^3-0.00019415844*pmax(age-59,0)^3+0.00026940813*pmax(age-65,0)^3-0.00014449267*pmax(age-71,0)^3+2.8738757e-05*pmax(age-80,0)^3+0.27621944*(t=="T2")+0.410323*(t=="T3")+0.42855775*(n=="N1")+0.24623505*(dgrade=="Intermediate")+0.50857222*(dgrade=="Poor/undifferentiated")

The function pmax() take one or more vectors as arguments, recycle them to common length, and return a single vector giving the *‘parallel’* maxima of the argument vectors.

Calibration and validation

The nomogram was applied to the US and the European countries for internal and external validations, respectively. The calibration plots presented very good agreement between nomogram-predicted and actual survival in the US, Belgium, and the Netherlands (**Figure 20**; plots were not shown in Slovenia or Norway where case number was too small to generate meaningful calibration). Generally the calibration was best for 2- and 3-year survival. In the training US cohort, the C-index for the established nomogram was significantly higher than that for the model based on both T and N stages (0.60, 95% CI=0.59-0.61 *vs.* 0.56, 95% CI=0.56-0.57). In the validation cohorts, C-indexes were also significantly higher for the nomogram than for the T and N stage-based model (**Table 48**).

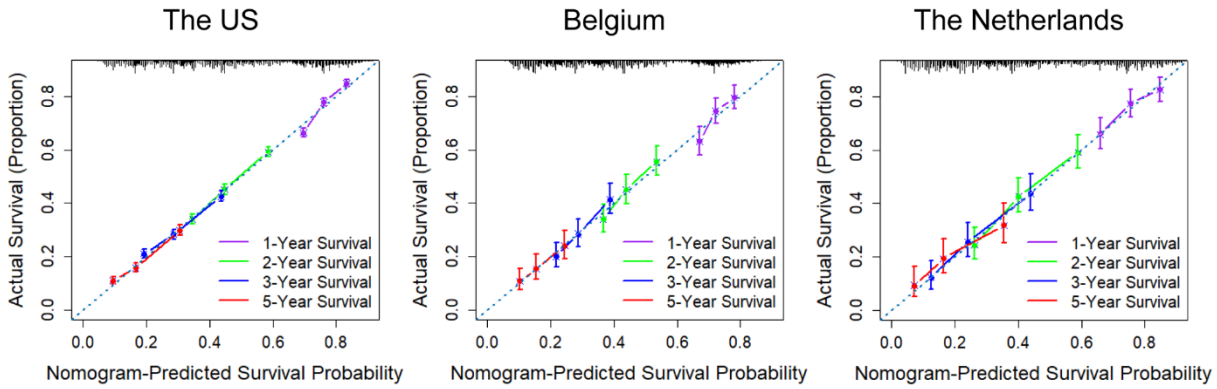

Figure 20. Calibration curves for 1-, 2-, 3-, and 5-year overall survival prediction in the primary training (the US) and validation cohorts (Belgium, the Netherlands, Slovenia, and Norway). Nomogram-predicted survival is plotted on the x axis, and actual survival on the y axis. The vertical bars at the top represent the frequency of the predicted probability of survival. A plot along the 45-degree line indicates a perfect calibration model where the predicted probabilities are identical to the actual proportions.

Table 48. Concordance indexes for resected pancreatic cancer in training and validation cohorts and in sensitivity analyses for the training US cohort

Model modification/subgroup	Concordance index	95% confidence interval
Training cohort		
The US, nomogram	0.60	0.59-0.61
The US, model based on both T and N stages	0.56	0.56-0.57
Validation cohorts		
Belgium, nomogram	0.58	0.55-0.60
Belgium, model based on both T and N stages	0.54	0.52-0.56
The Netherlands, nomogram	0.62	0.59-0.65
The Netherlands, model based on both T and N stages	0.56	0.54-0.59
Slovenia, nomogram	0.58	0.51-0.65
Slovenia, model based on both T and N stages	0.52	0.47-0.57
Norway, nomogram	0.63	0.55-0.71
Norway, model based on both T and N stages	0.61	0.54-0.68
Sensitivity analyses for the training US cohort		
Replacement		
Age group in place of continuous age	0.59	0.59-0.60
Metastatic lymph node number in place of N stage	0.60	0.59-0.61
Lymph node ratio in place of N stage	**0.61**	0.61-0.62
The 8th version of T stage in place of the original stage	**0.61**	0.60-0.61
The 8th version of N stage in place of the original stage	0.60	0.59-0.61
The 8th version of T & N stages in place of the original stages	**0.61**	0.60-0.62
Addition		
Harvested lymph node added	0.60	0.60-0.61
Tumor size added	**0.61**	0.60-0.61
Harvested lymph node & tumor size added	**0.61**	0.60-0.62
Subgroup		
Diagnosis after 2009	0.60	0.59-0.61
White ethnicity	0.60	0.59-0.61
Pancreas head	0.60	0.59-0.61
Pancreas body & tail	**0.61**	0.59-0.63

Concordance indexes in sensitivity analyses greater than that for the overall nomogram in the US are highlighted in bold.

Sensitivity analyses

Sensitivity analyses were performed for the derivative US cohort (**Table 48**). Using positive lymph node number or lymph node ratio instead of N stage in the nomogram did not obviously change the C-index (by 0.00 and +0.01, respectively). Replacing the sixth/seventh version of both T and N stages with the eighth version also had minimal impact on the C-index (by +0.01). After including examined lymph node number, tumor size, or both, the C-index only changed by 0.0, +0.01, and +0.01, respectively. Limiting the sample to patients diagnosed after 2009 or white people did not change the C-index. Within subgroups according to tumor location, C-index was slightly higher than the overall one in body/tail cancer (0.61).

3.1.5 Significance of examined lymph node number in accurate staging and long-term survival in resected stage I-II pancreatic cancer

3.1.5.1 Patient characteristics

A total of 15,791 eligible PaC patients in the US cohort (2004-2015) and 2,512 in the Netherlands cohort (2003-2014) undergoing cancer-directed resection were analyzed. Reasons for exclusion are detailed in **Table 49**. The proportion of females was 50% in SEER-18 and 47% in NCR. The mean age was 66 and 65 years in the SEER-18 and NCR cohorts, respectively (**Table 50**). Most resected tumors were located in pancreatic head (SEER-18, 73%; NCR, 82%), were not-otherwise-specified adenocarcinoma or ductal/lobular cancers (SEER-18, 88%; NCR, 90%), were of stage T3 (SEER-18, 78%; NCR, 69%), and were declared node-positive (SEER-18, 63%; NCR, 67%). Pancreatoduodenectomy was the most common type of resection (SEER-18, 73%; NCR, 86%). The mean ELN number was 16 in the US cohort and 11 in the Netherlands cohort, and in both countries the mean ELN number increased over time during the investigated periods (SEER-18, 11 to 18; NCR, 7 to 15; **Figure 21**). The mean PLN number was 2 in both cohorts. Median follow-up time was 58 months in the US cohort and 48 months in the Netherlands cohort.

Table 49. General information on the US and the Netherlands population-based pancreatic cancer cohorts

Source	Diagnosis period	Censoring date	Registered primary cases with eligible histology[1]	Excluded cases[2]						Eligible cases with ≥ 1 ELN
				DCO/ autopsy	Unknown survival	Not resected	Stage 0/III/ IV/missing	ELN missing	0 ELNs	
SEER-18[3]	Jan. 2004-Dec. 2015	Dec. 31, 2015	122826	3917 (3)	0 (0)	99448 (81)	2802 (2)	68 (<1)	800 (1)	15791
NCR	Jan. 2003-Dec. 2014	Feb. 1, 2015	22579	99 (<1)	0 (0)	19534 (87)	271 (1)	103 (<1)	60 (<1)	2512

[1]A preliminary data-cleaning process had been performed to exclude cases with ineligible histology types.

[2]Shown as n (percentage [%]).

[3]Data of the year 2003 were not analyzed, as the TNM stage (version 6/7) information was unavailable.

SEER, Surveillance, Epidemiology, and End Results Program; NCR, the Netherlands Cancer Registry; ELN, examine lymph node; DCO, death certificate only.

Table 50. Demographic and clinical characteristics of patients with resected stage I-II pancreatic cancer and with ≥ 1 examined lymph node[1]

Parameter		SEER-18, the US	NCR, the Netherlands
n		15791	2512
Sex	Female	7823 (50)	1192 (47)
Age (years)		66 ± 11, 67 (59-74)	65 ± 10, 66 (59-73)
Age group	< 50 years	1185 (8)	159 (6)
	50-59 years	2943 (19)	486 (19)
	60-69 years	5231 (33)	917 (37)
	70-79 years	4815 (30)	842 (34)
	≥ 80 years	1617 (10)	108 (4)
Tumor location[2]	Pancreas head	11589 (73)	2070 (82)
	Pancreas body	1110 (7)	82 (3)
	Pancreas tail	1659 (11)	171 (7)
	Overlapping lesion	672 (4)	64 (3)
	Other	761 (5)	125 (5)
Tumor histology[3]	Adenocarcinoma, NOS	7952 (50)	1504 (60)
	Ductal/lobular	6043 (38)	742 (30)
	Cystic/mucinous/serous	1151 (7)	212 (8)
	Other	645 (4)	54 (2)
T stage[4]	T1	1114 (7)	220 (9)
	T2	2278 (14)	571 (23)
	T3	12375 (78)	1721 (69)
N stage	N1	9910 (63)	1676 (67)
Differentiation[5]	Well	1661 (12)	226 (11)
	Intermediate	7309 (51)	1067 (52)
	Poor/undifferentiated	5355 (37)	770 (37)
Neoadjuvant chemotherapy[7]	Yes	NA	49 (2)
Neoadjuvant radiotherapy[7]	Yes	632 (4)	34 (1)
Resection type	Pancreatoduodenectomy	11462 (73)	2151 (86)
	Distal pancreatectomy	2206 (14)	234 (9)
	Total pancreatectomy	1906 (12)	39 (2)
	Other[6]	217 (1)	88 (4)
Examined lymph node count		16 ± 10, 14 (9-21)	11 ± 7, 10 (6-15)
Positive lymph node count		2 ± 3, 1 (0-3)	2 ± 3, 1 (0-3)
Lymph node ratio		0.16 ± 0.20, 0.08 (0.00-0.24)	0.21 ± 0.24, 0.14 (0.00-0.33)
Adjuvant chemotherapy[7]	Yes	10293 (65)	1040 (41)
Adjuvant radiotherapy[7]	Yes	4751 (30)	29 (1)
Follow up month[8]		58 (27-95)	48 (24-74)

[1]Enumeration data are shown as count (percentage [%]), and measurement data as mean ± standard deviation, median (interquartile range). Records are complete otherwise specified below.

[2]Pancreas duct and pancreas (NOS).

[3]Based on SEER broad groupings. Other: squamous cell, transitional cell, acinar cell, mucoepidermoid, complex, unspecified, and epithelial (NOS) neoplasms.

[4]Unkown T stage: the US, 24 (< 1%); the Netherlands, 0 (0%).

[5]Unknown differentiation: the US, 1466 (9%); the Netherlands, 449 (18%).

[6]Pancreatectomy (NOS) and local resection.

[7]In the US, neoadjuvant and adjuvant chemotherapy could not be differentiated from each other; the other category for the non-surgical variables was "No/unknown", considering the low sensitivity.

[8]Shown as median (interquartile range), and computed using the reverse Kaplan-Meier method.

SEER, Surveillance, Epidemiology, and End Results Program; NCR, the Netherlands Cancer Registry; NOS, not otherwise specified; NA, not available.

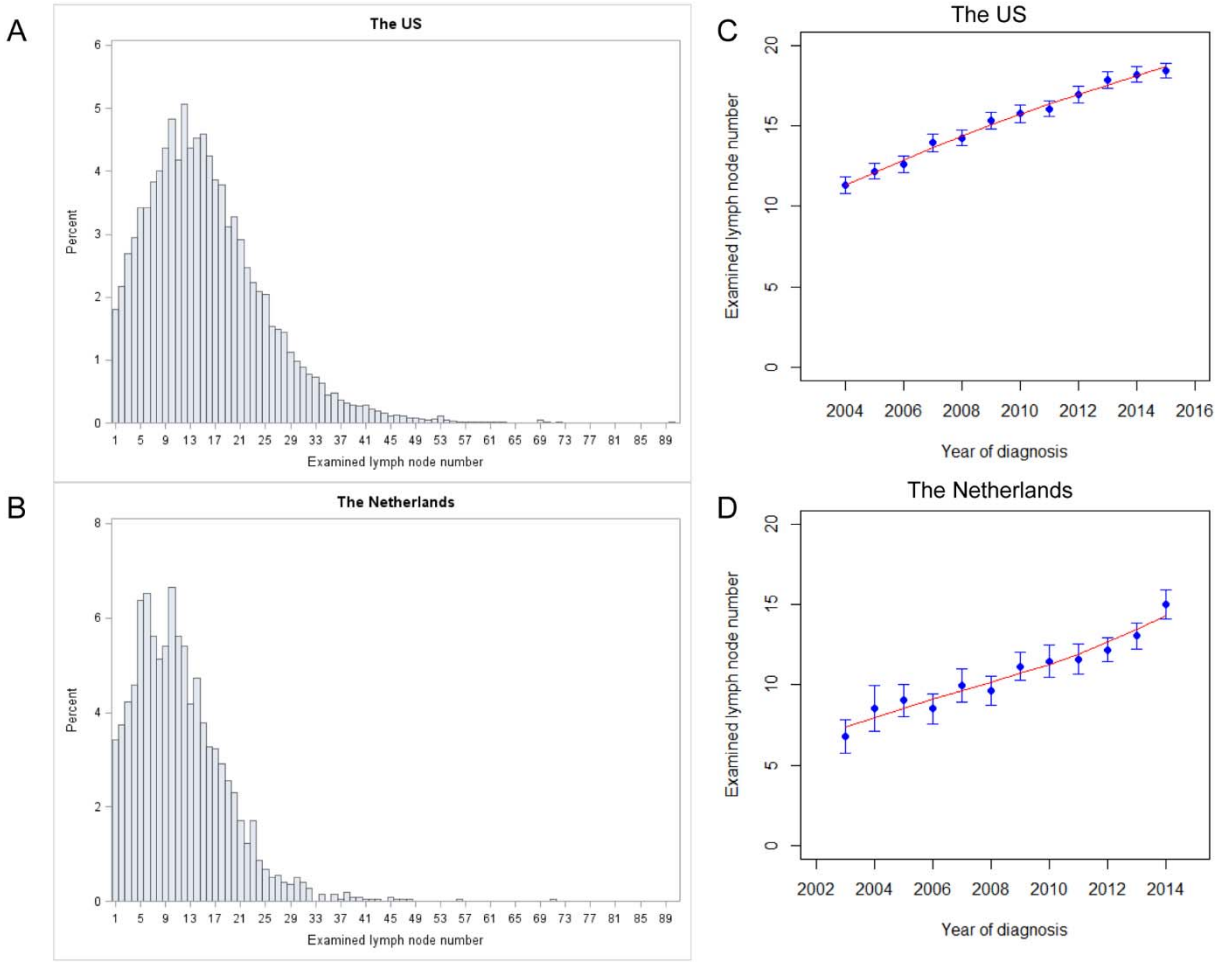

Figure 21. Distribution (**A** and **B**) and temporal trends (**C** and **D**) of examined lymph node (ELN) number in the United States (US) and the Netherlands databases. The yearly ELN number is shown as mean ± 95% confidence interval in blue. Patients with ≥1 ELN were included.

3.1.5.2 Examined lymph node number and stage migration

In both countries, the PLN number increased with more ELNs (**Figures 22A-B**). Accordingly, the odds for nodal stage migration increased with more ELNs, also after multivariable adjustment, both overall (per 1 additional ELN: $OR_{SEER\text{-}18}$=1.05, 95% CI=1.04-1.05; OR_{NCR}=1.10, 95% CI=1.08-1.12) and in most subgroups by sex, age group, tumor location, histology, T stage, differentiation, resection type, and chemotherapy and radiotherapy administration (**Table 51**). Interaction tests suggested that the association with stage migration was weaker in T1 and cystic/mucinous tumors in SEER-18 and in patients undergoing distal pancreatectomy in both cohorts, and stronger in male patients in NCR. Sensitivity analyses by inclusion of further potentially ELN-/PLN-associated covariates (SEER-18: tumor size; NCR: hospital type, neoadjuvant treatment, and comorbidities), by replacing the 7th edition TNM staging with the 8th edition in SEER-18 following Kamarajah *et al.* (Kamarajah et al., 2017), by limiting the study period to 2010 or later, and by limiting patients to those with pancreatic adenocarcinoma only or to those survived ≥1 or 3 months did not change the association patterns (data not shown).

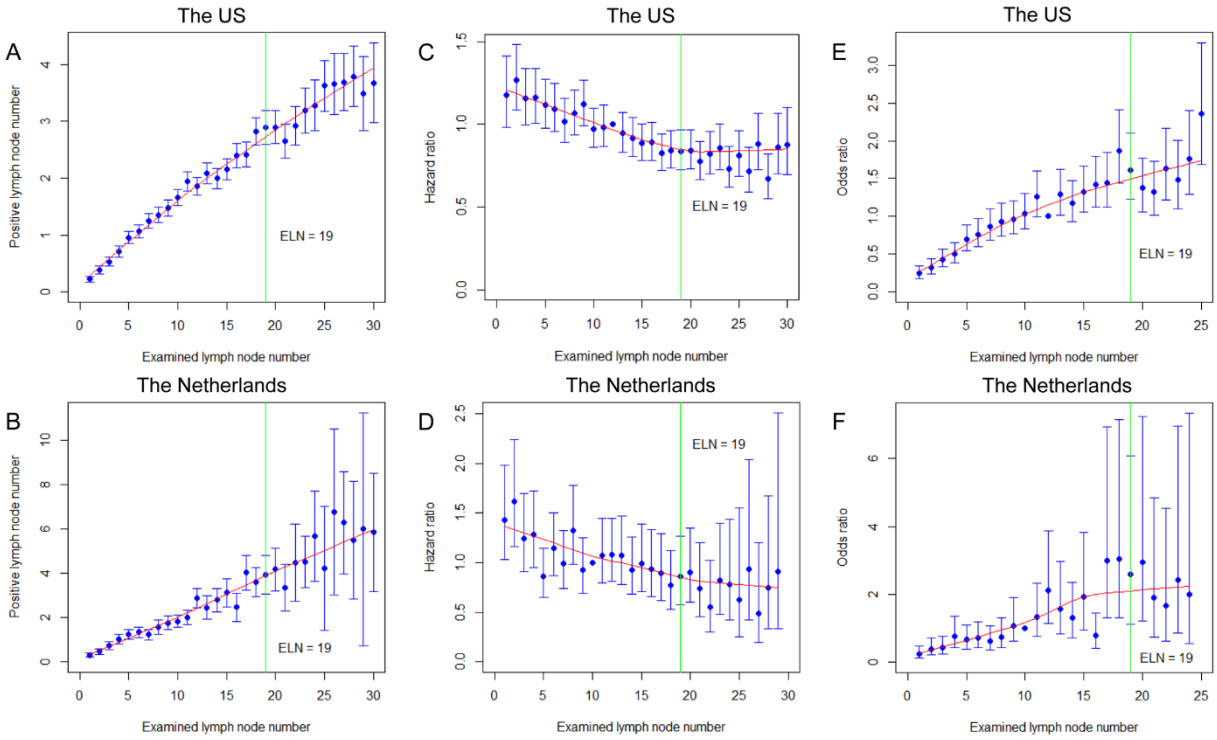

Figure 22. Associations of examined lymph node (ELN) number with positive lymph node number (**A** and **B**), hazard ratio for overall survival (**C** and **D**), and odds ratio for stage migration (**E** and **F**) in the United States (US) and the Netherlands cohorts. The point estimates and corresponding 95% confidence intervals for the variables associated with ELN number are shown in blue. LOWESS smoother-fitted curves with a fitting bandwidth of 2/3 are shown in red. The structural breaks determined by the Chow test for survival association in the US cohort are shown in green. Hazard ratio for survival was computed using multivariable Cox proportional hazards regression model adjusting for sex, age, tumor T stage, histology, and resection type. Odds ratio for stage migration was computed using multivariable logistic regression adjusting for T stage, histology, location, and resection type.

Table 51. Association of examined lymph node number (entered as a continuous variable) with nodal stage migration in resected pancreatic cancer patients with ≥ 1 examined lymph node[1]

Stratification	The US				The Netherlands			
	OR	**95% CI**	P_{OR}	$P_{interaction}$	**OR**	**95% CI**	P_{OR}	$P_{interaction}$
Overall	1.05	1.04-1.05	**< 0.001**		1.10	1.08-1.12	**< 0.001**	
Sex				0.829				**0.028**
Female	1.05	1.04-1.05	**< 0.001**		1.07	1.05-1.10	**< 0.001**	
Male	1.05	1.04-1.05	**< 0.001**		1.12	1.09-1.15	**< 0.001**	
Age group				0.359				0.589
< 50 years	1.04	1.02-1.05	**< 0.001**		1.10	1.02-1.18	**0.010**	
50-59 years	1.05	1.04-1.06	**< 0.001**		1.12	1.07-1.17	**< 0.001**	
60-69 years	1.04	1.03-1.05	**< 0.001**		1.11	1.08-1.15	**< 0.001**	
70-79 years	1.05	1.04-1.06	**< 0.001**		1.07	1.04-1.10	**< 0.001**	
≥ 80 years	1.05	1.04-1.07	**< 0.001**		1.24	1.02-1.51	**0.031**	
Tumor location				0.220				0.099
Pancreas head	1.05	1.04-1.05	**< 0.001**		1.11	1.09-1.13	**< 0.001**	
Pancreas body	1.04	1.02-1.05	**< 0.001**		1.08	0.94-1.23	0.282	
Pancreas tail	1.06	1.04-1.07	**< 0.001**		1.09	1.02-1.16	**0.014**	
Overlapping lesion	1.04	1.02-1.06	**< 0.001**		1.05	0.94-1.18	0.420	
Other[2]	1.05	1.03-1.07	**< 0.001**		1.02	0.96-1.08	0.501	
Tumor histology[3]				**0.013**				0.084
Adenocarcinoma, NOS	1.05	1.04-1.05	**< 0.001**		1.08	1.06-1.11	**< 0.001**	
Ductal/lobular	1.05	1.04-1.06	**< 0.001**		1.13	1.09-1.17	**< 0.001**	
Cystic/mucinous/serous	1.03	1.02-1.05	**< 0.001**		1.15	1.06-1.25	**0.001**	
Other	1.04	1.02-1.07	**< 0.001**		0.94	0.41-2.17	0.893	
T stage				**0.006**				0.655
T1	1.03	1.01-1.05	**< 0.001**		1.05	0.98-1.12	0.164	
T2	1.05	1.04-1.06	**< 0.001**		1.10	1.06-1.15	**< 0.001**	
T3	1.05	1.04-1.05	**< 0.001**		1.10	1.08-1.13	**< 0.001**	
Differentiation				0.952				0.593
Well	1.05	1.04-1.06	**< 0.001**		1.11	1.04-1.18	**0.001**	
Intermediate	1.05	1.04-1.05	**< 0.001**		1.10	1.07-1.13	**< 0.001**	
Poor/undifferentiated	1.05	1.04-1.05	**< 0.001**		1.09	1.06-1.12	**< 0.001**	
Resection type				**0.049**				**0.014**
Pancreatoduodenectomy	1.05	1.04-1.06	**< 0.001**		1.10	1.08-1.12	**< 0.001**	
Distal pancreatectomy	1.04	1.02-1.05	**< 0.001**		1.05	1.00-1.11	**0.042**	
Total pancreatectomy	1.05	1.04-1.07	**< 0.001**		1.23	0.91-1.64	0.175	
Other[4]	1.04	1.00-1.08	**0.039**		1.44	1.14-1.81	**0.003**	
Chemotherapy, yes	1.05	1.04-1.05	**< 0.001**		1.09	1.06-1.13	**< 0.001**	
Radiotherapy, yes	1.05	1.04-1.06	**< 0.001**		1.57	1.01-2.44	**0.045**	

[1]Odds ratios for association of examined lymph node number with positive versus negative nodal status overall and in stratifications were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age, tumor location, histology, T stage, differentiation, and resection type. In stratified analyses, the stratification factor was omitted from the model. Interactions between examined lymph node number and the stratification factors were also tested, where age group, tumor T stage, and differentiation were regarded as ordinal. Statistically significant *P* values are shown in bold.

[2]Pancreas duct and pancreas (NOS).

[3]Based on SEER broad groupings. Other: squamous cell, transitional cell, acinar cell, mucoepidermoid, complex, unspecified, and epithelial (NOS) neoplasms.

[4]Pancreatectomy (NOS) and local resection.

SEER, Surveillance, Epidemiology, and End Results Program; OR, odds ratio; CI, confidence interval; NOS, not otherwise specified.

LNR firstly decreased with more ELNs in both countries, and then the declining trend weakened in the US and disappeared in the Netherlands (**Figures 23A-B**). In both cohorts, more ELNs were associated with a lower probability of having ≥1 undetected PLN in patients who were considered to have node-negative disease (**Figure 24**). The association curves became less steep with more ELNs.

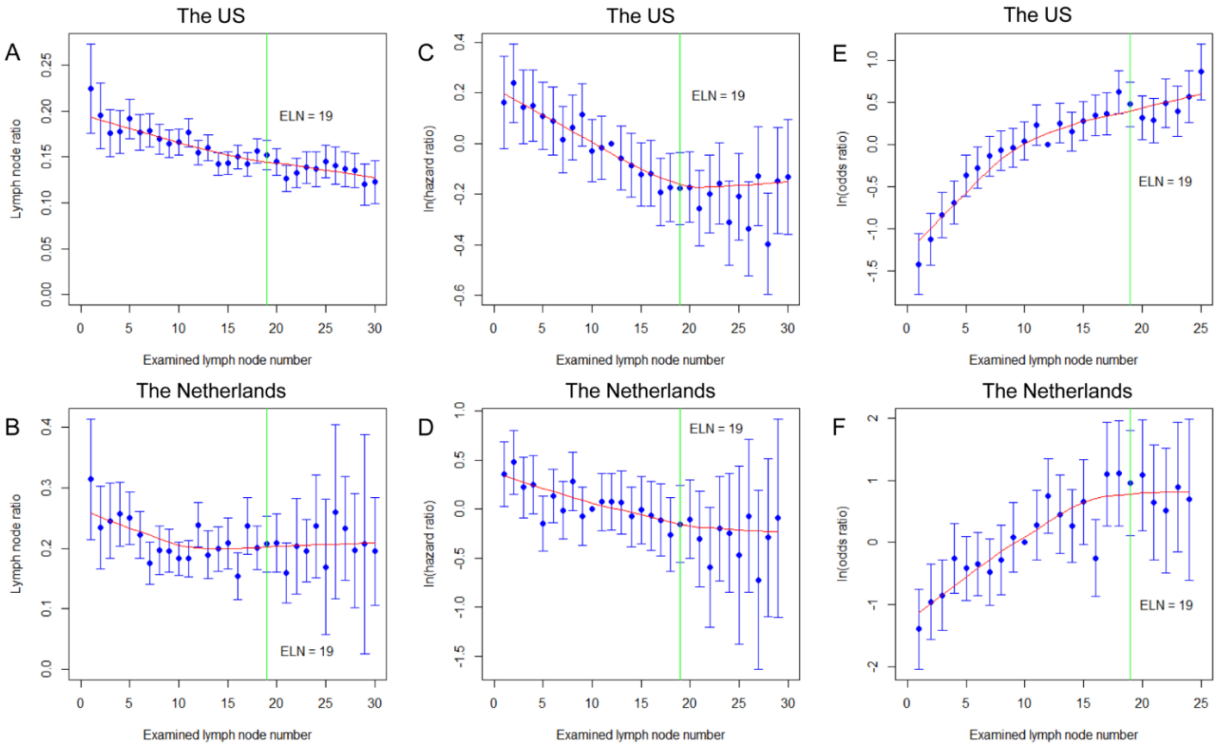

Figure 23. Associations of examined lymph node number (ELN) with lymph node ratio (**A** and **B**) and the logarithms of hazard ratio for survival (**C** and **D**) and odds ratio for stage migration (**E** and **F**) in the United States (US) and the Netherlands cohorts. The point estimates and corresponding 95% confidence intervals for the variables associated with ELN number are shown in blue. LOWESS smoother-fitted curves with a fitting bandwidth of 2/3 are shown in red. The structural breaks determined by the Chow test for the association with the hazard ratio for survival in the US cohort (19 ELNs) are shown in green.

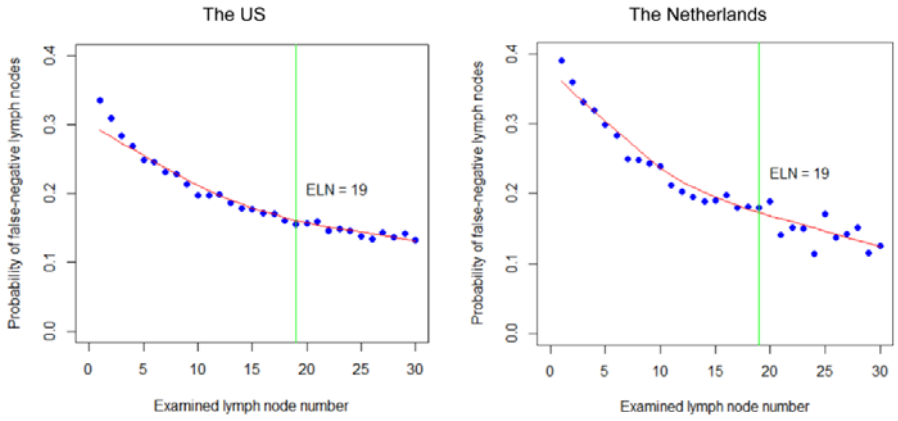

Figure 24. Associations of examined lymph node (ELN) number with probability of undetected positive lymph nodes in the United States (US) and the Netherlands cohorts. The point estimates and corresponding 95% confidence intervals for the variables associated with ELN number are shown in blue. LOWESS smoother-fitted curves with a fitting bandwidth of 2/3 are shown in red. The structural breaks determined by the Chow test for the association with the hazard ratio for survival in the US cohort (19 ELNs) are shown in green.

3.1.5.3 Examined lymph node number and overall survival

After controlling for other prognostic factors including sex, age, tumor location, histology, T stage, N stage, differentiation, and resection type, more ELNs were associated with better OS both overall ($HR_{SEER-18}$=0.98, 95% CI=0.98-0.99; HR_{NCR}=0.98, 95% CI=0.97-0.99) and in most subgroups (**Table 52**). Notably, the significant association persisted in both declared node-negative ($HR_{SEER-18}$=0.99, 95% CI=0.98-0.99; HR_{NCR}=0.98, 95% CI=0.96-1.00) and node-positive diseases ($HR_{SEER-18}$=0.98, 95% CI=0.98-0.99; HR_{NCR}=0.98, 95% CI=0.97-0.99). Association strengths in subgroups according to the same stratification factors were very similar despite a few significant interaction test results. Sensitivity analyses by inclusion of further potentially prognostic covariates (SEER-18: ethnicity, marital status, and tumor size; NCR: hospital type, resection margin, non-surgical treatment as static or time-dependent, and comorbidities), by replacing the 7th edition TNM staging with the 8th edition in SEER-18 following Kamarajah *et al.* (Kamarajah et al., 2017), by limiting the study period to 2010 or later, by limiting patients to those with pancreatic adenocarcinoma only or to those survived ≥1 or 3 months, and by use of disease-specific survival as the endpoint in SEER-18 did not change the association patterns (data not shown).

3.1.5.4 Cut-point analysis and validation

The fitting curves for associations of ELN number with PLN number, HR for survival, and OR for stage migration are shown in **Figure 22**, and the curves for associations with LNR and with the logarithms of the HR and OR in **Figure 23**. Based on the US cohort, the determined structural breakpoints for the various associations in the whole cohort and for the association with HR in various stratifications are listed in **Table 53**. Because survival is the most crucial endpoint and for representativeness and generalizability, the structural breakpoint for survival derived from the SEER-18 database (19 ELNs) was used as the optimal cut-point. While most of the identified breakpoints for survival were essentially in agreement with each other, notably the breakpoint was markedly smaller in observed node-negative (13) than node-positive disease (19), and in patients <60 years (12) than those aged 60-69 (18) or ≥70 years (19).

Table 52. Association of examined lymph node number (entered as a continuous variable) with overall survival in resected pancreatic cancer patients with ≥ 1 examined lymph node[1]

Stratification	The US				The Netherlands			
	HR	**95% CI**	P_{HR}	$P_{interaction}$	**HR**	**95% CI**	P_{HR}	$P_{interaction}$
Overall	0.98	0.98-0.99	**< 0.001**		0.98	0.97-0.99	**< 0.001**	
Sex				**0.023**				**0.028**
Female	0.99	0.98-0.99	**< 0.001**		0.97	0.96-0.98	**< 0.001**	
Male	0.98	0.98-0.99	**< 0.001**		0.98	0.97-1.00	**0.009**	
Age group				0.058				0.149
< 50 years	0.98	0.98-0.99	**0.001**		0.97	0.93-1.01	0.106	
50-59 years	0.99	0.98-0.99	**< 0.001**		0.98	0.96-1.01	0.129	
60-69 years	0.99	0.98-0.99	**< 0.001**		0.98	0.97-1.00	**0.017**	
70-79 years	0.98	0.98-0.99	**< 0.001**		0.97	0.95-0.98	**< 0.001**	
≥ 80 years	0.98	0.97-0.99	**< 0.001**		0.92	0.86-0.98	**0.009**	
Tumor location				**< 0.001**				0.576
Pancreas head	0.98	0.98-0.99	**< 0.001**		0.98	0.97-0.99	**< 0.001**	
Pancreas body	0.99	0.98-1.00	**0.005**		0.96	0.91-1.03	0.261	
Pancreas tail	0.99	0.98-1.00	**0.006**		0.94	0.89-0.98	**0.004**	
Overlapping lesion	0.99	0.98-1.00	0.144		0.94	0.88-1.00	**0.048**	
Other[2]	0.98	0.97-0.99	**< 0.001**		0.98	0.94-1.03	0.440	
Tumor histology[3]				**0.037**				0.182
Adenocarcinoma, NOS	0.99	0.98-0.99	**< 0.001**		0.98	0.97-0.99	**0.001**	
Ductal/lobular	0.98	0.98-0.99	**< 0.001**		0.97	0.95-0.98	**< 0.001**	
Cystic/mucinous/serous	0.98	0.97-0.99	**< 0.001**		0.98	0.95-1.02	0.370	
Other	1.00	0.98-1.01	0.539		0.91	0.72-1.15	0.427	
T stage				0.062				0.568
T1	0.99	0.97-1.00	**0.010**		0.96	0.92-1.01	0.113	
T2	0.99	0.98-0.99	**< 0.001**		0.97	0.95-0.99	**0.001**	
T3	0.98	0.98-0.99	**< 0.001**		0.98	0.97-0.99	**< 0.001**	
N stage				0.524				0.997
N0	0.99	0.98-0.99	**< 0.001**		0.98	0.96-1.00	**0.025**	
N1	0.98	0.98-0.99	**< 0.001**		0.98	0.97-0.99	**< 0.001**	
Differentiation				0.289				0.863
Well	0.99	0.98-1.00	**0.029**		0.99	0.96-1.02	0.442	
Intermediate	0.98	0.98-0.99	**< 0.001**		0.97	0.96-0.99	**< 0.001**	
Poor/undifferentiated	0.99	0.98-0.99	**< 0.001**		0.98	0.97-0.99	**0.006**	
Resection type				0.517				0.455
Pancreatoduodenectomy	0.98	0.98-0.99	**< 0.001**		0.98	0.97-0.99	**< 0.001**	
Distal pancreatectomy	0.99	0.98-0.99	**< 0.001**		0.96	0.93-0.99	**0.013**	
Total pancreatectomy	0.99	0.98-0.99	**< 0.001**		0.99	0.88-1.11	0.815	
Other[4]	0.98	0.96-1.01	0.113		0.98	0.90-1.07	0.656	
Chemotherapy, yes	0.99	0.98-0.99	**< 0.001**		0.97	0.96-0.99	**< 0.001**	
Radiotherapy, yes	0.99	0.98-0.99	**< 0.001**		0.82	0.65-1.03	0.086	

[1]Hazard ratios for associations of examined lymph node number with survival were calculated by Cox proportional hazards regression with adjustment for year of diagnosis, sex, age, tumor location, histology, T stage, metastatic lymph node number, differentiation, and resection type. In stratified analyses, the stratification factor was omitted from the model. Interactions between examined lymph node number and the stratification factors were also tested, where age group, tumor T stage, N stage, and differentiation were regarded as ordinal. Statistically significant *P* values are shown in bold.

[2]Pancreas duct and pancreas (NOS).

[3]Based on SEER broad groupings. Other: squamous cell, transitional cell, acinar cell, mucoepidermoid, complex, unspecified, and epithelial (NOS) neoplasms.

[4]Pancreatectomy (NOS) and local resection.

SEER, Surveillance, Epidemiology, and End Results Program; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.

Table 53. Structural breakpoints of examined lymph node number based on different parameters and based on hazard ratio for overall survival in different stratifications in the US cohort[1]

Parameter/subgroup	Comment/category	Structural breakpoint	*F*	*P*[4]
Based on different parameters				
Hazard ratio for survival		19	1036.6	**< 0.001**
Hazard ratio for survival	The Netherlands	19	165.1	**< 0.001**
ln(hazard ratio for survival)		19	1799.1	**< 0.001**
Odds ratio for stage migration		12	331.4	**< 0.001**
Odds ratio for stage migration	The Netherlands	14	127.9	**< 0.001**
ln(odds ratio for stage migration)		10	722.5	**< 0.001**
Positive lymph node number		14	298.1	**< 0.001**
Lymph node ratio		15	764.5	**< 0.001**
Based on hazard ratio for survival in different subgroups				
Sex	Female	19	986.9	**< 0.001**
	Male	17	558.1	**< 0.001**
Age group	< 60 years	12	1184.4	**< 0.001**
	60-69 years	18	711.3	**< 0.001**
	≥ 70 years	19	50.5	**< 0.001**
Tumor location	Pancreas head	17	372.0	**< 0.001**
	Pancreas body/tail	16	331.6	**< 0.001**
	Overlapping lesion/other[2]	21	919.5	**< 0.001**
Tumor histology	Adenocarcinoma, NOS/ductal/lobular	19	859.0	**< 0.001**
	Cystic/mucinous/serous	15	158.7	**< 0.001**
	Other[3]	19	652.3	**< 0.001**
T stage	T1	16	7215.1	**< 0.001**
	T2	17	31.0	**< 0.001**
	T3	18	633.3	**< 0.001**
N stage	N0	13	1212.5	**< 0.001**
	N1	19	1215.6	**< 0.001**
Differentiation	Well	18	93.3	**< 0.001**
	Intermediate	21	1763.4	**< 0.001**
	Poor/undifferentiated	17	382.3	**< 0.001**
Resection type	Pancreatoduodenectomy	17	538.9	**< 0.001**
	Distal pancreatectomy	20	2317.8	**< 0.001**
	Total pancreatectomy	21	1066.8	**< 0.001**
Chemotherapy	Yes	17	590.9	**< 0.001**
Radiotherapy	Yes	18	924.9	**< 0.001**

[1]Results are derived from the US cohort if not otherwise specified in the "Comment/category" column. Structure breakpoints were determined by Chow test for the LOWESS smoother-fitted associations of examined lymph node number with the indicated parameters overall and in stratifications. Odds ratios for association of examined lymph node number with positive versus negative nodal status overall and in stratifications were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age, tumor location, histology, T stage, differentiation, and resection type. Hazard ratios for associations of examined lymph node number with survival were calculated by Cox proportional hazards regression with adjustment for year of diagnosis, sex, age, tumor location, histology, T stage, metastatic lymph node number, differentiation, and resection type. In stratified analyses, the stratification factor was omitted from the model. Statistically significant *P* values are shown in bold.

[2]Pancreas duct and pancreas (NOS).

[3]Based on SEER broad groupings. Other: squamous cell, transitional cell, acinar cell, mucoepidermoid, complex, unspecified, and epithelial (NOS) neoplasms.

[4]The *P* values are for the Chow Test (*F* Test) at the given structural breakpoints.

SEER, Surveillance, Epidemiology, and End Results Program; NOS, not otherwise specified.

The chosen optimal cut-point was validated internally in the US cohort where it was generated and externally in the independent Netherlands cohort: Cox regression analysis confirmed significantly decreased all-cause mortality hazard for patients with ≥19 ELNs after multivariable adjustment, overall ($HR_{SEER-18}$=0.80, 95% CI=0.76-0.83; HR_{NCR}=0.74, 95% CI=0.62-0.88) and in most stratifications by sex, age group, tumor location, histology, T stage, differentiation, resection type, and chemotherapy and radiotherapy administration (**Table 54**). Notably, while the association remained significant in both declared node-negative (HR=0.80, 95% CI=0.73-0.88) and node-positive PaCs (HR=0.80, 95% CI=0.75-0.84) in the US, it was only significant in node-positive cancer in the Netherlands (HR=0.71, 95% CI=0.59-0.85; **Figure 25**). Furthermore, the odds for nodal stage migration significantly increased with ≥19 ELNs in multivariable analyses, both overall ($OR_{SEER-18}$=1.82, 95% CI=1.67-1.98; HR_{NCR}=2.87, 95% CI=2.03-4.06) and in nearly all of the subgroups (**Table 55**). Changes of HR, OR, the corresponding logarithms, lymph node ratio, and false-negative LN probability with more ELNs all became markedly less steep with more than 19 ELNs in both cohorts (**Figures 22-24**).

Twelve ELNs were further selected as the minimal threshold based on the ORs for stage migration (**Table 53**), which was validated using an approach similar with that for the optimal threshold in both overall (survival: $HR_{SEER-18}$=0.79, 95% CI=0.76-0.83; HR_{NCR}=0.84, 95% CI=0.75-0.95; stage migration: $OR_{SEER-18}$=1.99, 95% CI=1.84-2.15; OR_{NCR}=2.70, 95% CI=2.17-3.35) and stratified analyses (data not shown).

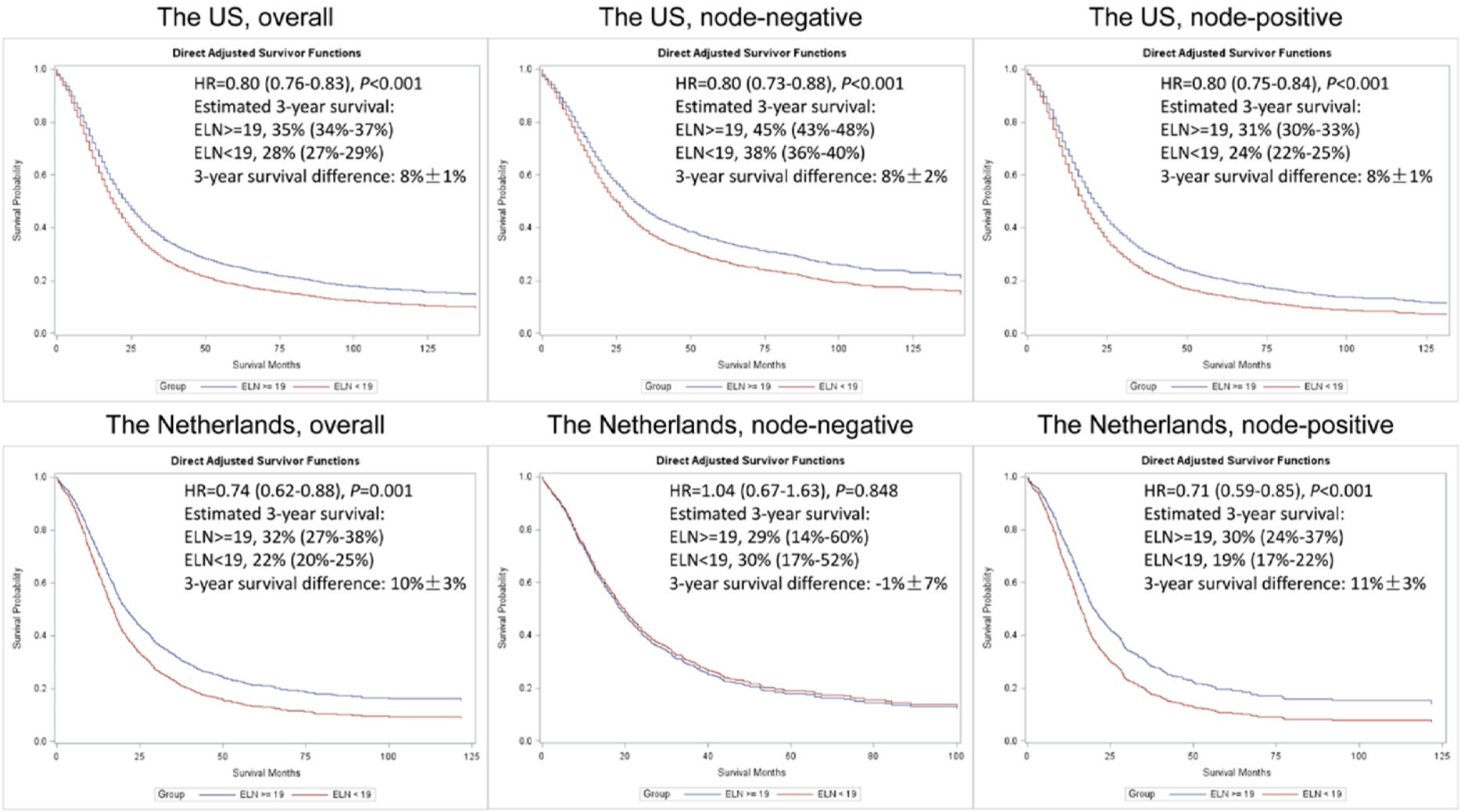

Figure 25. Stratification of overall survival in resected pancreatic cancer patients with the cut-point of 19 examined lymph nodes (ELNs) computed using multivariable Cox regression adjusting for sex, age, tumor T stage, histology, location, and resection type in patients with overall (**A** and **B**), node-negative (**C** and **D**), and node-positive diseases (**E** and **F**) in the United States (US) and the Netherlands cohorts. Positive lymph node number was also adjusted for overall and node-positive cases.

Table 54. Association of ≥ versus < 19 examined lymph nodes with overall survival in resected pancreatic cancer patients with ≥ 1 examined lymph node[1]

Stratification	The US				The Netherlands			
	HR	95% CI	P_{HR}	$P_{interaction}$	HR	95% CI	P_{HR}	$P_{interaction}$
Overall	0.80	0.76-0.83	**< 0.001**		0.74	0.62-0.88	**0.001**	
Sex				0.140				0.276
Female	0.80	0.74-0.85	**< 0.001**		0.68	0.53-0.87	**0.003**	
Male	0.79	0.74-0.85	**< 0.001**		0.78	0.61-0.99	**0.040**	
Age group				**0.006**				0.917
< 50 years	0.80	0.67-0.96	**0.019**		0.41	0.19-0.89	**0.023**	
50-59 years	0.85	0.77-0.95	**0.004**		0.60	0.40-0.91	**0.016**	
60-69 years	0.83	0.76-0.89	**< 0.001**		0.88	0.66-1.17	0.364	
70-79 years	0.77	0.71-0.83	**< 0.001**		0.70	0.51-0.95	**0.021**	
≥ 80 years	0.70	0.60-0.81	**< 0.001**		0.24	0.05-1.22	0.086	
Tumor location				0.129				0.347
Pancreas head	0.79	0.75-0.83	**< 0.001**		0.77	0.64-0.93	**0.006**	
Pancreas body/tail	0.83	0.73-0.94	**0.004**		0.64	0.32-1.27	0.200	
Overlapping lesion/other[2]	0.80	0.68-0.94	**0.005**		0.61	0.32-1.17	0.134	
Tumor histology[3]				**0.019**				0.786
Adenocarcinoma, NOS	0.79	0.74-0.84	**< 0.001**		0.80	0.64-1.00	0.051	
Ductal/lobular	0.79	0.74-0.85	**< 0.001**		0.71	0.52-0.96	**0.027**	
Cystic/mucinous/serous	0.74	0.59-0.94	**0.012**		0.53	0.26-1.10	0.088	
T stage				0.082				0.688
T1-2	0.82	0.73-0.93	**0.001**		0.68	0.48-0.96	**0.028**	
T3	0.79	0.75-0.83	**< 0.001**		0.77	0.63-0.94	**0.010**	
N stage				**< 0.001**				**< 0.001**
N0	0.80	0.73-0.88	**< 0.001**		1.04	0.67-1.63	0.848	
N1	0.80	0.75-0.84	**< 0.001**		0.71	0.59-0.85	**< 0.001**	
Differentiation				0.193				0.908
Well/intermediate	0.75	0.71-0.80	**< 0.001**		0.74	0.59-0.93	**0.009**	
Poor/undifferentiated	0.84	0.79-0.91	**< 0.001**		0.81	0.62-1.06	0.123	
Resection type				0.953				0.225
Pancreatoduodenectomy	0.80	0.76-0.84	**< 0.001**		0.74	0.62-0.89	**0.001**	
Distal pancreatectomy	0.80	0.70-0.92	**0.002**		0.53	0.26-1.08	0.080	
Total pancreatectomy	0.78	0.69-0.89	**< 0.001**		-	-	-	
Chemotherapy, yes	0.83	0.78-0.87	**< 0.001**		0.74	0.58-0.96	**0.021**	
Radiotherapy, yes	0.84	0.78-0.91	**< 0.001**		0.43	0.04-5.03	0.501	

[1]Hazard ratios for associations of ≥ versus < 19 examined lymph nodes with survival were calculated by Cox proportional hazards regression with adjustment for year of diagnosis, sex, age, tumor location, histology, T stage, metastatic lymph node number, differentiation, and resection type. In stratified analyses, the stratification factor was omitted from the model. Interactions between examined lymph node number and the stratification factors were also tested, where age group were regarded as ordinal. Significant *P* values are shown in bold.

[2]Pancreas duct and pancreas (NOS).

[3]Based on SEER broad groupings.

SEER, Surveillance, Epidemiology, and End Results Program; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; -, not estimable due to small case number.

Table 55. Association of ≥ versus < 19 examined lymph nodes with nodal stage migration in resected pancreatic cancer patients with ≥ 1 examined lymph node[1]

Stratification	The US				The Netherlands			
	OR	**95% CI**	P_{OR}	$P_{interaction}$	**OR**	**95% CI**	P_{OR}	$P_{interaction}$
Overall	1.82	1.67-1.98	**< 0.001**		2.87	2.03-4.06	**< 0.001**	
Sex				0.549				**0.036**
Female	1.88	1.68-2.12	**< 0.001**		1.98	1.26-3.11	**0.003**	
Male	1.75	1.55-1.97	**< 0.001**		4.44	2.54-7.76	**< 0.001**	
Age group				0.421				0.697
< 50 years	1.52	1.09-2.10	**0.013**		2.32	0.71-7.55	0.162	
50-59 years	2.26	1.85-2.78	**< 0.001**		3.69	1.65-8.26	**0.002**	
60-69 years	1.68	1.46-1.93	**< 0.001**		5.00	2.51-9.97	**< 0.001**	
≥ 70 years	1.82	1.60-2.07	**< 0.001**		1.93	1.10-3.39	**0.022**	
Tumor location				0.976				0.526
Pancreas head	1.80	1.63-1.99	**< 0.001**		3.00	2.01-4.47	**< 0.001**	
Pancreas body/tail	1.90	1.55-2.33	**< 0.001**		4.16	1.42-12.22	**0.009**	
Overlapping lesion/other[2]	1.84	1.39-2.42	**< 0.001**		1.22	0.44-3.39	0.703	
Tumor histology[3]				0.179				0.447
Adenocarcinoma, NOS	1.82	1.61-2.04	**< 0.001**		2.56	1.64-4.01	**< 0.001**	
Ductal/lobular	1.92	1.68-2.19	**< 0.001**		4.18	2.21-7.89	**< 0.001**	
Cystic/mucinous/serous	1.77	1.23-2.53	**0.002**		3.49	0.80-15.29	0.098	
T stage				0.784				0.093
T1-2	1.89	1.57-2.29	**< 0.001**		2.00	1.10-3.62	**0.023**	
T3	1.80	1.64-1.98	**< 0.001**		3.57	2.30-5.52	**< 0.001**	
Differentiation				0.869				0.932
Well/intermediate	1.85	1.66-2.05	**< 0.001**		2.87	1.84-4.47	**< 0.001**	
Poor/undifferentiated	1.78	1.55-2.05	**< 0.001**		2.93	1.68-5.14	**< 0.001**	
Resection type				0.174				0.729
Pancreatoduodenectomy	1.86	1.69-2.06	**< 0.001**		3.06	2.08-4.49	**< 0.001**	
Distal pancreatectomy	1.52	1.21-1.91	**< 0.001**		2.15	0.82-5.64	0.119	
Total pancreatectomy	1.93	1.51-2.47	**< 0.001**		-	-	-	
Chemotherapy, yes	1.81	1.63-2.01	**< 0.001**		3.29	2.00-5.42	**< 0.001**	
Radiotherapy, yes	2.05	1.76-2.38	**< 0.001**		-	-	**-**	

[1]Odds ratios for association of examined lymph node number (≥ versus < 19) with nodal status (positive versus negative) overall and in stratifications were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age, tumor location, histology, T stage, differentiation, and resection type. In stratified analyses, the stratification factor was omitted from the model. Interactions between examined lymph node number and the stratification factors were also tested, where age group were regarded as ordinal. Statistically significant *P* values are shown in bold.

[2]Pancreas duct and pancreas (NOS).

[3]Based on SEER broad groupings. Other: squamous cell, transitional cell, acinar cell, mucoepidermoid, complex, unspecified, and epithelial (NOS) neoplasms.

[4]Pancreatectomy (NOS) and local resection.

SEER, Surveillance, Epidemiology, and End Results Program; OR, odds ratio; CI, confidence interval; NOS, not otherwise specified; -, not estimable due to small case number.

3.2 Gastric cancer

3.2.1 Characteristics of overall and resected gastric cancer patients

Overall, 133,321 GC patients registered in the population-based registries were initially included (**Table 56**). Patients with DCO/autopsy-based diagnosis (1%), without microscopically-confirmed or eligible pathology (11%), with non-invasive diseases (1%), and without information on distant metastasis status (8%) were excluded. Exclusion of patients with unknown metastasis status affected overall resection rates by only 0-2% in the US, the Netherlands, Sweden, and Norway, but markedly increased the resection rate in Belgium (51% to 61%), where the proportion of unknown metastasis was high (22%; **Table 57**). Finally 105,922 patients were analyzed, among whom 65,707 (62%) had non-metastatic disease. Characteristics of overall and resected cancer patients without and with distant metastasis are shown in **Tables 58-59**.

Table 56. General information on participating population-based registries for Chapter 3.2.1

Source	Country	Diagnosis period	Registered cases	Excluded cases[1]				Analyzed cases
				DCO/ autopsy	Not pathologically diagnosed/eligible[2]	Precancerous /*in situ*	Unknown metastasis	
SEER-18[3]	the US	Jan. 2004-Dec. 2014	79091	855 (1)	11003 (14)	780 (1)	5344 (7)	61109
NCR	Netherlands	Jan. 2005-Dec. 2014	18346	48 (<1)	387 (2)	343 (2)	711 (4)	16857
BCR	Belgium	Jan. 2004-Dec. 2013	14122	NA	1750 (12)	23 (<1)	3076 (22)	9273
SCR	Sweden	Jan. 2006-Aug. 2016	7909	NA	169 (2)	0 (0)	471 (6)	7269
CRN	Norway	Jan. 2003-Dec. 2014	6194	53 (1)	737 (12)	5 (<1)	362 (6)	5037
CRS	Slovenia	Jan. 2003-Dec. 2013	5265	NA	472 (9)	9 (<1)	236 (4)	4548
ECR	Estonia	Jan. 2009-Dec. 2014	2394	67 (3)	253 (11)	0 (0)	245 (10)	1829

[1]Shown as n (percentage [%]).
[2]Preliminary case selection according to cancer histology had been performed by the national cancer registries of Netherlands and Sweden.
[3]Data of the year 2003 was not analyzed, as the TNM stage (version 6/7) information was unavailable.
SEER, Surveillance, Epidemiology, and End Results Program; NCR, Netherlands Cancer Registry; BCR, Belgian Cancer Registry; SCR, Swedish Cancer Registry; CRN, Cancer Registry of Norway; CRS, Cancer Registry of Slovenia; ECR, Estonian Cancer Registry; DCO, death certificate only; NA, not available.

Table 57. Overall resection rates of all gastric cancer patients and patients after exclusion of non-pathologically diagnosed/eligible cases, those with unknown metastasis status, and both

Patients	**The US**	**The Netherlands**	**Belgium**	**Sweden**	**Norway**	**Slovenia**	**Estonia**
	Rate (%)	Rate (%)	Rate (%)	Rate (%)	Rate (%)	Rate (%)	Rate (%)
All patients	46	45	51	36	43	51	50
After exclusion of non-pathologically diagnosed/eligible cases	44	46	50	36	44	52	52
After exclusion of those with unknown metastasis status	49	47	61	38	45	54	56
After exclusion of both	47	47	61	38	45	55	57
Patients finally included	46	46	61	38	45	55	57

Table 58. Demographic and clinical characteristics of total and resected non-metastatic gastric cancer patients[1]

Variable	Category	the US		The Netherlands		Belgium		Sweden	
Year of diagnosis		2004-2015		2005-2014		2004-2013		2006-2016	
Without metastasis		***Total***	***Resected***	***Total***	***Resected***	***Total***	***Resected***	***Total***	***Resected***
n		37829	25070 (66)	9745	6605 (68)	6468	5096 (79)	4486	2501 (56)
Sex	Male	24063 (64)	15989 (64)	6287 (65)	4367 (66)	4274 (66)	3420 (67)	2821 (63)	1587 (63)
Age at diagnosis	Year; as continuous	69 ± 13	67 ± 13	71 ± 12	68 ± 12	70 ± 13	69 ± 12	72 ± 12	69 ± 11
Age group	< 60 years	8672 (23)	6603 (26)	1699 (17)	1423 (22)	1274 (20)	1110 (22)	714 (16)	506 (20)
	60-69 years	8865 (23)	6559 (26)	2280 (23)	1815 (27)	1390 (22)	1191 (23)	1043 (23)	720 (29)
	70-79 years	10528 (28)	7286 (29)	3144 (32)	2230 (34)	2122 (33)	1733 (34)	1394 (31)	831 (33)
	≥ 80 years	9764 (26)	4622 (18)	2622 (27)	1137 (17)	1682 (26)	1062 (21)	1335 (30)	444 (18)
Tumor location[2]	Gastric cardia	12731 (48)	7387 (42)	2630 (37)	1622 (33)	2024 (55)	1520 (54)	1387 (39)	737 (35)
	Gastric fundus/body	4461 (17)	2992 (17)	1576 (22)	1132 (23)	483 (13)	368 (13)	1018 (28)	611 (29)
	Gastric antrum/pylorus	9578 (36)	7208 (41)	2957 (41)	2236 (45)	1152 (32)	939 (33)	1196 (33)	762 (36)
	Other	11059 (29)	7483 (30)	2582 (27)	1615 (24)	2809 (43)	2269 (45)	885 (20)	391 (16)
Histology	Adenocarcinoma	28795 (76)	19231 (77)	7316 (75)	4869 (74)	5100 (79)	3979 (78)	NA	NA
	Signet ring cell carcinoma	6780 (18)	4586 (18)	1850 (19)	1333 (20)	972 (15)	802 (16)	NA	NA
	Other[3]	2254 (6)	1253 (5)	579 (6)	403 (6)	396 (6)	315 (6)	NA	NA
Differentiation[4]	Well	1923 (6)	1487 (6)	261 (4)	211 (4)	60 (12)	479 (11)	-	-
	Moderate	9737 (29)	6753 (29)	1738 (28)	1369 (29)	1729 (31)	1371 (31)	-	-
	Poor/undifferentiated	21399 (65)	14968 (65)	4310 (68)	3163 (67)	3158 (57)	2590 (58)	-	-
Local invasion[5]	Lamina propria/submucosa	11585 (34)	7070 (29)	1335 (17)	1219 (19)	1426 (23)	1114 (22)	545 (15)	432 (18)
	Muscularis propria/subserosa	14824 (43)	11791 (48)	4278 (53)	3509 (55)	2887 (47)	2451 (49)	1950 (53)	1199 (51)
	Serosa	5071 (15)	4373 (18)	1509 (19)	1283 (20)	1609 (26)	1326 (26)	804 (22)	570 (24)
	Adjacent structures	3032 (9)	1569 (6)	910 (11)	368 (6)	268 (4)	157 (3)	383 (10)	144 (6)
Positive lymph node[6]	0	20041 (54)	11631 (47)	4030 (47)	2955 (46)	2787 (46)	2228 (45)	2274 (55)	1275 (51)
	1-6	12359 (33)	9040 (36)	3414 (40)	2418 (37)	2381 (39)	1908 (38)	1385 (34)	849 (34)
	≥ 7	4507 (12)	4335 (17)	1138 (13)	1081 (17)	948 (16)	856 (17)	464 (11)	361 (15)
Harvested node no.		\	15 ± 13	\	16 ± 16	\	NA	\	18 ± 14
Resection type[7]	Partial/subtotal gastrectomy	\	16764 (67)	\	4564 (69)	\	NA	\	860 (62)
	Total/near-total gastrectomy	\	5075 (20)	\	1656 (25)	\	NA	\	475 (34)
	Other	\	3231 (13)	\	385 (6)	\	NA	\	50 (4)
Resection margin[8]	Positive	\	NA	\	886 (15)	\	NA	\	338 (15)
Neoadjuvant CHT[9]	Yes	\	NA	\	2326 (35)	\	1155 (23)	\	840 (34)
Neoadjuvant RT[9]	Yes	\	2509 (10)	\	183 (3)	\	204 (4)	\	188 (8)
Total/adjuvant CHT[9]	Yes	16872 (45)	11694 (47)	3176 (33)	1251 (19)	2543 (39)	1646 (32)	NA	NA
Total/adjuvant RT[9]	Yes	12071 (32)	5766 (23)	810 (8)	215 (3)	1037 (16)	645 (13)	NA	NA

[1]Categorical data are shown as count (percentage [%]), and numeric data as mean ± standard deviation. Records are complete otherwise specified below.

[2]The percentages of gastric cardia, fundus/body, and antrum/pylorus cancers are the proportions compared to the total tumor cases of the 3 locations; 'other' includes lesser curvature, greater curvature, and overlapping lesion of stomach and stomach (NOS), and its proportion is relative to the whole cases.

[3]Cystic/mucinous/serous (excluding signet ring cell), squamous cell, ductal/lobular, complex, unspecified, and epithelial (NOS) neoplasms.

[4]Unknown differentiation: **total patients:** the US, 4770 (13%); the Netherlands, 3436 (35%); Belgium, 941 (15%); Sweden, 3507 (78%); Norway, 804 (25%); Slovenia, 680 (24%); Estonia, 159 (15%); **resected patients:** the US, 1862 (7%); the Netherlands, 1862 (28%); Belgium, 656 (13%); Sweden, 1552 (62%); Norway, 399 (19%); Slovenia, 348 (16%); Estonia, 104 (13%).

[5]Unknown tumor local invasion: **total patients:** the US, 3317 (9%); the Netherlands, 1713 (18%); Belgium, 278 (4%); Sweden, 804 (18%); Norway, 1544 (47%); Slovenia, 437 (15%); Estonia, 108 (11%); **resected patients:** the US, 267 (1%); the Netherlands, 226 (3%); Belgium, 48 (1%); Sweden, 156 (6%); Norway, 780 (38%); Slovenia, 40 (2%); Estonia, 38 (5%). Invasion of serosa and adjacent structures could not be differentiated from each other in Norway or Slovenia.

[6]Unknown positive lymph node: **total patients:** the US, 922 (2%); the Netherlands, 1163 (12%); Belgium, 352 (5%); Sweden, 363 (8%); Norway, 794 (24%); Slovenia, 319 (11%); Estonia, 90 (9%); **resected patients:** the US, 64 (<1%); the Netherlands, 151 (2%); Belgium, 104 (2%); Sweden, 16 (1%); Norway, 564 (27%); Slovenia, 19 (1%); Estonia, 95 (12%).

[7]Gastrectomy (NOS) or local resection. Available in Sweden since 2010.

[8]Unkown resection margin for resected non-metastatic cancer: the Netherlands, 628 (10%); Sweden, 286 (11%); Slovenia, 26 (3%). In Slovenia margin status was not available before 2009.

[9]Non-surgical therapies in the US and Estonia had low sensitivity, and the counterpart category of "Yes" was "No/unknown". In Norway and Estonia, neoadjuvant and adjuvant therapies could not be distinguished from each other. Total CHT/RT is for total patients, and (neo)adjuvant CHT/RT for resected patients.

CHT, chemotherapy; RT, radiotherapy; NOS, not otherwise specified; \, resection-specific variables not applicable for total patients; -, not shown due to > 60% missing values; NA, not available.

Table 58. Demographic and clinical characteristics of total and resected non-metastatic gastric cancer patients[1] (continued)

Variable	Category	Norway		Slovenia		Estonia	
Year of diagnosis		2003-2014		2003-2013		2009-2014	
Without metastasis		***Total***	***Resected***	***Total***	***Resected***	***Total***	***Resected***
n		3258	2057 (63)	2893	2172 (75)	1028	807 (79)
Sex	Male	2036 (62)	1323 (64)	1821 (63)	1384 (64)	568 (55)	445 (55)
Age at diagnosis	Year; as continuous	72 ± 12	70 ± 12	69 ± 12	67 ± 12	68 ± 12	67 ± 12
Age group	< 60 years	520 (16)	379 (18)	642 (22)	56 (26)	223 (22)	194 (24)
	60-69 years	725 (22)	530 (26)	662 (23)	553 (25)	273 (27)	222 (28)
	70-79 years	968 (30)	664 (32)	1000 (35)	770 (35)	332 (32)	261 (32)
	≥ 80 years	1045 (32)	484 (24)	589 (20)	282 (13)	200 (19)	130 (16)
Tumor location[2]	Gastric cardia	857 (39)	480 (32)	461 (27)	314 (23)	96 (12)	70 (11)
	Gastric fundus/body	486 (22)	322 (22)	459 (27)	414 (30)	423 (52)	342 (53)
	Gastric antrum/pylorus	865 (39)	678 (46)	779 (46)	654 (47)	291 (36)	237 (37)
	Other	1050 (32)	577 (28)	1194 (41)	790 (36)	218 (21)	158 (20)
Histology	Adenocarcinoma	2785 (85)	1771 (86)	2693 (93)	2069 (95)	626 (61)	503 (62)
	Signet ring cell carcinoma	278 (9)	178 (9)	74 (3)	48 (2)	283 (28)	221 (27)
	Other[3]	195 (6)	108 (5)	126 (4)	55 (3)	119 (12)	83 (10)
Differentiation[4]	Well	101 (4)	68 (4)	223 (10)	184 (10)	66 (8)	53 (8)
	Moderate	694 (28)	491 (30)	594 (27)	501 (27)	249 (29)	203 (29)
	Poor/undifferentiated	1659 (68)	1099 (66)	1396 (63)	1139 (62)	554 (64)	447 (64)
Local invasion[5]	Lamina propria/submucosa	250 (15)	195 (15)	483 (20)	447 (21)	182 (20)	164 (21)
	Muscularis propria/subserosa	669 (39)	540 (42)	1061 (43)	978 (46)	515 (56)	424 (55)
	Serosa	582 (34)	417 (33)	722 (29)	614 (29)	184 (20)	157 (20)
	Adjacent structures	213 (12)	125 (10)	190 (8)	93 (4)	39 (4)	24 (3)
Positive lymph node[6]	0	1793 (73)	991 (66)	1128 (44)	855 (40)	503 (54)	401 (52)
	1-6	545 (22)	408 (27)	808 (31)	720 (33)	332 (35)	282 (36)
	≥ 7	126 (5)	94 (6)	638 (25)	578 (27)	103 (11)	95 (12)
Harvested node no.		\	NA	\	NA	\	NA
Resection type[7]	Partial/subtotal gastrectomy	\	NA	\	NA	\	NA
	Total/near-total gastrectomy	\	NA	\	NA	\	NA
	Other	\	NA	\	NA	\	NA
Resection margin[8]	Positive	\	NA	\	68 (7)	\	NA
Neoadjuvant CHT[9]	Yes	\	NA	\	124 (6)	\	NA
Neoadjuvant RT[9]	Yes	\	NA	\	61 (3)	\	NA
Total/adjuvant CHT[9]	Yes	614 (19)	453 (22)	813 (28)	620 (29)	177 (17)	134 (17)
Total/adjuvant RT[9]	Yes	188 (6)	88 (4)	695 (24)	563 (26)	36 (4)	34 (4)

[1]Categorical data are shown as count (percentage [%]), and numeric data as mean ± standard deviation. Records are complete otherwise specified below.

[2]The percentages of gastric cardia, fundus/body, and antrum/pylorus cancers are the proportions compared to the total tumor cases of the 3 locations; 'other' includes lesser curvature, greater curvature, and overlapping lesion of stomach and stomach (NOS), and its proportion is relative to the whole cases.

[3]Cystic/mucinous/serous (excluding signet ring cell), squamous cell, ductal/lobular, complex, unspecified, and epithelial (NOS) neoplasms.

[4]Unknown differentiation: **total patients:** the US, 4770 (13%); the Netherlands, 3436 (35%); Belgium, 941 (15%); Sweden, 3507 (78%); Norway, 804 (25%); Slovenia, 680 (24%); Estonia, 159 (15%); **resected patients:** the US, 1862 (7%); the Netherlands, 1862 (28%); Belgium, 656 (13%); Sweden, 1552 (62%); Norway, 399 (19%); Slovenia, 348 (16%); Estonia, 104 (13%).

[5]Unknown tumor local invasion: **total patients:** the US, 3317 (9%); the Netherlands, 1713 (18%); Belgium, 278 (4%); Sweden, 804 (18%); Norway, 1544 (47%); Slovenia, 437 (15%); Estonia, 108 (11%); **resected patients:** the US, 267 (1%); the Netherlands, 226 (3%); Belgium, 48 (1%); Sweden, 156 (6%); Norway, 780 (38%); Slovenia, 40 (2%); Estonia, 38 (5%). Invasion of serosa and adjacent structures could not be differentiated from each other in Norway or Slovenia.

[6]Unknown positive lymph node: **total patients:** the US, 922 (2%); the Netherlands, 1163 (12%); Belgium, 352 (5%); Sweden, 363 (8%); Norway, 794 (24%); Slovenia, 319 (11%); Estonia, 90 (9%); **resected patients:** the US, 64 (<1%); the Netherlands, 151 (2%); Belgium, 104 (2%); Sweden, 16 (1%); Norway, 564 (27%); Slovenia, 19 (1%); Estonia, 95 (12%).

[7]Gastrectomy (NOS) or local resection. Available in Sweden since 2010.

[8]Unkown resection margin for resected non-metastatic cancer: the Netherlands, 628 (10%); Sweden, 286 (11%); Slovenia, 26 (3%). In Slovenia margin status was not available before 2009.

[9]Non-surgical therapies in the US and Estonia had low sensitivity, and the counterpart category of "Yes" was "No/unknown". In Norway and Estonia, neoadjuvant and adjuvant therapies could not be distinguished from each other. Total CHT/RT is for total patients, and (neo)adjuvant CHT/RT for resected patients.

CHT, chemotherapy; RT, radiotherapy; NOS, not otherwise specified; \, resection-specific variables not applicable for total patients; -, not shown due to > 60% missing values; NA, not available.

Table 59. Demographic and clinical characteristics of total and resected metastatic gastric cancer patients[1]

Variable	Category	the US		The Netherlands		Belgium		Sweden	
Year of diagnosis		2004-2015		2005-2014		2004-2013		2006-2016	
Without metastasis		***Total***	***Resected***	***Total***	***Resected***	***Total***	***Resected***	***Total***	***Resected***
n		23280	3232 (14)	7112	1201 (17)	2805	598 (21)	2783	254 (9)
Sex	Male	14864 (64)	1914 (59)	4637 (65)	750 (62)	1894 (68)	385 (64)	1711 (61)	144 (57)
Age at diagnosis	Year; as continuous	65 ± 14	64 ± 14	68 ± 12	67 ± 12	69 ± 13	67 ± 13	70 ± 12	68 ± 11
Age group	< 60 years	8071 (35)	1211 (37)	1574 (22)	283 (24)	648 (23)	176 (29)	483 (17)	54 (21)
	60-69 years	5763 (25)	795 (25)	1948 (27)	338 (28)	690 (25)	138 (23)	752 (27)	74 (29)
	70-79 years	5585 (24)	764 (24)	2345 (33)	399 (33)	879 (31)	179 (30)	902 (32)	85 (33)
	≥ 80 years	3861 (17)	462 (14)	1245 (18)	181 (15)	588 (21)	105 (18)	646 (23)	41 (16)
Tumor location[2]	Gastric cardia	7145 (50)	518 (27)	2143 (47)	266 (34)	889 (60)	175 (54)	856 (44)	52 (25)
	Gastric fundus/body	3165 (22)	395 (21)	1116 (24)	194 (25)	289 (19)	52 (16)	629 (32)	57 (28)
	Gastric antrum/pylorus	3950 (28)	981 (52)	1352 (29)	329 (42)	315 (21)	99 (30)	458 (24)	98 (47)
	Other	9020 (39)	1338 (41)	2501 (35)	412 (34)	1312 (47)	272 (46)	840 (30)	47 (19)
Histology	Adenocarcinoma	16181 (70)	2160 (67)	5445 (77)	890 (74)	2226 (79)	443 (74)	NA	NA
	Signet ring cell carcinoma	5129 (22)	860 (27)	1221 (17)	248 (21)	414 (15)	120 (20)	NA	NA
	Other[3]	1970 (8)	212 (7)	446 (6)	63 (5)	165 (6)	35 (6)	NA	NA
Differentiation[4]	Well	374 (2)	46 (2)	65 (2)	14 (2)	173 (7)	24 (5)	-	5 (4)
	Intermediate	4021 (22)	552 (19)	847 (22)	167 (21)	635 (27)	123 (23)	-	21 (17)
	Poor/undifferentiated	13715 (76)	2383 (80)	3010 (77)	603 (77)	1532 (66)	390 (73)	-	95 (79)
Local invasion[5]	Lamina propria/submucosa	3875 (28)	182 (6)	111 (3)	19 (2)	90 (5)	14 (2)	48 (2)	10 (4)
	Muscularis propria/subserosa	3797 (28)	1073 (35)	1805 (53)	409 (49)	641 (36)	192 (33)	797 (38)	86 (35)
	Serosa	1773 (13)	1023 (33)	586 (17)	265 (32)	742 (42)	284 (49)	418 (20)	102 (42)
	Adjacent structures	4256 (31)	788 (26)	878 (26)	147 (18)	291 (17)	95 (16)	819 (39)	46 (19)
Positive lymph node[6]	0	7743 (44)	554 (18)	1002 (18)	160 (15)	268 (15)	62 (11)	504 (24)	49 (20)
	1-6	8308 (47)	1288 (42)	4150 (76)	700 (67)	1067 (58)	252 (44)	1127 (54)	107 (43)
	≥ 7	1630 (9)	1237 (40)	287 (5)	187 (18)	519 (28)	262 (46)	470 (22)	95 (38)
Harvested node no.		\	13 ± 13	\	9 ± 17	\	NA	\	19 ± 17
Resection type[7]	Partial/subtotal gastrectomy	\	1914 (59)	\	847 (71)	\	NA	\	91 (62)
	Total/near-total gastrectomy	\	755 (23)	\	299 (25)	\	NA	\	47 (32)
	Other	\	563 (17)	\	55 (5)	\	NA	\	9 (6)
Neoadjuvant CHT[8]	Yes	\	NA	\	225 (19)	\	172 (29)	\	62 (24)
Neoadjuvant RT[8]	Yes	\	148 (5)	\	17 (1)	\	32 (5)	\	6 (2)
Total/adjuvant CHT[8]	Yes	12501 (54)	1724 (53)	2732 (38)	338 (28)	1745 (62)	284 (48)	NA	NA
Total/adjuvant RT[8]	Yes	3714 (16)	380 (12)	519 (7)	62 (5)	279 (10)	54 (9)	NA	NA

[1]Categorical data are shown as count (percentage [%]), and numeric data as mean ± standard deviation. Records are complete otherwise specified below.

[2]The percentages of gastric cardia, fundus/body, and antrum/pylorus cancers are the proportions compared to the total tumor cases of the 3 locations; 'other' includes lesser curvature, greater curvature, and overlapping lesion of stomach and stomach (NOS), and its proportion is relative to the whole cases.

[3]Cystic/mucinous/serous (excluding signet ring cell), squamous cell, ductal/lobular, complex, unspecified, and epithelial (NOS) neoplasms.

[4]Unknown differentiation: **total patients:** the US, 5170 (22%); the Netherlands, 3190 (45%); Belgium, 465 (17%); Sweden, 2614 (94%); Norway, 597 (34%); Slovenia, 712 (43%); Estonia, 209 (26%); **resected patients:** the US, 251 (8%); the Netherlands, 417 (35%); Belgium, 61 (10%); Sweden, 133 (52%); Norway, 45 (20%); Slovenia, 48 (15%); Estonia, 19 (16%).

[5]Unknown tumor local invasion: **total patients:** the US, 9579 (41%); the Netherlands, 3732 (53%); Belgium, 1041 (37%); Sweden, 701 (25%); Norway, 1162 (65%); Slovenia, 825 (50%); Estonia, 243 (30%); **resected patients:** the US, 166 (5%); the Netherlands, 361 (30%); Belgium, 13 (2%); Sweden, 903 (4%); Norway, 107 (48%); Slovenia, 26 (8%); Estonia, 15 (13%). Invasion of serosa and adjacent structures could not be differentiated from each other in Norway or Slovenia.

[6]Unknown positive lymph node: **total patients:** the US, 5599 (24%); the Netherlands, 1673 (24%); Belgium, 951 (34%); Sweden, 682 (25%); Norway, 1263 (71%); Slovenia, 1037 (63%); Estonia, 473 (59%); **resected patients:** the US, 153 (5%); the Netherlands, 154 (13%); Belgium, 22 (4%); Sweden, 3 (1%); Norway, 123 (55%); Slovenia, 36 (11%); Estonia, 28 (24%).

[7]Gastrectomy (NOS) or local resection. Available in Sweden since 2010.

[8]Non-surgical therapies in the US and Estonia had low sensitivity, and the counterpart category of "Yes" was "No/unknown". In Norway and Estonia, neoadjuvant and adjuvant therapies could not be distinguished from each other. Total CHT/RT is for total patients, and (neo)adjuvant CHT/RT for resected patients.

CHT, chemotherapy; RT, radiotherapy; NOS, not otherwise specified; \, resection-specific variables not applicable for total patients; -, not shown due to > 60% missing values; NA, not available.

Table 59. Demographic and clinical characteristics of total and resected metastatic gastric cancer patients[1] (continued)

Variable	Category	Norway		Slovenia		Estonia	
Year of diagnosis		2003-2014		2003-2013		2009-2014	
Without metastasis		***Total***	***Resected***	***Total***	***Resected***	***Total***	***Resected***
n		1779	222 (12)	1655	323 (20)	801	119 (15)
Sex	Male	1083 (61)	121 (55)	1057 (64)	200 (62)	471 (59)	68 (57)
Age at diagnosis	Year; as continuous	69 ± 13	68 ± 14	67 ± 12	64 ± 12	68 ± 13	65 ± 14
Age group	< 60 years	398 (22)	58 (26)	424 (26)	110 (34)	199 (25)	37 (31)
	60-69 years	415 (23)	47 (21)	424 (26)	91 (28)	213 (27)	33 (28)
	70-79 years	517 (29)	65 (29)	561 (34)	100 (31)	260 (32)	35 (29)
	≥ 80 years	449 (25)	52 (23)	246 (15)	22 (7)	129 (16)	14 (12)
Tumor location[2]	Gastric cardia	465 (46)	30 (22)	240 (37)	29 (19)	70 (14)	5 (6)
	Gastric fundus/body	257 (25)	37 (27)	171 (26)	54 (36)	296 (61)	41 (53)
	Gastric antrum/pylorus	289 (29)	70 (51)	236 (36)	66 (44)	123 (25)	31 (40)
	Other	768 (43)	85 (38)	1008 (61)	174 (54)	312 (39)	42 (35)
Histology	Adenocarcinoma	1454 (82)	177 (80)	1393 (84)	289 (89)	425 (53)	69 (58)
	Signet ring cell carcinoma	174 (10)	28 (13)	101 (6)	19 (6)	249 (31)	36 (30)
	Other[3]	151 (8)	17 (8)	161 (10)	15 (5)	127 (16)	14 (12)
Differentiation[4]	Well	30 (3)	2 (1)	48 (5)	11 (4)	27 (5)	4 (4)
	Intermediate	248 (21)	43 (24)	214 (23)	55 (20)	154 (26)	26 (26)
	Poor/undifferentiated	904 (76)	132 (75)	681 (72)	209 (76)	411 (69)	70 (70)
Local invasion[5]	Lamina propria/submucosa	-	4 (3)	20 (2)	5 (2)	3 (1)	1 (1)
	Muscularis propria/subserosa	-	39 (34)	163 (20)	69 (23)	260 (47)	44 (42)
	Serosa	-	72 (63)	377 (45)	169 (57)	228 (41)	48 (46)
	Adjacent structures	-		270 (33)	54 (18)	67 (12)	11 (11)
Positive lymph node[6]	0	-	16 (16)	-	19 (7)	18 (5)	5 (5)
	1-6	-	50 (51)	-	75 (26)	233 (71)	44 (48)
	≥ 7	-	33 (33)	-	193 (67)	77 (23)	42 (46)
Harvested node no.		\	NA	\	NA	\	NA
Resection type[7]	Partial/subtotal gastrectomy	\	NA	\	NA	\	NA
	Total/near-total gastrectomy	\	NA	\	NA	\	NA
	Other	\	NA	\	NA	\	NA
Neoadjuvant CHT[8]	Yes	\	NA	\	27 (8)	\	NA
Neoadjuvant RT[8]	Yes	\	NA	\	7 (2)	\	NA
Total/adjuvant CHT[8]	Yes	522 (29)	58 (26)	408 (25)	120 (37)	254 (32)	36 (30)
Total/adjuvant RT[8]	Yes	140 (8)	10 (5)	114 (7)	34 (11)	19 (2)	5 (4)

[1]Categorical data are shown as count (percentage [%]), and numeric data as mean ± standard deviation. Records are complete otherwise specified below.

[2]The percentages of gastric cardia, fundus/body, and antrum/pylorus cancers are the proportions compared to the total tumor cases of the 3 locations; 'other' includes lesser curvature, greater curvature, and overlapping lesion of stomach and stomach (NOS), and its proportion is relative to the whole cases.

[3]Cystic/mucinous/serous (excluding signet ring cell), squamous cell, ductal/lobular, complex, unspecified, and epithelial (NOS) neoplasms.

[4]Unknown differentiation: **total patients:** the US, 5170 (22%); the Netherlands, 3190 (45%); Belgium, 465 (17%); Sweden, 2614 (94%); Norway, 597 (34%); Slovenia, 712 (43%); Estonia, 209 (26%); **resected patients:** the US, 251 (8%); the Netherlands, 417 (35%); Belgium, 61 (10%); Sweden, 133 (52%); Norway, 45 (20%); Slovenia, 48 (15%); Estonia, 19 (16%).

[5]Unknown tumor local invasion: **total patients:** the US, 9579 (41%); the Netherlands, 3732 (53%); Belgium, 1041 (37%); Sweden, 701 (25%); Norway, 1162 (65%); Slovenia, 825 (50%); Estonia, 243 (30%); **resected patients:** the US, 166 (5%); the Netherlands, 361 (30%); Belgium, 13 (2%); Sweden, 903 (4%); Norway, 107 (48%); Slovenia, 26 (8%); Estonia, 15 (13%). Invasion of serosa and adjacent structures could not be differentiated from each other in Norway or Slovenia.

[6]Unknown positive lymph node: **total patients:** the US, 5599 (24%); the Netherlands, 1673 (24%); Belgium, 951 (34%); Sweden, 682 (25%); Norway, 1263 (71%); Slovenia, 1037 (63%); Estonia, 473 (59%); **resected patients:** the US, 153 (5%); the Netherlands, 154 (13%); Belgium, 22 (4%); Sweden, 3 (1%); Norway, 123 (55%); Slovenia, 36 (11%); Estonia, 28 (24%).

[7]Gastrectomy (NOS) or local resection. Available in Sweden since 2010.

[8]Non-surgical therapies in the US and Estonia had low sensitivity, and the counterpart category of "Yes" was "No/unknown". In Norway and Estonia, neoadjuvant and adjuvant therapies could not be distinguished from each other. Total CHT/RT is for total patients, and (neo)adjuvant CHT/RT for resected patients.

CHT, chemotherapy; RT, radiotherapy; NOS, not otherwise specified; \, resection-specific variables not applicable for total patients; -, not shown due to > 60% missing values; NA, not available.

3.2.1.1 Non-metastatic gastric cancer patients

Among overall patients with non-metastatic disease, most were males (55%-66%), and the mean ages were 68-72 years, with patients ≥70 years comprising the majority (51%-62%). Gastric cardia was the most common cancer site across countries (37%-55%), except in Slovenia (27%) and Estonia (12%). Most tumors were adenocarcinomas followed by SRCs. Except Slovenia with a particularly low proportion of reported SRCs (3%) and Estonia with a particularly high proportion of SRCs (28%), the proportions of non-SRC adenocarcinomas were 75%-85% in the other countries. Most cancers were poorly-/undifferentiated (57%-68%). Approximately half of the cancers invaded muscularis propria/subserosa (39%-56%), and did not involve lymph nodes (44%-73%). Only 4%-12% of cancers invaded adjacent structures. Over the studied period, resection rates were 56% (Sweden) to 79% (Belgium and Slovenia). In the investigated countries except the US and Estonia where non-surgical therapies had low sensitivity, chemotherapy was administered to 19% (Norway) to 39% (Belgium) of the patients, and radiotherapy was less often applied (6% (Norway) to 24% (Slovenia)).

Resected patients were younger (mean ages, 67-70 years), with smaller proportions of patients ≥70 years (47%-56%). Cardia cancers comprised smaller proportions (11%-54%), and smaller proportions of cancers invaded adjacent structures (3%-10%) or spared lymph nodes (40%-66%). On average, 15-18 lymph nodes were harvested. Partial/subtotal gastrectomy was the most common resection type (62%-69%), and proportions of positive resection margin were 15% in the Netherlands and Sweden and 7% in Slovenia. In countries with available information of high sensitivity, neoadjuvant chemotherapy was administered for 6% (Slovenia) to 35% of the patients (the Netherlands), while neoadjuvant radiotherapy was rarely administered (3% (the Netherlands and Slovenia) to 8% (Sweden)); adjuvant chemotherapy was used for 19%-32% of patients, while adjuvant radiotherapy was less frequently administered (3%-26%).

3.2.1.2 Metastatic gastric cancer patients

Compared to those with non-metastatic disease, patients with metastatic cancers were younger (mean age, 65-70 years) with smaller proportions of patients ≥70 years (41%-55%). Metastatic cancers were more frequently located in the cardia (37%-60%; Estonia, 14%) and poorly-/undifferentiated (66%-77%). They more often invaded adjacent structures (12%-39%) and less often spared lymph nodes (5%-24%; the US, 44%). Notably, 9% (Sweden) to 21% (Belgium) of metastatic cancers were resected. In countries with available non-surgical treatment data of high sensitivity, chemotherapy was administered to 25% (Slovenia) to 62% (Belgium) of patients, and radiotherapy was less often applied (7%-10%).

Resected metastatic cancer patients were less often males compared to overall patients with metastatic diseases (55%-64% *vs.* 59%-68%), and were 1-3 years younger on average. Resected

metastatic cancers were much less frequently located in the cardia (6%-54%), and less often invaded adjacent structures (11%-26%). On average, 9-19 lymph nodes were harvested. In countries with high-quality non-surgical therapy information, neoadjuvant chemotherapy was administered for 8% (Slovenia) to 29% of patients (Belgium), while neoadjuvant radiotherapy was rarely administered (1%-5%); adjuvant chemotherapy was used for 26% (Norway) to 48% of patients (Belgium), while adjuvant radiotherapy was much less frequently administered (5%-11%).

3.2.2 Resection trends for gastric cancer

For non-metastatic cancer, age-standardized resection rates decreased over time in all countries (**Figure 26**). The largest average decreases were observed in Norway (2003-2004 to 2013-2014: 78% to 54%; P_{trend}<0.001) and Sweden (2005-2006 to 2013-2014: 69% to 54%; P_{trend}<0.001). Moderate decreases were observed in the US (2003-2004 to 2013-2014: 72% to 60%; P_{trend}<0.001) and Estonia (2009-2010 to 2013-2014: 80% to 74%; P_{trend}=0.020). Netherlands (2005-2006 to 2013-2014: 72% to 68%; P_{trend}=0.005), Belgium (2003-2004 to 2013-2014: 80% to 75%; P_{trend}<0.001), and Slovenia (2003-2004 to 2013-2014: 77% to 70%; P_{trend}=0.002) showed the slightest decreases. When limiting the cancers to those without adjacent structure invasion and those invading beyond submucosa and/or with positive lymph nodes, the decreasing trends remained in all countries (data not shown).

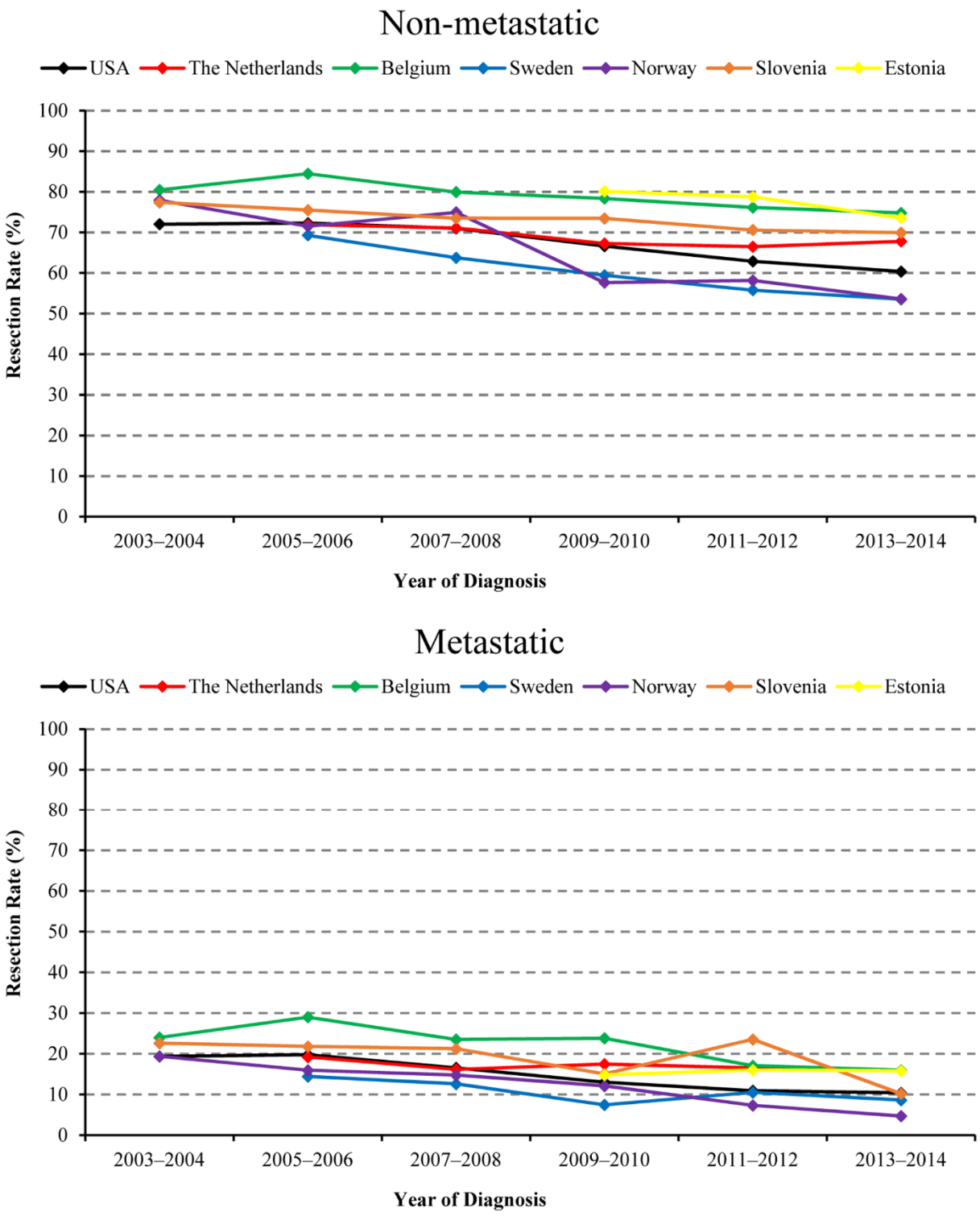

Figure 26. Age-standardized resection rates for non-metastatic and metastatic gastric cancers. In the US and Norway, the decreasing trends started from as early as the 1980s and the 1960s, respectively (data not shown).

For metastatic cancers (**Figure 26**), significant decreasing trends were observed in all countries except the Netherlands (P_{trend}=0.132), Slovenia (P_{trend}=0.139), and Estonia (P_{trend}=0.329). The strongest decrease was observed in Norway (2003-2004 to 2013-2014: 19% to 5%; P_{trend}<0.001), and the slightest decrease in Sweden (2005-2006 to 2013-2014: 14% to 9%; P_{trend}=0.004). In the US

(2003-2004 to 2013-2014: 19% to 10%; P_{trend}<0.001) and Belgium (2003-2004 to 2013-2014: 24% to 16%; P_{trend}=0.001), moderate decreases were observed.

Subgroup analyses according to age group and tumor location were further conducted for non-metastatic cancers (**Figure 27**). Resection rates were higher in younger patients, and the decreasing trends were weaker or disappeared in patients <70 years compared to those ≥70 years in the Netherlands (2005-2006 to 2013-2014: 83% to 83%, P_{trend}=0.915 *vs.* 63% to 54%, P_{trend}<0.001), Sweden (2005-2006 to 2013-2014: 80% to 66%, P_{trend}=0.011 *vs.* 60% to 43%, P_{trend}<0.001), and Slovenia (2003-2004 to 2013-2014: 84% to 84%, P_{trend}=0.807 *vs.* 71% to 58%, P_{trend}=0.002). The decreasing trends were stronger in patients <70 years in Norway (2003-2004 to 2013-2014: 90% to 60%, P_{trend}<0.001 *vs.* 68% to 48%, P_{trend}=0.001) and Estonia (2009-2010 to 2013-2014: 89% to 80%, P_{trend}=0.011 *vs.* 72% to 68%, P_{trend}=0.149). The magnitudes of decrease were similar in both age groups in Belgium (2003-2004 to 2013-2014: 86% to 80%, P_{trend}=0.010 *vs.* 75% to 70%, P_{trend}<0.001).

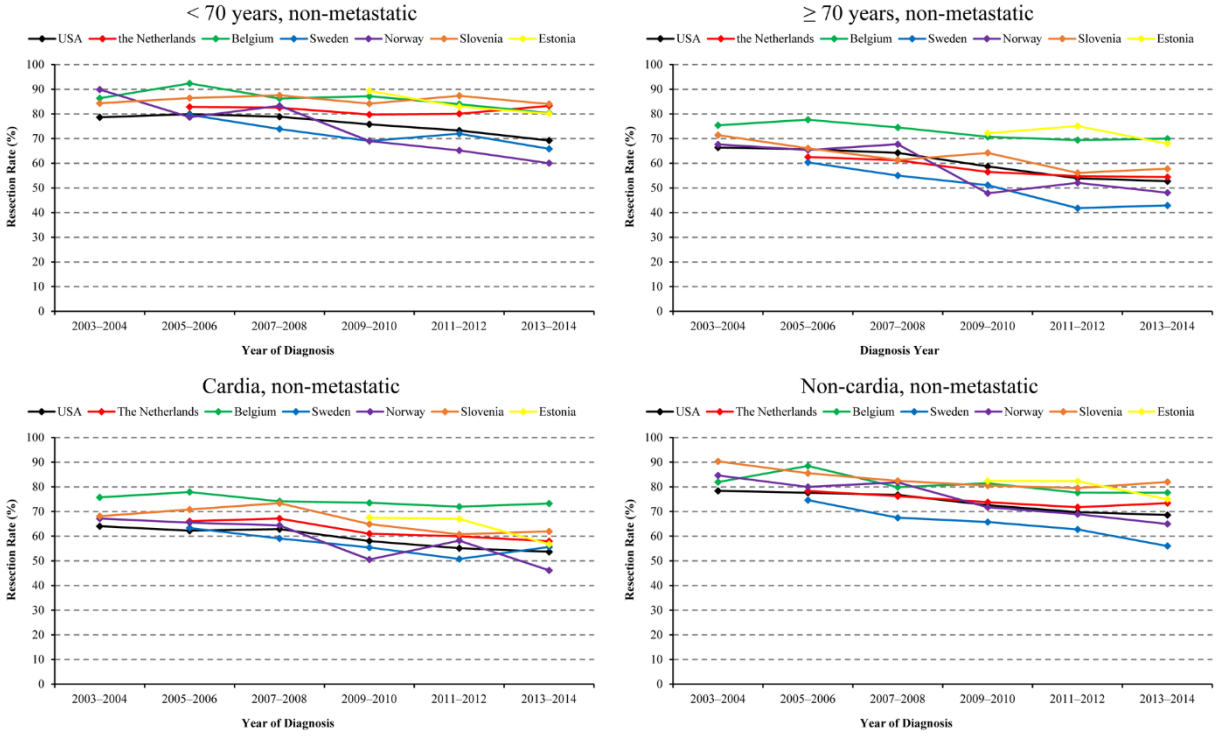

Figure 27. Age-standardized resection rates for non-metastatic gastric cancer by age and tumor location

Resection rates for cardia cancers were lower than those for non-cardia tumors. The magnitude of decrease was weaker in cardia cancers than non-cardia ones in Sweden (2005-2006 to 2013-2014: 63% to 56%, P_{trend}=0.008 *vs.* 75% to 56%, P_{trend}<0.001). The trends were only significant in non-cardia cancers in Belgium (2003-2004 to 2013-2014: 82% to 78%; P_{trend}=0.016), Slovenia (2003-2004 to 2013-2014: 90% to 82%; P_{trend}=0.006), and Estonia (2009-2010 to 2013-2014: 82% to 75%; P_{trend}=0.035). Similar decreasing trends in cardia and non-cardia cancers were observed in the US (2003-2004 to 2013-2014: 64% to 54%, P_{trend}<0.001 *vs.* 78% to 69%, P_{trend}<0.001), the Netherlands

(2005-2006 to 2013-2014: 66% to 58%, P_{trend}<0.001 *vs.* 78% to 73%, P_{trend}=0.016), and Norway (2003-2004 to 2013-2014: 67% to 46%, P_{trend}=0.001 *vs.* 85% to 65%, P_{trend}<0.001).

3.2.3 Recent resection rates for gastric cancer by age group and tumor location

The patients were limited to those diagnosed in 2010 or later, a recent period when all countries had data, to calculate the resection rates according to age group and tumor location (**Figure 28**). For non-metastatic cancers, resection rates decreased with increasing ages in all countries. The rates were markedly lower in patients ≥80 years (27% (Sweden) to 66% (Estonia)) compared to the other age groups (<60 years: 65% (Norway) to 88% (Slovenia); 60-69 years: 63% (Norway) to 87% (Slovenia); 70-79 years: 55% (Sweden) to 79% (Belgium)), with large variations across countries. In most countries, resection rates were lower for cardia cancers (49% (Sweden) to 74% (Belgium)) than for fundus/body (54% (Sweden) to 88% (Slovenia)) or pylorus/antrum cancers (58% (Sweden) to 81% (Slovenia)).

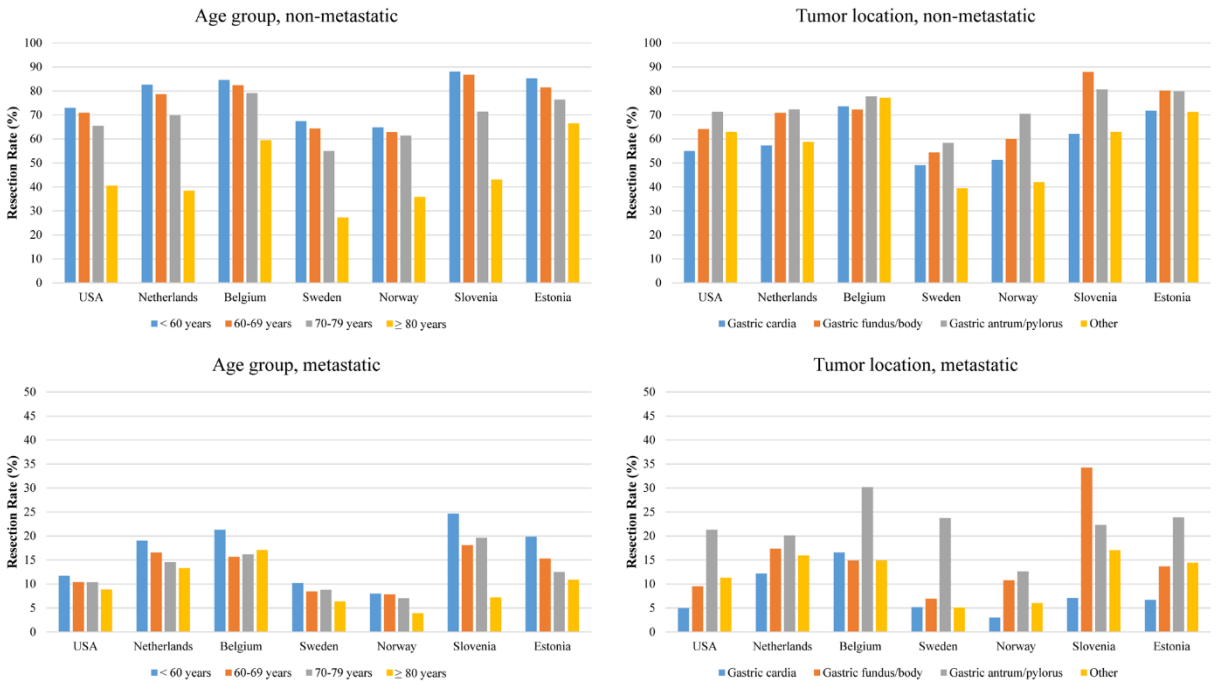

Figure 28. Resection rates for non-metastatic and metastatic gastric cancers by age group and tumor location in 2010 or later

For metastatic cancers, while the resection rates were markedly lower, the stratified patterns were similar to those for non-metastatic tumors, but with more fluctuations. In most countries, resection rates were markedly lower in patients ≥80 years (4% (Norway) to 17% (Belgium)) than in others (<60 years: 8% (Norway) to 25% (Slovenia); 60-69 years: 8% (Sweden and Norway) to 18% (Slovenia); 70-79 years: 7% (Norway) to 20% (Slovenia)). Also, resection rates were mostly lower in cardia cancers (3% (Norway) to 17% (Belgium)) than in fundus/body (7% (Sweden) to 34% (Slovenia)) or

pylorus/antrum cancers (13% (Norway) to 30% (Belgium)).

3.2.4 Factors associated with resection

Variables associated with resection were further investigated in each country using multivariable-adjusted models (**Table 60**), which further supported the decreasing resection rates in both non-metastatic (odds ratio per year (OR)=0.86-0.96 across countries) and metastatic cancers (OR=0.88-0.98, except Slovenia and Estonia).

Table 60. Association of demographic and clinical parameters with resection for gastric cancer without and with distant metastasis using multivariable logistic regression

Variable	Category	the US	The Netherlands	Belgium	Sweden
		OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]
Without metastasis					
Year of diagnosis	Per 1 year	**0.94** (0.93-0.94)	**0.96** (0.94-0.97)	**0.94** (0.92-0.97)	**0.91** (0.89-0.93)
Sex	Female *vs.* male	0.96 (0.92-1.01)	**0.85** (0.77-0.94)	**0.87** (0.76-0.99)	0.94 (0.83-1.08)
Age group	60-69 years	**0.93** (0.87-1.00)	**0.75** (0.64-0.89)	0.88 (0.70-1.10)	0.92 (0.74-1.14)
< 60 years as reference	70-79 years	**0.68** (0.64-0.73)	**0.44** (0.38-0.51)	**0.62** (0.50-0.75)	**0.60** (0.49-0.73)
	≥ 80 years	**0.24** (0.23-0.26)	**0.13** (0.11-0.15)	**0.23** (0.19-0.28)	**0.18** (0.15-0.23)
Tumor location	Gastric fundus/body	**1.77** (1.64-1.91)	**2.08** (1.79-2.41)	**1.39** (1.09-1.78)	**1.62** (1.36-1.94)
Gastric cardia as reference	Gastric antrum/pylorus	**2.79** (2.62-2.98)	**2.77** (2.43-3.14)	**2.05** (1.69-2.48)	**2.03** (1.70-2.41)
	Other[2]	**1.78** (1.68-1.89)	**1.29** (1.14-1.46)	**1.73** (1.49-2.01)	0.87 (0.72-1.04)
Tumor histology	SRC *vs.* non-SRC	**0.80** (0.76-0.85)	0.99 (0.88-1.12)	1.03 (0.86-1.24)	-
Adjacent structure invasion	Yes *vs.* no	**0.28** (0.26-0.31)	**0.09** (0.08-0.11)	**0.22** (0.17-0.29)	**0.24** (0.19-0.31)
With metastasis					
Year of diagnosis	Per 1 year	**0.91** (0.90-0.92)	**0.98** (0.96-1.00)	**0.93** (0.90-0.96)	**0.95** (0.91-0.99)
Sex	Female *vs.* male	1.07 (0.99-1.16)	1.06 (0.93-1.21)	1.15 (0.94-1.41)	1.16 (0.88-1.52)
Age group	60-69 years	0.97 (0.88-1.07)	0.97 (0.80-1.15)	**0.68** (0.53-0.89)	0.84 (0.58-1.24)
< 60 years as reference	70-79 years	**0.89** (0.81-0.99)	0.90 (0.76-1.07)	**0.70** (0.55-0.90)	0.73 (0.50-1.06)
	≥ 80 years	**0.73** (0.65-0.83)	**0.74** (0.60-0.91)	**0.59** (0.44-0.78)	**0.44** (0.28-0.68)
Tumor location	Gastric fundus/body	**1.75** (1.52-2.02)	**1.49** (1.21-1.82)	0.93 (0.65-1.32)	**1.55** (1.04-2.31)
Gastric cardia as reference	Gastric antrum/pylorus	**4.09** (3.64-4.60)	**2.26** (1.88-2.71)	**1.93** (1.43-2.62)	**4.41** (3.05-6.37)
	Other[2]	**2.12** (1.90-2.36)	**1.38** (1.16-1.63)	1.01 (0.80-1.26)	0.93 (0.61-1.40)
Tumor histology	SRC *vs.* non-SRC	**1.11** (1.02-1.22)	**1.18** (1.00-1.38)	**1.51** (1.18-1.93)	-
Adjacent structure invasion	Yes *vs.* no	**0.56** (0.51-0.61)	**0.39** (0.31-0.48)	0.80 (0.60-1.07)	**0.28** (0.20-0.39)

[1]Odds ratios and 95% confidence intervals for resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and histology. For the association with adjacent structure invasion, this factor was additionally added into the main model. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. ORs shown in bold are statistically significant.

[2]Lesser curvature, greater curvature, and overlapping lesion of stomach, and stomach (not otherwise specified).

OR, odds ratio; CI, confidence interval; SRC, signet ring cell carcinoma; -, not available.

Table 60. Association of demographic and clinical parameters with resection for gastric cancer without and with distant metastasis using multivariable logistic regression (continued)

Variable	Category	Norway	Slovenia	Estonia
		OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]
Without metastasis				
Year of diagnosis	Per 1 year	**0.89** (0.87-0.91)	**0.95** (0.93-0.98)	**0.86** (0.78-0.94)
Sex	Female *vs.* male	**0.84** (0.71-0.99)	1.04 (0.85-1.26)	1.22 (0.89-1.68)
Age group	60-69 years	0.99 (0.76-1.28)	**0.67** (0.48-0.93)	0.65 (0.39-1.07)
< 60 years as reference	70-79 years	**0.70** (0.55-0.89)	**0.42** (0.32-0.56)	**0.50** (0.31-0.81)
	≥ 80 years	**0.25** (0.19-0.32)	**0.11** (0.08-0.15)	**0.25** (0.15-0.43)
Tumor location	Gastric fundus/body	**1.90** (1.48-2.44)	**5.14** (3.50-7.55)	**1.70** (1.00-2.88)
Gastric cardia as reference	Gastric antrum/pylorus	**3.84** (3.05-4.84)	**3.25** (2.41-4.38)	**1.79** (1.03-3.12)
	Other[2]	1.17 (0.96-1.42)	1.14 (0.89-1.46)	1.01 (0.58-1.76)
Tumor histology	SRC *vs.* non-SRC	**0.74** (0.56-0.97)	**0.43** (0.25-0.72)	0.73 (0.51-1.04)
Adjacent structure invasion	Yes *vs.* no	**0.45** (0.33-0.62)	**0.09** (0.06-0.13)	**0.25** (0.13-0.51)
With metastasis				
Year of diagnosis	Per 1 year	**0.88** (0.84-0.92)	0.97 (0.93-1.01)	1.04 (0.93-1.17)
Sex	Female *vs.* male	1.21 (0.90-1.63)	1.19 (0.92-1.55)	1.16 (0.77-1.74)
Age group	60-69 years	0.70 (0.46-1.07)	0.78 (0.57-1.08)	0.75 (0.44-1.28)
< 60 years as reference	70-79 years	0.70 (0.47-1.04)	**0.58** (0.42-0.79)	0.65 (0.39-1.10)
	≥ 80 years	**0.57** (0.37-0.87)	**0.25** (0.15-0.42)	**0.45** (0.23-0.89)
Tumor location	Gastric fundus/body	**2.38** (1.41-4.00)	**3.48** (2.09-5.81)	2.20 (0.83-5.83)
Gastric cardia as reference	Gastric antrum/pylorus	**4.65** (2.89-7.49)	**3.16** (1.94-5.16)	**4.75** (1.74-12.97)
	Other[2]	**1.78** (1.14-2.77)	**1.59** (1.04-2.43)	2.15 (0.81-5.70)
Tumor histology	SRC *vs.* non-SRC	1.01 (0.64-1.59)	0.75 (0.44-1.28)	0.86 (0.55-1.34)
Adjacent structure invasion	Yes *vs.* no	-	**0.25** (0.17-0.37)	0.76 (0.38-1.55)

[1]Odds ratios and 95% confidence intervals for resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and histology. For the association with adjacent structure invasion, this factor was additionally added into the main model. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. ORs shown in bold are statistically significant.

[2]Lesser curvature, greater curvature, and overlapping lesion of stomach, and stomach (not otherwise specified).

OR, odds ratio; CI, confidence interval; SRC, signet ring cell carcinoma; -, not available.

For non-metastatic cancers, while resection was less frequently conducted in females in the Netherlands (OR=0.85), Belgium (OR=0.87), and Norway (OR=0.84), it was less often done with older age and for cardia cancer in all countries. Specifically, compared to patients <60 years, ORs for resection in patients aged 70-79 and ≥80 years were 0.42-0.70 and 0.11-0.25, respectively. Compared to cardia cancers, ORs for resection of fundus/body and antrum/pylorus cancers were 1.39-5.14 and 1.79-3.84, respectively. Resection was less often conducted for SRCs in the US (OR=0.80), Norway (OR=0.74), and Slovenia (OR=0.43). Adjacent structure invasion was associated with less frequent resection in all countries with available information (OR=0.09-0.45).

In metastatic GC, no significant associations of resection with sex were observed, and resection was more often performed for SRCs in the US (OR=1.11), the Netherlands (OR=1.18), and Belgium

(OR=1.51). For the other variables, compared to non-metastatic cancers, while the association patterns were similar, the strengths differed. Older age (versus <60 years, $OR_{70\text{-}79\ years}$=0.58-0.90; $OR_{\geq 80\ years}$=0.25-0.74) and adjacent structure invasion (OR=0.25-0.80) were less strongly associated, but pylorus/antrum cancers were more strongly associated with more frequent resection (versus cardia cancers, OR=1.93-5.77) in most countries.

Associations of resection with further variables available in certain countries for non-metastatic cancers are shown in **Table 61**. Management in academic hospitals was associated with more frequent resection in the Netherlands (OR=2.59), Belgium (OR=1.49), and Sweden (OR=1.43). In the Netherlands and Sweden, a smaller hospital volume was associated with less frequent resection ($OR_{<10\ vs.\ \geq 20\ resections/year}$=0.48 and 0.64, respectively). In the US, resection was more frequently performed for smaller tumors (*e.g.*, $OR_{<2\ vs.\ \geq 4\ cm}$=1.80). With higher ECOG (*e.g.*, ≥3 *vs.* 0-1, $OR_{Belgium}$=0.15; OR_{Sweden}=0.06) and ASA scores (*e.g.*, ≥4 *vs.* 1-2, OR_{Sweden}=0.13), resection was much less often performed. Cardiac disease ($OR_{Eindhoven}$=0.73), vascular disease ($OR_{Eindhoven}$=0.65), diabetes ($OR_{Eindhoven}$=0.77), and pulmonary disease ($OR_{Eindhoven}$=0.73, $OR_{Belgium}$=0.73) were significantly associated with less frequent resection. More than 2 comorbidities were associated with 39% reduced resection odds in Eindhoven. The decreasing resection trends over time remained after incorporating these factors (data not shown).

Table 61. Association of hospital type, volume, tumor size, performance status, and comorbidities with resection in non-metastatic gastric cancer in registries with available information using multivariable logistic regression

Variable	Category	the US		The Netherlands	
		n	OR (95% CI)[1]	n	OR (95% CI)
Hospital type	Non-academic	-	-	7857	1.00 (reference)
	Academic	-	-	1875	**2.59** (2.25-2.98)
Hospital volume	< 10	-	-	1232	**0.48** (0.39-0.60)
(resections/year)	10-20	-	-	1374	**0.51** (0.42-0.63)
	≥ 20	-	-	1000	1.00 (reference)
Tumor size (cm)	< 2	1694	**1.80** (1.63-1.99)	-	-
	2-4	2747	**1.26** (1.17-1.36)	-	-
	≥ 4	5056	1.00 (reference)	-	-
Comorbidity	Cardiac disease	-	-	615/1437	**0.73** (0.59-0.91)
	Vascular disease	-	-	349/1703	**0.65** (0.50-0.84)
	Hypertension	-	-	588/1464	0.99 (0.79-1.23)
	Diabetes	-	-	336/1716	**0.77** (0.59-1.00)
	Pulmonary disease	-	-	255/1797	**0.73** (0.55-0.98)
Comorbidity no.	0	-	-	609	1.00 (reference)
	1	-	-	548	0.87 (0.65-1.16)
	≥ 2	-	-	895	**0.61** (0.47-0.80)

[1]Odds ratios and 95% confidence intervals for associations of hospital type, tumor size, ECOG score, and comorbidity with resection versus non-resection were calculated by adding these variables one by one into the main multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and histology. The reference categories for each comorbidity were those without the corresponding comorbidity. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. Statistically significant odds ratios are shown in bold. Numbers for comorbidities were shown for with/without the respective comorbidity.

OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists; -, not available.

Table 61. Association of hospital type, volume, tumor size, performance status, and comorbidities with resection in non-metastatic gastric cancer in registries with available information using multivariable logistic regression (continued)

Variable	Category	Belgium		Sweden	
		n	HR (95% CI)	n	HR (95% CI)
Hospital type	Non-academic	3906	1.00 (reference)	2515	1.00 (reference)
	Academic	2510	**1.49** (1.30-1.70)	1971	**1.43** (1.25-1.64)
Hospital volume	< 10	-	-	872	**0.64** (0.51-0.80)
(resections/year)	10-20	-	-	931	0.88 (0.71-1.09)
	≥ 20	-	-	1373	1.00 (reference)
ECOG score	0-1	4285	1.00 (reference)	3194	1.00 (reference)
	2	510	**0.52** (0.42-0.64)	763	**0.27** (0.22-0.32)
	≥ 3	159	**0.15** (0.11-0.22)	287	**0.06** (0.04-0.09)
ASA score	1-2	-	-	2949	1.00 (reference)
	3	-	-	1166	**0.46** (0.39-0.53)
	≥ 4	-	-	236	**0.13** (0.09-0.19)
Comorbidity	Cardiac disease	3405/3063	0.90 (0.79-1.03)	-	-
	Diabetes	980/5488	0.87 (0.73-1.02)	-	-
	Pulmonary disease	370/6098	**0.73** (0.57-0.93)	-	-

[1]Odds ratios and 95% confidence intervals for associations of hospital type, tumor size, ECOG score, and comorbidity with resection versus non-resection were calculated by adding these variables one by one into the main multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and histology. The reference categories for each comorbidity were those without the corresponding comorbidity. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. Statistically significant odds ratios are shown in bold. Numbers for comorbidities were shown for with/without the respective comorbidity.

OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists; -, not available.

Subgroup analyses were performed for non-metastatic cancers according to age (**Table 62**) and tumor location (**Table 63**). While association patterns were mostly similar between subgroups, in all countries except Slovenia and Estonia, associations of resection with tumor location were stronger in patients ≥70 years than those <70 years, and associations with age were stronger in cardia than non-cardia cancers. In the Netherlands and Slovenia, the association of year of diagnosis with resection became insignificant in patients <70 years after multivariable adjustment. In SRCs and in cancers invading adjacent structures, association patterns and strengths were mostly similar with those for total non-metastatic cancers (data not shown).

Table 62. Association of demographic and clinical characteristics with resection in non-metastatic gastric cancer patients aged < and ≥ 70 years using multivariable logistic regression

Variable	Category	the US	The Netherlands	Belgium	Sweden
		OR (95% CI)[1]	OR (95% CI)	OR (95% CI)	OR (95% CI)
< 70 years					
Resected/total no.		13162/17537	3238/3979	2301/2664	1226/1757
Year of diagnosis	Per 1 year	**0.95** (0.94-0.96)	0.99 (0.96-1.02)	**0.92** (0.88-0.95)	**0.92** (0.89-0.95)
Sex	Female *vs.* male	**1.09** (1.01-1.18)	0.89 (0.74-1.06)	1.07 (0.83-1.39)	1.07 (0.85-1.33)
Age group	60-69 *vs.* < 60 years	0.94 (0.88-1.01)	**0.75** (0.64-0.89)	0.92 (0.74-1.16)	0.92 (0.75-1.14)
Tumor location	Gastric fundus/body	**1.41** (1.25-1.58)	**1.75** (1.35-2.27)	1.16 (0.72-1.88)	1.22 (0.92-1.62)
Gastric cardia as reference	Gastric antrum/pylorus	**2.25** (2.03-2.49)	**2.19** (1.74-2.76)	**1.46** (1.01-2.10)	**1.41** (1.07-1.87)
	Other[2]	**1.43** (1.31-1.56)	0.92 (0.75-1.13)	1.16 (0.90-1.51)	0.85 (0.63-1.14)
Tumor histology	SRC *vs.* non-SRC	**0.86** (0.79-0.94)	0.99 (0.81-1.21)	1.38 (1.00-1.90)	-
Adjacent structure invasion	Yes *vs.* no	**0.26** (0.23-0.29)	**0.08** (0.06-0.10)	**0.18** (0.11-0.28)	**0.29** (0.21-0.42)
≥ 70 years					
Resected/total no.		11908/20292	3367/5766	2795/3804	1275/2729
Year of diagnosis	Per 1 year	**0.93** (0.92-0.94)	**0.94** (0.92-0.96)	**0.96** (0.93-0.98)	**0.90** (0.87-0.93)
Sex	Female *vs.* male	**0.90** (0.85-0.96)	**0.84** (0.74-0.94)	**0.81** (0.69-0.95)	0.88 (0.74-1.04)
Age group	≥ 80 *vs.* 70-79 years	**0.35** (0.33-0.37)	**0.30** (0.26-0.33)	**0.36** (0.31-0.42)	**0.30** (0.25-0.35)
Tumor location	Gastric fundus/body	**2.10** (1.91-2.33)	**2.37** (1.97-2.84)	**1.54** (1.15-2.05)	**1.98** (1.57-2.50)
Gastric cardia as reference	Gastric antrum/pylorus	**3.30** (3.04-3.58)	**3.21** (2.74-3.76)	**2.40** (1.91-3.01)	**2.54** (2.03-3.18)
	Other[2]	**2.13** (1.97-2.30)	**1.58** (1.36-1.85)	**2.09** (1.74-2.51)	0.92 (0.72-1.17)
Tumor histology	SRC *vs.* non-SRC	**0.77** (0.71-0.84)	1.01 (0.87-1.18)	0.89 (0.70-1.12)	-
Adjacent structure invasion	Yes *vs.* no	**0.31** (0.28-0.35)	**0.10** (0.08-0.13)	**0.25** (0.18-0.35)	**0.21** (0.15-0.29)

[1]Odds ratios and 95% confidence intervals for resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and histology. For association with adjacent structure invasion, this factor was additionally added into the main model. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. ORs shown in bold are statistically significant.

[2]Lesser curvature, greater curvature, and overlapping lesion of stomach and stomach (not otherwise specified).

OR, odds ratio; CI, confidence interval; SRC, signet ring cell carcinoma; -, not available.

Table 62. Association of demographic and clinical characteristics with resection in non-metastatic gastric cancer patients aged < and ≥ 70 years using multivariable logistic regression (continued)

Variable	Category	Norway	Slovenia	Estonia
		OR (95% CI)	OR (95% CI)	OR (95% CI)
< 70 years				
Resected/total no.		909/1245	1120/1304	416/496
Year of diagnosis	Per 1 year	**0.85** (0.81-0.88)	1.00 (0.95-1.05)	**0.81** (0.70-0.94)
Sex	Female *vs.* male	0.86 (0.65-1.15)	0.99 (0.69-1.41)	1.11 (0.66-1.85)
Age group	60-69 *vs.* < 60 years	0.99 (0.76-1.30)	0.69 (0.50-0.95)	0.68 (0.41-1.13)
Tumor location	Gastric fundus/body	1.43 (0.95-2.14)	**6.85** (3.38-13.88)	1.80 (0.81-3.99)
Gastric cardia as reference	Gastric antrum/pylorus	**2.57** (1.72-3.86)	**3.39** (2.07-5.55)	1.72 (0.73-4.04)
	Other[2]	0.73 (0.53-1.01)	1.38 (0.94-2.02)	0.92 (0.40-2.14)
Tumor histology	SRC *vs.* non-SRC	0.85 (0.54-1.33)	**0.32** (0.17-0.63)	1.02 (0.60-1.72)
Adjacent structure invasion	Yes *vs.* no	**0.39** (0.23-0.67)	**0.08** (0.05-0.13)	**0.26** (0.10-0.71)
≥ 70 years				
Resected/total no.		1148/2013	1052/1589	391/532
Year of diagnosis	Per 1 year	**0.90** (0.88-0.93)	**0.93** (0.90-0.96)	0.90 (0.80-1.01)
Sex	Female *vs.* male	0.82 (0.68-1.00)	1.06 (0.83-1.34)	1.30 (0.86-1.95)
Age group	≥ 80 *vs.* 70-79 years	**0.34** (0.28-0.42)	**0.27** (0.21-0.34)	**0.48** (0.32-0.72)
Tumor location	Gastric fundus/body	**2.40** (1.74-3.31)	**4.37** (2.73-7.01)	1.69 (0.83-3.43)
Gastric cardia as reference	Gastric antrum/pylorus	**5.00** (3.74-6.67)	**3.01** (2.05-4.40)	1.85 (0.89-3.86)
	Other[2]	**1.57** (1.22-2.04)	0.99 (0.71-1.38)	1.07 (0.51-2.28)
Tumor histology	SRC *vs.* non-SRC	0.70 (0.49-1.02)	0.64 (0.27-1.52)	**0.53** (0.32-0.86)
Adjacent structure invasion	Yes *vs.* no	**0.48** (0.32-0.70)	**0.10** (0.06-0.16)	**0.22** (0.08-0.59)

[1]Odds ratios and 95% confidence intervals for resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and histology. For association with adjacent structure invasion, this factor was additionally added into the main model. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. ORs shown in bold are statistically significant.

[2]Lesser curvature, greater curvature, and overlapping lesion of stomach and stomach (not otherwise specified).

OR, odds ratio; CI, confidence interval; SRC, signet ring cell carcinoma; -, not available.

Table 63. Association of demographic and clinical characteristics with resection in non-metastatic gastric cancer located in cardia and non-cardia using multivariable logistic regression

Variable	Category	the US	The Netherlands	Belgium	Sweden
		OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]
Cardia					
Resected/total no.		7387/12731	1622/2630	1520/2024	737/1387
Year of diagnosis	Per 1 year	**0.95** (0.94-0.96)	**0.94** (0.91-0.97)	0.97 (0.93-1.01)	**0.93** (0.89-0.96)
Sex	Female *vs.* male	0.93 (0.85-1.02)	0.96 (0.78-1.17)	0.90 (0.70-1.17)	0.87 (0.66-1.14)
Age group	60-69 years	**0.82** (0.74-0.91)	**0.65** (0.49-0.85)	0.89 (0.64-1.24)	0.90 (0.64-1.25)
< 60 years as reference	70-79 years	**0.55** (0.50-0.61)	**0.33** (0.25-0.43)	**0.52** (0.38-0.70)	**0.54** (0.39-0.74)
	≥ 80 years	**0.17** (0.15-0.19)	**0.07** (0.06-0.10)	**0.18** (0.13-0.25)	**0.10** (0.07-0.15)
Tumor histology	SRC *vs.* non-SRC	**0.75** (0.67-0.85)	0.80 (0.62-1.03)	0.99 (0.68-1.45)	-
Adjacent structure invasion	Yes *vs.* no	**0.29** (0.24-0.34)	**0.09** (0.06-0.14)	**0.44** (0.23-0.85)	**0.26** (0.16-0.41)
Non-cardia					
Resected/total no.		10200/14039	3368/4533	1307/1635	1373/2215
Year of diagnosis	Per 1 year	**0.93** (0.92-0.94)	**0.97** (0.94-0.99)	**0.91** (0.87-0.96)	**0.89** (0.86-0.92)
Sex	Female *vs.* male	0.98 (0.91-1.06)	**0.83** (0.72-0.96)	**0.73** (0.56-0.94)	0.99 (0.82-1.19)
Age group	60-69 years	0.99 (0.87-1.13)	0.88 (0.66-1.18)	0.73 (0.43-1.24)	1.00 (0.72-1.38)
< 60 years as reference	70-79 years	**0.79** (0.70-0.89)	**0.53** (0.41-0.68)	**0.59** (0.37-0.94)	0.80 (0.59-1.07)
	≥ 80 years	**0.28** (0.25-0.31)	**0.15** (0.11-0.19)	**0.23** (0.15-0.37)	**0.26** (0.19-0.35)
Tumor location	Fundus/body *vs.* antrum/pylorus	**0.64** (0.59-0.69)	**0.74** (0.64-0.86)	**0.68** (0.52-0.89)	**0.81** (0.67-0.97)
Tumor histology	SRC *vs.* non-SRC	**0.76** (0.69-0.84)	1.04 (0.87-1.24)	1.18 (0.83-1.67)	-
Adjacent structure invasion	Yes *vs.* no	**0.27** (0.23-0.30)	**0.07** (0.06-0.09)	**0.26** (0.15-0.45)	**0.27** (0.19-0.37)

[1]Odds ratios and 95% confidence intervals for resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and histology. For associations with tumor adjacent structure invasion, this factor was additionally added into the main model. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. Results were not shown for countries with <50 resected and/or <100 total cases (resected/total no.: cardia: Estonia, 70/96). ORs shown in bold are statistically significant.

OR, odds ratio; CI, confidence interval; SRC, signet ring cell carcinoma; -, not available; \, not shown due to small case number.

Table 63. Association of demographic and clinical characteristics with resection in non-metastatic gastric cancer located in cardia and non-cardia using multivariable logistic regression (continued)

Variable	Category	Norway	Slovenia	Estonia
		OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]
Cardia				
Resected/total no.		480/857	314/461	70/96
Year of diagnosis	Per 1 year	**0.91** (0.87-0.95)	0.94 (0.88-1.01)	\
Sex	Female *vs.* male	0.84 (0.60-1.18)	0.95 (0.58-1.56)	\
Age group	60-69 years	0.98 (0.64-1.49)	1.24 (0.68-2.27)	\
< 60 years as reference	70-79 years	**0.47** (0.31-0.71)	0.72 (0.42-1.25)	\
	≥ 80 years	**0.17** (0.11-0.27)	**0.18** (0.09-0.36)	\
Tumor histology	SRC *vs.* non-SRC	**0.53** (0.30-0.95)	0.38 (0.11-1.29)	\
Adjacent structure invasion	Yes *vs.* no	**0.37** (0.21-0.65)	**0.06** (0.02-0.14)	\
Non-cardia				
Resected/total no.		1000/1351	1068/1238	579/714
Year of diagnosis	Per 1 year	**0.89** (0.86-0.92)	**0.92** (0.87-0.97)	**0.83** (0.74-0.93)
Sex	Female *vs.* male	0.80 (0.61-1.03)	1.00 (0.70-1.42)	1.40 (0.94-2.08)
Age group	60-69 years	0.85 (0.52-1.39)	**0.47** (0.23-0.93)	**0.36** (0.18-0.72)
< 60 years as reference	70-79 years	0.82 (0.52-1.30)	**0.35** (0.19-0.66)	**0.32** (0.17-0.63)
	≥ 80 years	**0.25** (0.16-0.38)	**0.09** (0.05-0.17)	**0.16** (0.08-0.33)
Tumor location	Fundus/body *vs.* antrum/pylorus	**0.50** (0.38-0.65)	**1.56** (1.07-2.29)	0.96 (0.65-1.42)
Tumor histology	SRC *vs.* non-SRC	0.77 (0.49-1.22)	0.57 (0.18-1.77)	0.66 (0.42-1.02)
Adjacent structure invasion	Yes *vs.* no	0.57 (0.32-1.01)	**0.07** (0.04-0.13)	**0.27** (0.11-0.68)

[1]Odds ratios and 95% confidence intervals for resection versus non-resection were calculated using multivariable logistic regression models adjusting for year of diagnosis, sex, age group, tumor location, and histology. For associations with tumor adjacent structure invasion, this factor was additionally added into the main model. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. Results were not shown for countries with <50 resected and/or <100 total cases (resected/total no.: cardia: Estonia, 70/96). ORs shown in bold are statistically significant.

OR, odds ratio; CI, confidence interval; SRC, signet ring cell carcinoma; -, not available; \, not shown due to small case number.

3.2.5 Rates of non-surgical therapies in addition to resection

The trends of non-surgical therapies in addition to resection were further investigated for all patients irrespective of distant metastasis status (**Figure 29**). Relevant information was available in all countries except Sweden, and had low sensitivity in the US and Estonia where results are not shown. Regarding rates of ≥1 therapy (resection, chemotherapy, and/or radiotherapy), they mostly showed increasing trends (the Netherlands (2005-2006 to 2013-2014: 61% to 64%; P_{trend}=0.003); Belgium (2003-2004 to 2013-2014: 74% to 77%; P_{trend}=0.024)) or remained stable ($OR_{Slovenia}$=0.828). In Norway, still a slight decreasing trend was observed (2003-2004 to 2013-2014: 66% to 60%; P_{trend}=0.007).

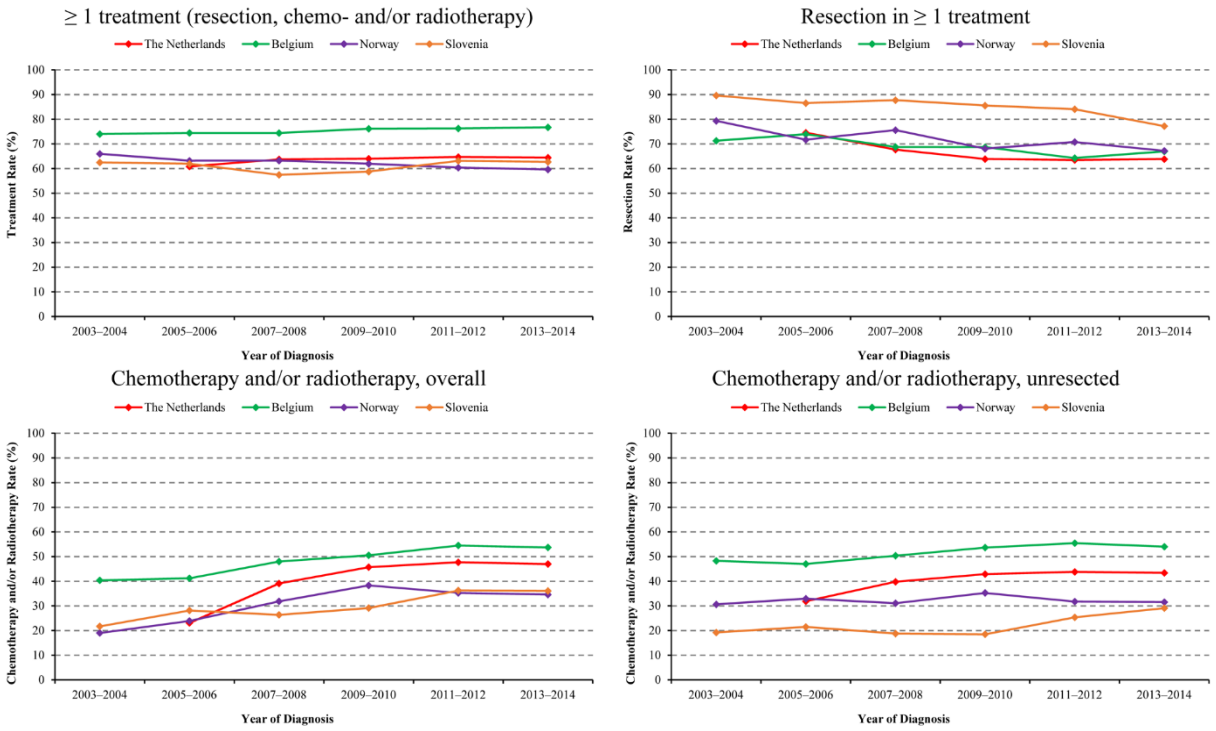

Figure 29. Proportions of gastric cancer patients undergoing ≥1 treatment modality (resection, chemotherapy, and/or radiotherapy) in overall patients, of resected cancer patients in those receiving ≥1 treatment, and of patients receiving non-surgical therapies in overall and unresected patients.

The proportion of resected patients in those receiving ≥1 treatment significantly decreased in all countries. The strongest decrease was observed in the Netherlands (2005-2006 to 2013-2014: 75% to 64%; P_{trend}=0.001), and the slightest decrease occurred in Belgium (2003-2004 to 2013-2014: 71% to 67%; P_{trend}=0.002). Norway (2003-2004 to 2013-2014: 79% to 67%; P_{trend}=0.014) and Slovenia (2003-2004 to 2013-2014: 90% to 77%; P_{trend}=0.003) showed moderate decreasing proportions.

Rates of non-surgical therapies significantly increased in all countries. The largest increase was observed in the Netherlands (2005-2006 to 2013-2014: 23% to 47%; P_{trend}=0.001), followed by Norway (2003-2004 to 2013-2014: 19% to 36%; P_{trend}<0.001). Belgium (2003-2004 to 2013-2014: 40%

to 54%; P_{trend}<0.001) and Slovenia (2003-2004 to 2013-2014: 22% to 36%; P_{trend}<0.001) showed moderate increases. For unresected cancer patients, while the changes were insignificant in Norway (P_{trend}=0.552) and Slovenia (P_{trend}=0.051), increasing rates were observed in the Netherlands (2005-2006 to 2013-2014: 32% to 43%; P_{trend}=0.001) and Belgium (2003-2004 to 2013-2014: 48% to 54%; P_{trend}=0.001).

Results were similar after stratifying patients by metastasis status (data not shown).

4 DISCUSSION

4.1 Pancreatic cancer

4.1.1 Resection of pancreatic cancer in Europe and the US

(This part has been published (Huang *et al.*, 2017).)

This part of the large international study described the use of surgical resection for PaC in Europe and the US in the early 21st century. Overall low resection rates were observed, albeit with major variations across countries. Various factors were found to be associated with resection application.

Variations in resection rates between countries and over time have been rarely investigated for PaC. This study showed that the overall resection rates were low in all participating countries. Even within patients with stage I-II PaCs, who however only comprised 19%-36% of all diagnosed cases, only 35%-69% were resected in 2012-2014. Increases in resection rates over time were only detected in the US, the Netherlands, and Denmark. Compared with overall PaCs, variations in resection rates across countries were stronger for stage I-II cancers. Notably, centralization and/or specialization which potentially explains in part the observed geographical and temporal variations was implemented in all three countries showing increasing resection rates. Centralization could contribute to increases in resection rates (de Wilde *et al.*, 2012). Centralization started in the Netherlands regionally in 2005 (Gooiker *et al.*, 2014; Lemmens *et al.*, 2011) and nationally in 2011 (van der Geest *et al.*, 2016a), and in Denmark in 2000 (Cronin-Fenton *et al.*, 2011). Nationally, the number of hospitals performing pancreatoduodenectomy for PaC decreased from 39 to 23 during 2004-2009 in the Netherlands, and the proportion of patients operated at medium-/high-volume centers with >10 resections per year increased from 53% to 91%, which is accompanied by an increase in the number of pancreatoduodenectomy from 258 (11%) to 394 (18%) (de Wilde *et al.*, 2012; Onete *et al.*, 2015). In 2011, an annual volume standard of 20 pancreatoduodenectomies per hospital was set by the Dutch Health Inspectorate (van der Geest *et al.*, 2016b). In Eindhoven, the Netherlands, the number of hospitals conducting resection decreased from 6 to 3 during 2005-2008, and the annual number of resections per hospital increased from 5 to 16 (Lemmens *et al.*, 2011). In western Netherlands, pancreatic surgery was centralized into two high-volume hospitals since 2006 (Gooiker *et al.*, 2011). In the US, nationwide centralization in pancreatic surgery has also been occurring with state-specific variations (O'Mahoney *et al.*, 2016; Ryan *et al.*, 2015). Between 1992-1994 and 2010-2012 in Florida, the number of pancreatic surgeons decreased from 363 to 196, while the number of resections increased from 729 to 1,569 (Ryan *et al.*, 2015). In Denmark, only 4 university hospitals are allowed to do pancreatectomy, two with ≥75 yearly resections and the other two with ≥25. In Belgium, a

population-based study (Topal *et al.*, 2007) proposed centralization in 2007. While the number of treating hospitals decreased from 77 to 68 with the average number of resections per hospital increasing from 6 to 7 in 2009-2014, only 4 hospitals kept doing >15 pancreatectomies per year. In Slovenia, pancreatectomy is centralized in 3 centers. Patients undergoing resection in higher-volume centers had better survival (Ahola *et al.*, 2017; Ryan *et al.*, 2015). Morbidity and hospital duration could also be reduced by centralization (O'Mahoney *et al.*, 2016; Topal *et al.*, 2007; Young *et al.*, 2013).

Although in countries with centralization the resection rates increased, they remained low. It was observed that resection was less frequently conducted with more advanced cancer stage, with larger lesion size, with older age, in pancreatic body cancer, and with poorer performance status. Notably, patients with stage III-IV cancers (64%-81%) and those ≥70 years (53%-60%) comprised the majority of all the PaC cases across all investigated countries, which largely contributed to the low resection rates on the basis of the strong associations of resection application with patient age and cancer stage. Patients aged ≥70 years remained the majority among those with stage I-II PaCs (53%-61%).

Advanced cancer stage is a negative prognostic factor and is often regarded as contraindicative to resection (Swanson *et al.*, 2014). Tumor size was found to be negatively associated with the frequency of resection, possibly in part because larger tumors are more prone to vessel involvement and are thus often associated with more advanced cancer stages. Pancreatologists' consensus states that localized PaCs without major vessel involvement (mostly TNM stage I-II) are mostly clearly resectable (Ducreux *et al.*, 2015b; Tempero *et al.*, 2014). For 'unresectable' tumors, resection is seldom recommended (Balaban *et al.*, 2016; Sohal *et al.*, 2016). Per guidelines (Ducreux *et al.*, 2015b; Tempero *et al.*, 2014), cancers which circumferentially encase celiac axis or superior mesenteric artery (T4/stage III) and metastatic tumors (M1/stage IV) are deemed to be unresectable, largely because of the high possibility of incomplete resection, which is associated with worse survival (Conroy *et al.*, 2011). Many resected 'unresectable' cancers are detected unsuspectedly during surgery (Kim *et al.*, 2016). With increasing experience in vascular surgery, vessel involvement which characterizes T4/stage III cancers is less frequently regarded as resection-contraindicative (Hartwig *et al.*, 2013). The term 'borderline resectable' was brought about to define a specific subgroup within locally-advanced PaCs for which curative resection is potentially applicable. While borderline resectable PaCs might be associated with resection rates higher than the other stage III cancers, they could not be investigated here due to the newly-emerged, continuously-evolving, and non-uniform definition (Katz *et al.*, 2013; Khorana *et al.*, 2016).

Resectability criteria are a key and hot issue in PaC treatment. While there might be differences in the management guidelines across countries, concerning resectability the participating countries all follow the NCCN guidelines (Tempero *et al.*, 2014). While there remain differences, major progresses have been made in the definition which is becoming more and more uniform and standardized in recent years (Balaban *et al.*, 2016; Bockhorn *et al.*, 2014; Ducreux *et al.*, 2015b; Tempero *et al.*, 2017;

Wolfgang *et al.*, 2013). However, since the criteria are relatively complicated for routine registration practice especially at the population-based level and were mostly evolving during the study period, resectability status was mostly not readily registered in the participating countries. Subgroup analyses were performed according to TNM stage, which is commonly used and which could hopefully help to identify a subgroup of patients for which resection is more likely. Notably, the resectability criteria could not be substituted by the TNM staging system. Locally advanced, unresectable PaCs defined by the ISGPS and the NCCN are different from T4/stage III cancers according to the AJCC/UICC. Even some TNM stage II cancers can be locally-advanced and/or unresectable according to the ISGPS and the NCCN guidelines. A uniform and standardized resectability definition is hopefully to be implemented in the clinical and registry practice in the near future.

Older age is also a negative prognostic factor (Swanson *et al.*, 2014), and is associated with higher prevalence of comorbidities (Kimura *et al.*, 2014) and complications (Sukharamwala *et al.*, 2012). Whether older age should be regarded as contraindicative to resection remains controversial. Some small studies suggested that resection was associated with higher survival in elderly patients (He *et al.*, 2015; Marmor *et al.*, 2016), which however could be at least in part explained by the selection of fitter patients for resection. Some studies showed that compared to younger people, fit elderly patients might gain similar survival benefits from resection, which could be safely performed for the group of patients (Barbas *et al.*, 2012; van der Geest *et al.*, 2016a). However, some other large monocentric studies have identified age as a risk factor for operative mortality in scores predicting post-pancreatoduodenectomy mortality (Kimura *et al.*, 2014; Venkat *et al.*, 2011). The operative mortality in octogenarians was 4% in a series of 2,000 pancreatoduodenectomies (Cameron and He, 2015). Thus, the general pre-treatment condition of elderly patients should be carefully assessed to ensure that it allows pancreatectomy to be safely performed with an acceptable perioperative risk. As more than half of the PaC patients were 70 years or older at diagnosis, further studies are needed to investigate the benefit and harm of PaC resection for elderly patients, which should be well balanced (van der Geest *et al.*, 2016a).

Tumor location was another factor associated with PaC resection. Pancreatic body cancers were less often resected, which could be potentially explained by that pancreatic body lesions might be most challenging to manage, due to the common involvement of major vasculatures and accordingly the advanced stage at diagnosis (Hartwig *et al.*, 2013; Wolfgang *et al.*, 2013). It was also observed that higher ECOG scores, which are associated with higher perioperative morbidity and mortality risks, were negatively associated with the frequency of resection. Specific comorbidities were also inversely associated with resection frequencies.

The aspects discussed above potentially explain in part surgeons' option of resection for PaC and the low resection rates. Further reasons especially for the low resection rates for stage I-II cancers remain to be revealed. Notably, resectability might be largely impacted by surgeons' abilities and experience, surgical techniques, equipment, skills, and procedure (Hartwig *et al.*, 2013). Tumor

biology, symptom burden, patient preferences, operative tolerance, support systems, and quality of life (QoL) are important aspects to consider beyond standard resectability classification. Based on SEER-18, for 96.8% of unresected cancer patients, resection was not recommended by doctors. QoL decreases considerably in the early postoperative phase and its full recovery might take up to half a year (Heerkens *et al.*, 2016). However, in the longer term resection overall does not worsen and even benefits QoL in most PaC survivors (Laitinen *et al.*, 2017). Patient choice might be influenced by the health insurance coverage, his/her socioeconomic status, marriage status, and trust in doctor (Schildmann *et al.*, 2013). Notably, some people might have limited access to medical care because of the distance from care facilities. Future studies especially on patient preferences and access to care are warranted.

There are some limitations for this study. Due to the retrospective design, some important variables (*e.g.*, performance status, comorbidities, and tumor size) were not available in some registries or the missing number was too high to be included in the main analyses. Furthermore, the heterogeneity in the available variables across registries might lead to information bias which potentially impacts robust inferences of the data. This highlights the need for improving the level of standardization and comprehensiveness in the registration practice. Another limitation was that the proportions of patients with unknown TNM stages were relatively high. Nevertheless, patterns remained the same after multiple imputations. Furthermore, treatment patterns in other European countries (*e.g.*, the United Kingdom and France) were not investigated in this study, and no Asian or African registries were included. The treatment patterns in these countries or continents need to be clarified in future investigations. Notably, the US and the Netherlands registries contributed the largest numbers of cases among participating registries. However, results for each registry were presented separately, and no pooled-analysis was conducted, which reduces the concern of the potential impact of these large registries on the interpretation of the results.

Differences in cancer stage across registries were detected, which potentially highlights the variation in the quality of PaC staging, since it is often difficult to correctly stage T4 cancers with arterial invasion compared with T1-3 cancers, and there could be relevant inter-observer variations. There could even be relevant differences at the national level (Minicozzi *et al.*, 2017). In most of the investigated countries, many of those patients are discussed by multidisciplinary teams (MDTs), which is required by law. In Denmark and Estonia, almost all patients are evaluated by MDTs. In Belgium, the proportion of MDT-discussed patients increased from 57.8% in 2005 to 84.5% in 2012. In the Netherlands, about two-third of the patients were discussed by MDTs in 2012 (van Rijssen *et al.*, 2016).

Strengths of this study include the use of high-quality data from multiple population-based cancer registries, the large sample size, the strict inclusion criteria, the careful case selection, and the uniformly defined and standardized variables across registries.

4.1.2 Non-surgical therapies for resected and unresected pancreatic cancer in Europe and the US

(This part has been published (Huang *et al.*, 2018b).)

This part of the large international study with a focus on the administration of non-surgical therapies for resected and unresected PaCs highlighted the geographical and temporal variations and revealed the factors associated with the administration. The rates of the non-surgical treatment remained generally low and varied greatly across the European countries and the US. Most of the resected and unresected patients did not receive any non-surgical treatment. Major increases in the use rate were observed for chemotherapy, but not for radiotherapy.

The NCCN (Tempero *et al.*, 2014), American Society of Clinical Oncology (ASCO) (Khorana *et al.*, 2016), and ESMO guidelines (Ducreux *et al.*, 2015b) recommend that patients with resectable PaCs undergo resection and receive adjuvant chemotherapy with or without radiotherapy, and that those with unresectable tumors receive palliative chemotherapy or chemoradiation. Although resection can markedly improve survival for patients with resectable PaC, locoregional disease relapses after surgery in about three-fourth of patients as a result of occult metastasis and residual cancer cells, which necessitates the use of adjuvant therapy (Ferrone *et al.*, 2012). Although RCTs have demonstrated better survival in patients with resected localized cancers who have received postsurgical chemotherapy (Mukherjee *et al.*, 2013; Neoptolemos *et al.*, 2001; Neoptolemos *et al.*, 2004; Oettle *et al.*, 2013; Oettle *et al.*, 2007; Uesaka *et al.*, 2016), the use of adjuvant therapy could be limited by poor tolerance. Neoadjuvant therapy might be offered as an alternative to upfront surgery and has been indicated to be well-tolerated and effective for PaC patients (Khorana *et al.*, 2016), but prospective evidence which supports survival benefits is very limited (Crane *et al.*, 2011; Kim *et al.*, 2013; Mokdad *et al.*, 2016). Neoadjuvant therapy was rarely administered in Europe. Side effects associated with the use of chemotherapy and radiotherapy require special attention when planning these treatment modalities.

While guidelines are comparable across countries regarding chemotherapy use, great geographical variation in chemotherapy administration were found across Europe. A nationwide Dutch study focusing on resected PaCs during 2008-2013 further reported great inter-center variations (26%-74%) (Bakens *et al.*, 2016). These variations are not very likely explainable by differences in patient or tumor characteristics, which were mostly similar across registries. Potential reasons for the variations include differences in patient and/or clinician preferences, socioeconomic factors, healthcare system, and health insurance coverage. All patients in the Netherlands and most of the patients in Estonia are covered by insurance.

Despite the disparities, chemotherapy use increased strongly over time, particularly for resected cancer patients. The strongest increase was observed in the Netherlands, where reimbursement for gemcitabine was possible since November 2008 (Bakens *et al.*, 2016), with use rates increasing from

10% in 2003-2005 to 56% in 2012-2014 among resected cancer patients. The observed trends and disparities might also be associated with centralization and/or specialization of PaC care (Faluyi *et al.*, 2017), and management in academic hospitals was associated with more frequent adjuvant chemotherapy use. In the Netherlands, all hospitals are eligible to prescribe the chemotherapey drugs. In Estonia, chemotherapy is provided in three hospitals, and radiotherapy in two hospitals. These hospitals are distributed adequately in the country. The characterization of PaC as a chemoresistant cancer has been greatly challenged through the past years (Conroy *et al.*, 2016). A decade ago, a meta-analysis on adjuvant chemotherapy for PaC revealed a benefit of only a 3-month prolongation of median survival (Boeck *et al.*, 2007). However, a recent network meta-analysis showed that adjuvant chemotherapy reduced mortality by nearly one third after resection (Liao *et al.*, 2013). Several landmark RCTs were key in establishing the standard and might explain the trends. The results of the ESPAC-1 trial (Neoptolemos *et al.*, 2004) showed that 5-year overall survival (OS) nearly tripled among resected cancer patients receiving adjuvant 5-flourouracil-based chemotherapy compared to those who did not (21% *vs.* 8%). The absolute clinical benefits of adjuvant gemcitabine versus placebo to median OS (23 *vs.* 20 months) and 5-year survival rate (21% *vs.* 10%) were shown in the phase III CONKO-001 trial (Oettle *et al.*, 2007). Westerners tend to be more sensitive to gemcitabine-based therapies (Khorana *et al.*, 2016). Notably, chemotherapy-associated survival improvement does not compromise QoL or pain control (Kristensen *et al.*, 2016). A RCT even showed better QoL with adjuvant treatment (Morak *et al.*, 2010).

Radiotherapy was mostly used as an addition to chemotherapy. The role of radiotherapy remains uncertain for resectable PaC, and combination of chemotherapy with radiotherapy has shown controversial results for locally-advanced unresectable PaC (Chauffert *et al.*, 2008; Loehrer *et al.*, 2011). The geographical disparity might be explained by the conflicting evidence from RCTs regarding the addition of radiotherapy on the two sides of the Atlantic, which makes chemoradiotherapy considered as the optimal approach in the US, but chemotherapy alone as the standard of care in Europe (Herreros-Villanueva *et al.*, 2012). European trials on adjuvant radiotherapy for PaC mostly revealed non-superior or even harmful effects, which is in contrast to the beneficial effects according to the US reports (Chauffert *et al.*, 2008; Klinkenbijl *et al.*, 1999; Loehrer *et al.*, 2011; Neoptolemos *et al.*, 2004). The small EORTC trial (Klinkenbijl *et al.*, 1999) suggested potential survival benefits of concurrent chemoradiotherapy compared with observation for resected PaC. For locally-advanced PaCs which are mostly considered to be unresectable, the ECOG-4201 trial (Loehrer *et al.*, 2011) showed that chemoradiotherapy was associated with higher OS compared to chemotherapy alone (11 *vs.* 9 months), albeit with more toxicity. However, the FFCD-SFRO study (Chauffert *et al.*, 2008) showed reverse survival outcomes, and the ESPAC-1 trial (Neoptolemos *et al.*, 2004) likewise did not reveal any benefit. The ESMO does not recommend the routine use of adjuvant chemoradiotherapy (Ducreux *et al.*, 2015b).

Consistent with these discrepancies, it was observed that for resected PaC radiotherapy use rates

were markedly higher in the US than the European countries. When focusing on the period 2012-2013, great disparities across SEER-18 sub-registries were found, and a pattern consistent with an earlier SEER-based study that patients treated in the western US had a lower likelihood of undergoing non-surgical therapy was shown (Krzyzanowska *et al.*, 2003). Interestingly, even in the US, adjuvant radiotherapy rates decreased, which might be accompanied with the more frequent use of intensified chemotherapy (Conroy *et al.*, 2011; Kamisawa *et al.*, 2016; Uesaka *et al.*, 2016; Von Hoff *et al.*, 2013). Within the subset of unresected cancer patients, both the US and the European countries were conservative in radiotherapy use. In unresected cancer patients who often have more advanced tumors, chemotherapy might be preferred over radiotherapy for systemic control, as radiotherapy as a local procedure more often causes serious complications especially fibrosis and does not address the systemic disease (Wo *et al.*, 2014). Given the lack of consistent findings across clinical trials, further trials on radiotherapy might be warranted to establish the optimal treatment modality.

Cancer stage, location, patient age, performance status, certain comorbidities, and hospital type were associated with chemotherapy use. Older ages were associated with lower rates in both resected and unresected cancer patients. While it has been shown that chemotherapy is safe for elderly patients with resectable or unresectable PaC, with survival benefits similar to those for younger patients (Berger *et al.*, 2014; Nagrial *et al.*, 2014; Sehgal *et al.*, 2014), it is important to well balance benefits and harms for the elderly patients, a heterogeneous population who might have poorer performance status and more frequent and serious comorbidities and who might be more prone to toxicity. Older patients are often neglected in clinical trials, which makes the determination of the optimal therapy for this population difficult. The preferred treatment for patients with early-stage PaC is resection, after which patients' physical and mental statuses might not allow for further aggressive therapy (Khorana *et al.*, 2016). In patients with advanced unresectable cancers, palliative chemotherapy is considered to be the first and possibly only effective option (Balaban *et al.*, 2016; Sohal *et al.*, 2016). Interestingly, within resected cancer patients, no prominent associations between cancer stage and chemotherapy use were observed, which is probably due to the small case numbers; while in unresected cancer patients, chemotherapy was more often used for stage III and IV PaCs than for stage I-II tumors. Tumor location was not significantly associated with chemotherapy administration within resected cancer patients, while among unresected cancer patients, both pancreatic body and tail cancer patients received more frequently chemotherapy. This could be possibly explained in part by the attempt to downstage body/tail cancers which are more often advanced in stage with major vessel involvement due to the usual late detection, and to render them resectable (Balaban *et al.*, 2016).

Radiotherapy use was associated with patient age, performance status, cancer stage, hospital type, and resection type (in resected PaC). Among both resected and unresected cancer patients, radiotherapy was less frequently administered with increasing age, although chemoradiotherapy in both the adjuvant and palliative settings was found to be non-inferior to observation concerning survival among the very old patients (Horowitz *et al.*, 2011; Mattiucci *et al.*, 2015; Miyamoto *et al.*,

2010). However, tolerance in the heterogeneous aged patient groups with more frequent comorbidities should be of note. Compared with stage I-II PaCs, radiotherapy was more often used for stage III cancers, but less frequently for metastatic cancers. The higher rate for stage III cancer might be based on the attempt to downstage cancers which could facilitate the subsequent resection and to achieve local control which would be complimentary to surgery (Balaban *et al.*, 2016). Notably, radiotherapy use might be largely at clinicians' disposal. According to the SEER-18, only 1.2% of unresected and 0.8% of resected PaC patients did not receive radiotherapy because of patient and/or guardian refusal.

This study has some limitations. Firstly, some potentially treatment-associated factors were not studied due to being unavailable in some registries. Particularly, data on comorbidities were only available in Eindhoven, the Netherlands. Patients' socioeconomic and marital statuses, access to care, tolerance, recovery from resection, and treatment response are important factors that should be studied in future investigations. No reliable data on chemotherapy use are available in the SEER dataset (Noone *et al.*, 2016). Since data on the time intervals between diagnosis/surgery and chemotherapy/radiotherapy use was not available in all registries, a cut-off for the time intervals was applied in the sensitivity analyses rather than in the main analyses. Furthermore, treatment patterns in other countries should be investigated in future studies.

The main strengths of this study include the international population-based design, the large sample sizes, and the strict inclusion criteria and methodology, which enable this work to well reflect the status quo of the use of non-surgical therapies for PaC in Europe and the US, warranting caregivers' and policymakers' attention.

4.1.3 Stratified survival of resected and overall pancreatic cancer patients in Europe and the US

(This part has been published (Huang *et al.*, 2018a).)

This part of the large international population-based study comprehensively provided the overall survival estimates for overall and resected PaC patients by cancer TNM stage and patient age. Furthermore, the temporal trends of survival for the overall and resected cancer patients with clearly-resectable (stage I-II) and mostly-unresectable (stage III-IV) PaCs in four European countries and the US were shown separately. In both stage I-II and III-IV cancers, survival rates decreased prominently with increasing age. Limited but encouraging progresses in survival over time were detected.

According to the EUROCARE-5 study (De Angelis *et al.*, 2014; Lepage *et al.*, 2015b), overall, the 1-, 3-, and 5-year survival rates of European PaC patients diagnosed in 1999-2007 were only 26%, 9%, and 7%, respectively. For the European countries participating in this study, the 1-year survival was 19%-34% and the 5-year survival was 4%-11%. In the US, the overall 5-year survival was 7% to 10% (Brenner *et al.*, 2007; Sirri *et al.*, 2016). Stage- and treatment-specific survival was not provided by the previous studies (De Angelis *et al.*, 2014; Lepage *et al.*, 2015b). This study provided more

up-to-date estimates by including patients diagnosed in 2003-2014 and further showed survival by cancer TNM stage and patient age. Survival decreased with advancing stage and older age. It is important to provide stratified survival for clinical counseling.

It is stated by guidelines (Balaban *et al.*, 2016; Ducreux *et al.*, 2015b; Khorana *et al.*, 2016; Sohal *et al.*, 2016; Tempero *et al.*, 2014) that localized (stage I-II) PaCs are mostly resectable, while T4/stage III and M1/stage IV cancers are largely unresectable. The results showed that resected patients with stages I-II PaCs had higher survival estimates through all age groups compared with the usually reported and widely available overall survival. For instance, resected cancer patients aged <60 years had 3%-19%, 1%-13%, and 1%-9% units higher 1-, 3-, and 5-year survival than the overall patients across countries, respectively. These differences may reflect the effects of both resection and selection of fitter patients for surgery. Given that most patients would perceive the overall PaC prognosis as dismal and thus feel extremely distressed, which also generates great burdens to their family and caregivers, it would be important to show the objective survival estimates especially for the resected cancer patients to them, which potentially helps to rebuild the hope of life.

Survival of patients with stage III-IV PaCs, who took up the majority of the diagnosed cases, was much lower than that of those with stage I-II cancers, especially in the longer term. For locally-advanced PaC, the average overall survival remains <12 months (Loehrer *et al.*, 2011), and for metastatic cancers, the median survival is <6 months (Hammel *et al.*, 2016), with 5-year survival of only about 2% (Wolfgang *et al.*, 2013). It was shown that even for those aged <60 years, the overall 3- and 5-year survival was as low as 2%-5% and 1%-4%, respectively. Most patients with stage III-IV PaCs are considered to be unresectable (Balaban *et al.*, 2016; Sohal *et al.*, 2016). This may, however, improve in the years to come with the increasing administration of the FOLFIRINOX regimen (Suker *et al.*, 2016). In many of the cases in which patients with metastatic PaCs underwent resection, the metastasis was unexpectedly found only during resection (Kim *et al.*, 2016). Although resection rates for advanced cancers were low, notably, in patients with stage III-IV PaCs substantially higher survival was observed for resected cancer patients compared to overall patients in all age groups, and resected cancer patients aged <70 years could have 3-year survival of 5%-34%. Even in those aged ≥70 years, higher survival estimates for the resected cancer patient subgroup were observed (1-year, 16%-42% *vs.* 5%-14%; 3-year, 2%-14% *vs.* 1%-1%). While this difference might again at least in part reflect patient selection, *i.e.*, inclusion of fitter and healthier patients or those with more favorable cancer characteristics for surgery, the results indicated that not all stage III-IV PaC patients had such dismal prognosis as indicated by the overall survival estimates. These strong differences again underline the importance of showing respective outcomes for stratified resected cancer patients for enhanced counseling of these patients.

The perioperative survival should be of note, especially for elderly patients. It is volume-dependent, and is mainly impacted by surgical expertise and failure to rescue (Krautz *et al.*, 2018). While resection could be performed safely for some proportion of the usually more vulnerable

elderly patients (Barbas *et al.*, 2012; van der Geest *et al.*, 2016a), at the population level, it was found that in patients with stage III-IV PaCs, which is associated with inferior general status, the 1-month survival dropped from 94%-99% in patients aged <70 years to 81%-96% in those aged ≥70 years, which was more dramatic compared with stage I-II cancers. Age was inversely associated with survival, which necessitates it to be a stratification factor when showing survival outcomes. Increasing ages are associated with more frequent comorbidities and complications, which decreases the potential survival benefits of resection. However, some studies indicated that compared with younger individuals, fit elderly patients might obtain comparable survival benefits from resection (Barbas *et al.*, 2012; van der Geest *et al.*, 2016a). The higher survival observed for the younger patients might be partly explained by the more aggressive treatment strategies used, which might contribute to improvements in survival of the fit elderly patients too (Lepage *et al.*, 2015b). These highlight the importance of geriatric assessment before treatment.

No substantial survival alterations (5-year, 5%-6%) were shown for PaC in the EUROCARE-5 study (Lepage *et al.*, 2015b) during the period 1999-2007. In the US, the 5-year survival increased from 6% in 1992-1996 to 8% in 2002-2006 (Pulte *et al.*, 2012) and from 8% in 2002-2004 to 12% in 2008-2010 (Sirri *et al.*, 2016); especially for localized cancers, strong improvement in 5-year survival by 7% units from 1998 through 2003 was detected (Brenner *et al.*, 2007). Modest but nevertheless encouraging improvements in survival of patients both with stage I-II and with III-IV cancers from 2003-2005 to 2009-2011 were observed, which potentially reflects the advancement in surgical skill, technique, and perioperative care. In the US, the 3-year survival increased by 4% units in patients with stage I-II PaCs overall, but by only <1% units in those with stage III-IV tumors. For resected PaCs, survival increased by 5% units among patients with stage I-II cancers. In Europe, the 3-year survival for both overall and resected patients with stage I-II PaCs increased in all participating countries, and a large increase was detected in the Netherlands (overall, 8% units; resected, 11% units), in which postoperative mortality is decreasing (de Wilde *et al.*, 2012). Notably, the centralization agreement was implemented in the Netherlands since 2005, and it promoted more resections (Lemmens *et al.*, 2011), which might be associated with the continuous improvement in survival (van der Geest *et al.*, 2016b). While further major survival improvement in resected cancer patients could be limited even with modification of surgical technique, better outcomes are likely to come from more effective systemic therapies (*e.g.*, FOLFIRINOX) combined with resection. The discrepant trends between overall and resected cancer patients further highlight the need to provide survival data in specific patient subgroups.

This study covered the periods when the sixth and seventh TNM staging systems were in effect, and both are compatible/identical with each other (Ducreux *et al.*, 2015b). While potentially improved imaging technique might result in a shift in stage categorization, the proportions of each stage remained relatively stable in the participating countries (data not shown). In the era of the eighth TNM staging, in which the definitions of the T4 and M1 categories suggesting mostly unresectable tumors

remain unchanged (Shi *et al.*, 2018), the results would still be applicable for survival counselling.

This study was limited by the relatively small case numbers in some subgroups. Further potentially prognostically-important factors (*e.g.*, comorbidities) were not considered due to being unavailable or unknown in the national registries of most participating countries. Although older patient ages and more advanced cancer stages herein studied were the most outstanding negative prognostic factors and might contraindicate surgery, precise and personalized factors should be considered for the evaluation of individual patient prognosis. Some survival-predicting tools (*e.g.*, nomogram) might offer more precise prognostic data for a given patient. Non-surgical therapies were not incorporated considering the low sensitivity in recording in some participating registries and the varying regimens administered. Data from more countries would increase the comprehensiveness of the study. However, data on TNM staging or treatment were mostly not readily available in the other national population-based registries. This study was based on complete-case analysis. Some differences in data recording especially of TNM stage should be of note, and the proportion of stage I-II cancers varied from 25% (Norway and Slovenia) to 38% (Belgium). There could be underreporting especially of advanced-stage cancers with various extents, besides the potential impact of unknown staging data. These differences highlight the need for standardization in the registration practice. Potential variation in the registration practice especially for stage might influence outcomes, and inter-country comparisons were not made considering the probable heterogeneity. Results were only analyzed and interpreted separately in the respective country without pooling or comparison with other countries. Results from a specific national population-based registry might not be generalizable to another country. For counselling for patients from other countries, other aspects (*e.g.*, treatment profiles and health care systems) should be considered.

In the main analyses, PaC cases regardless of microscopic confirmation were included, which is in accordance with the real-world situation (Asbun *et al.*, 2014), and which is also consistent with the approach used in the EUROCARE studies (De Angelis *et al.*, 2014; Lepage *et al.*, 2015b). While resected cases were mostly microscopically confirmed, the confirmation rates for overall cases varied. The rates of microscopic confirmation for PaC have been relatively low (Lepage *et al.*, 2015b), and it has always been difficult to microscopically verify especially unresectable PaC. In this complete-case analysis, inclusion of patients with known stage might influence the observed rates of confirmation. After restricting the overall cases to the microscopically confirmed ones in sensitivity analyses, the survival estimates mostly became higher in all included countries except in Belgium, where the rates of microscopic confirmation were high. Furthermore, the survival increase was most prominent in patients aged ≥70 years, who are generally frailer and for whom the selection of treatment is commonly more cautious. While including microscopically-confirmed cases only could help to further increase the probability of selecting the real PaC patients, those not receiving any treatment and usually having inferior patient and/or cancer characteristics might be more likely excluded, which potentially explains in part the higher observed survival estimates in the sensitivity analyses.

It was shown that it is important to provide survival estimates to resected patients separately for counseling, as the resected PaC patient subgroup has substantially higher survival than the overall estimation. The results for unresected cancer patients were not shown and direct comparisons between the resected and the unresected cancer patients were avoided, as they may to a large extent reflect the selection effects which are related to various factors including patients' health status and hospital characteristics. In the resected cancer patient subgroup, curative and palliative resections were not differentiated from each other, considering the greatly geographically and temporally varying standards for defining clear resection margins in PaC resection.

Nevertheless, the large international population-based nature of this study with the country-specific respective analysis adds important new survival data to the literature. In particular, results stratified by cancer TNM stage and patient age for resected and overall cancer patients will further aid patient counseling in clinical practice, which provides more specific survival information for specific PaC patient populations.

4.1.4 Prognostic factors and development and international validation of a benchmark population-based survival-predicting model in patients with resected stage I-II pancreatic adenocarcinoma receiving chemotherapy

In this part of the large population-based study, various factors independently associated with survival after resection of PaC were identified, and for the first time a population-based nomogram for predicting survival in resected PaC patients receiving chemotherapy was established and internationally validated, which is robust, accurate, reliable, and practical.

Through multivariable analyses, it was revealed that older age, more advanced T and N stages, and poorer differentiation were independently associated with lower overall survival in resected PaC across most countries. These findings are mostly consistent with previous literature (Kuhlmann *et al.*, 2004; Schnelldorfer *et al.*, 2008). In registries with available information, resection margin, hospital type, tumor size, metastatic and harvested lymph node numbers, lymph node ratio, and comorbidity number were also associated with prognosis. While previous studies differ in conclusion regarding association between resection type and survival (Kuhlmann *et al.*, 2004; Schnelldorfer *et al.*, 2008), this population-based investigation of chemotherapy-treated resected cases did not show a significant association. Furthermore, mostly insignificant associations of survival with tumor location were found.

Notably, overall the contribution of T or N stage to postoperative survival was mostly not greater than differentiation. Categorization of tumor size and number of metastatic lymph nodes following the 8th TNM staging system (Allen *et al.*, 2017; Schlitter *et al.*, 2017) well discriminated survival, supporting the implementation of the new system. Notably, harvested lymph node number was positively associated with survival. Its relevance for survival has remained controversial in PaC (Huebner *et al.*, 2012; Murakami *et al.*, 2010). Possible reasons supporting the favorable association include that potentially more metastasized lymph nodes will be removed with more extensive

sampling, which also results in more precise staging, guiding appropriate postsurgical treatment.

Estimating mortality risk might impact treatment planning, and provide information helpful for patient stratification in study design, contributing to better equivalence between study arms (Hammel *et al.*, 2016). PaC is remarkably heterogeneous concerning postsurgical survival of individual patients, even with the same TNM stage (Benassai *et al.*, 2015; Jouffret *et al.*, 2015; Luberice *et al.*, 2017). The nomogram developed is the first one derived from a large population-based database with long-term follow-up for predicting overall survival in patients with resected stage I-II PaC receiving chemotherapy, with international validations in multiple European national datasets. There is a previous institutional nomogram (Brennan *et al.*, 2004) developed by Memorial Sloan-Kettering Cancer Center (MSKCC) in 2004 for predicting postsurgical survival in Western PaC patients not accounting for chemotherapy, with three external institutional validation attempts (Clark *et al.*, 2008; de Castro *et al.*, 2009; Ferrone *et al.*, 2005). Based on institutional patient cohorts diagnosed many years ago (Brennan *et al.*, 2004; Clark *et al.*, 2008; de Castro *et al.*, 2009; Ferrone *et al.*, 2005), the score assignment of several variables might not be optimal currently using the MSKCC nomogram, which might also be limited in generalizability. It did not employ a backward selection process, and incorporated some detailed surgical (*e.g.*, portal vein resection and splenectomy) and symptom parameters (back pain and weight loss). Notably, portal vein resection and splenectomy might not be routine procedures during pancreatectomy, and reporting of symptoms might show great interpersonal variations. The population-based nomogram thus represents a more updated prognostic model compared to the MSKCC nomogram (**Table 64**). The wide geographical distribution of patients and large sample size further enhanced the international representativeness and generalizability of the nomogram.

Table 64. Comparison of the Memorial Sloan-Kettering Cancer Center nomogram with the newly developed one for survival for Western patients with resected pancreatic cancer

Nomogram	Dataset	Authors	Cohort origin	Publication year	Study design	Resection period	Follow-up end	Sample size
The newly developed	Training	Huang *et al.*	The US	-	Population-based	2004-2015	2015	9519
	Validation	Huang *et al.*	Belgium, The Netherlands, Norway, Slovenia	-	Multinational population-based	2003-2014	2016	2318
Memorial Sloan-Kettering Cancer Center	Training	Brennan *et al.*	The US	2004	Single institutional	1983-2000	2002	555
	Validation I	Ferrone *et al.*	The US	2005	Single institutional	1985-2003	Not reported	375
	Validation II	Clark *et al.*	UK	2008	Single institutional	1995-2005	Not reported	63
	Validation III	de Castro *et al.*	The Netherlands	2009	Single institutional	1985-2004	2007	263

-, not available.

Table 64. Comparison of the Memorial Sloan-Kettering Cancer Center nomogram with the newly developed one for survival for Western patients with resected pancreatic cancer (continued)

Nomogram	Dataset	Authors	Survival index	Additional factors	Backward selection	Concordance index	95% confidence interval	External validation
The newly developed	Training	Huang *et al.*	Median survival time, 1-/2-/3-/5-year survival rate	-	Yes	0.60	0.59-0.61	-
	Validation	Huang *et al.*	Median survival time, 1-/2-/3-/5-year survival rate	-	-	0.58-0.63	Shown in **Table 48**	Accurate
Memorial Sloan-Kettering Cancer Center	Training	Brennan *et al.*	3-year survival	Portal vein resection, splenectomy, resection margin, back pain, weight loss, maximum pathologic axis	Unspecified	0.64	Not reported	-
	Validation I	Ferrone *et al.*	3-year survival	-	-	0.62	Not reported	Accurate
	Validation II	Clark *et al.*	3-year survival	-	-	Not reported	Not reported	Not accurate
	Validation III	de Castro *et al.*	3-year survival	-	-	0.61	Not reported	Accurate

-, not available.

Resection margin has not received a universal standard definition in PaC (Konstantinidis *et al.*, 2013; Tempero *et al.*, 2014), and has highly controversial survival relevance (Butturini *et al.*, 2008; Chandrasegaram *et al.*, 2015). A meta-analysis (Butturini *et al.*, 2008) even showed overall no significant postsurgical survival differences between patients with negative and positive margins. While a positive association of survival with negative margin in the Netherlands was shown, the strength was not greater than T, N stage, or differentiation, and the association was insignificant in Slovenia. This variable was not incorporated in the nomogram for better generalizability. It is encouraged to incorporate margin status into the nomogram when a standard definition comes.

Calibration plots demonstrated very good agreement between nomogram-predicted and actual survival, which assures the repeatability and reliability of the nomogram. Importantly, the model based on the US dataset also fits the multiple European national cohorts well, which supports the potential for the generalization and international utilization of the nomogram, *irrespective of the potential health care disparity across countries*. Discrimination of the nomogram, as highlighted by the C-index, was significantly and markedly higher compared to the model based on T and N stages only. In the external validation cohorts, the discriminative potency only slightly changed. The model performed

similarly well across countries, potentially facilitating patient allocation in international studies.

In sensitivity analyses, various alternative models were tried via for instance incorporating positive lymph node number or lymph node ratio as a continuous variable in place of N stage into the nomogram, and the discrimination ability basically remained the same, supporting the robustness of the model.

Notably, the eighth edition of TNM staging system has been implemented since 2018 (Allen *et al.*, 2017; Schlitter *et al.*, 2017). Compared to the sixth/seventh version, in the eighth version new categories of tumor size (≤2, 2-4, and >4 *vs.* ≤2 and >2 cm) and positive node number (0, 1-3, and ≥4 *vs.* 0 and ≥1) are incorporated into T and N staging, respectively (Allen *et al.*, 2017; Kamarajah *et al.*, 2017; Schlitter *et al.*, 2017). However, after integrating these factors either as continuous or corresponding categorical variables into the nomogram, the performance did not markedly change. After transforming the SEER-18 staging data according to the eighth edition following Kamarajah *et al.* (Kamarajah *et al.*, 2017), the performance also remained very similar. Moreover, it will take considerable follow-up time for the survival associated with the new staging system to be adequately assessed. Therefore, the nomogram will still be applicable without compromised accuracy in the coming years.

Strengths of this study include the international population-based design, the largest number of resected PaC patients ever investigated, the extensive potential prognostic factors studied, the *uniformly- and consistently-defined variables* especially TNM stage across countries, and the consistency and quality control in reporting through applying rigorous registry data standards. *Analyses were performed separately in each respective country without pooling*, which avoids the impact of the potential heterogeneity across countries.

Resected PaC patients do not respond equally to chemotherapy, and accordingly, the calibration plots also suggest that individual survival varied greatly despite the relatively consistent comprehensive survival across countries. This study will help to initially stratify this patient population into subgroups with discrepant survival, and might potentially serve as a platform for developing further endeavors to understand factors associated with chemotherapy responses and survival in resected PaC, including precise, individualized, and personalized genomic and proteomic survivorship investigations.

Like any observational registry-based investigation, this study also has some limitations. The model predicts survival at the average population level, and when applying this model in specific centers or regions with different care patterns, there could be some inconsistencies between predicted and actual survival. Nevertheless, as revealed by the calibration plots, the real-world survival was still in good accordance with the prediction for a single individual. Residual confounding is a concern. Some significant variables (*e.g.*, tumor size) were only registered in certain databases. Differences in survival pattern across countries might be partly associated with variation in the prescription of chemotherapy and/or the underlying ethnic/racial distribution, even though association results

remained similar after limiting the US cohort to white. Notably there were some differences in patient and tumor characteristics across registries. For instance, in Slovenia, tumors were generally more advanced and poorly-differentiated, and the actual survival was the lowest. Nevertheless, these variables were adjusted for in the multivariable analyses.

Furthermore, population-based registries collected limited information on variables including family and patient health history and individual-level socioeconomic status, and the molecular or genetic subtype of PaC could not be determined (Cancer Genome Atlas Research Network. Electronic address and Cancer Genome Atlas Research, 2017), which probably plays a role in prognosis and explains the moderate C-index of the nomogram. Accordingly, the nomogram is limited by failure to incorporate these and other recognized prognostic parameters (*e.g.*, lymphatic and neurovascular invasion and type of chemotherapy). Further efforts on collection and incorporation of more relevant variables are encouraged to improve this model.

Notably, all known models predicting PaC survival perform very modestly (Brennan et al., 2004; Clark et al., 2008; de Castro et al., 2009; Ferrone et al., 2005; Tol et al., 2015). This nomogram with selection of only chemotherapy-treated resected PaC patients does not perform better compared to previous models with selection of all patients undergoing resection (Brennan et al., 2004; Clark et al., 2008; de Castro et al., 2009; Ferrone et al., 2005; Tol et al., 2015), which might limit the added value of the selection for the current nomogram. Furthermore, during the study period, the type of chemotherapy is mainly gemcitabine monotherapy, while the landscape of systemic treatment and treatment sequence for PaC are rapidly changing, which might limit the possible use of this nomogram.

Despite the moderate C-index, the agreement between predicted and actual survival was almost excellent. All variables included in the practical easy-to-use nomogram are easily-available in clinics, compared to the not-routinely-measured and costly molecular markers. It is herein the first time that the contributions of these risk factors are quantified and integrated into a single model for survival prediction in resected and chemotherapy-treated PaC with international validations.

4.1.5 Significance of examined lymph node number in accurate staging and long-term survival in resected stage I-II pancreatic cancer

In this part of the large population-based study, the association of ELN number with stage migration and long-term survival in resected PaC was analyzed. Stage migration analysis suggested that more ELNs were associated with a larger proportion of observed node-positive diseases in the entire resected PaC population of both the US and the Netherlands cohorts, after multivariable adjustment. This association was further confirmed by the trends of the mean PLN number and the probability of accuracy for observed node-negative disease with increasing ELN count. In both cohorts, associations between more ELNs and higher survival in both overall and node-positive diseases were observed. A minimal (12 ELNs) and optimal cut-point (19 ELNs) was then determined based on the associations

with stage migration and survival, respectively, in the derivative US cohort, and validated in both cohorts with the ability to well discriminate different probabilities of both survival and stage migration.

The ISGPS has recommended that the ELN number be reported in PaC pathologic analysis (Tol *et al.*, 2014b). However, there is no uniform conclusion yet on the association of ELN count with survival or on the threshold ELN number that could best address both stage migration and long-term survival in PaC (Ashfaq *et al.*, 2014; Hellan *et al.*, 2008; Huebner *et al.*, 2012; Lahat *et al.*, 2016; Michalski *et al.*, 2007; Pedrazzoli *et al.*, 1998; Riall *et al.*, 2005; Slidell *et al.*, 2008; Sun *et al.*, 2014; Tol *et al.*, 2014b; Valsangkar *et al.*, 2013; Wu *et al.*, 2014; Yeo *et al.*, 2002; Yeo *et al.*, 1999). Even the latest edition of TNM staging could not account for the heterogeneity of patient populations, surgical practice, and LN distribution maps. The PLN number at each ELN count was lower in the US than in the Netherlands, and the different ELN numbers observed in this study might reflect the discrepancy in practice patterns of surgeons and pathologists between the US and the Netherlands. The differences might be possibly explained by pathologists' practice, since the minimum requirement of 10 ELNs in the Netherlands could preclude some pathologists from searching for more, which would actually be associated with more accurate staging further.

In this observational hypothesis-generating analysis, while the association of more ELNs with higher survival was significant in multivariable-adjusted models both overall and in extensive stratifications, and ELN number was prognostically significant irrespective of the PLN number in patients with node-positive disease, *these do NOT suggest any causal relationship between ELN number and survival*. Several reasons potentially explain the observed survival association. First, more ELNs were associated with more accurate staging. Second, sampling of more LNs might reduce the risk of undetected PLNs. More ELNs were associated with better survival in patients with resectable node-positive disease where no stage migration would occur. Third, patients with observed node-negative disease and with fewer ELNs may include some who actually had node-positive disease. While evidence on the association of ELN number with long-term survival in resected PaC remains contradictory (Ashfaq *et al.*, 2014; Hellan *et al.*, 2008; Huebner *et al.*, 2012; Lahat *et al.*, 2016; Michalski *et al.*, 2007; Pedrazzoli *et al.*, 1998; Riall *et al.*, 2005; Slidell *et al.*, 2008; Sun *et al.*, 2014; Tol *et al.*, 2014b; Valsangkar *et al.*, 2013; Wu *et al.*, 2014; Yeo *et al.*, 2002; Yeo *et al.*, 1999), the results suggest the hypothesis of a positive association at the large population level. This hypothesis should be tested and validated in prospective studies. *Importantly, the survival association does not suggest causality, and might be largely due to stage migration.*

A minimal (12) and optimal cutoff of ELNs (19) for overall resected PaC were then identified, which might serve as an effective quality reference and metric to determine adequate LN sampling. So far, recommendations on ELN number have not been uniform in PaC, although some retrospective analyses have tried to set a benchmark, with proposed ELN number ranging from 11 to 17 for overall PaC (Ashfaq *et al.*, 2014; Huebner *et al.*, 2012; Valsangkar *et al.*, 2013). For correct staging of

pancreas body/tail cancers, an institutional report even suggested ≥20 LNs to be examined (Malleo *et al.*, 2018). A significant and independent association of ≥12 or ≥19 ELNs with decreased risk of mortality were further shown, especially in node-positive disease, in both cohorts. In standard lymphadenectomy for pancreatoduodenectomy where 12 LN stations are recommended to be resected (Tol *et al.*, 2014a), twelve ELNs could be achievable, while 19 ELNs might be somehow challenging. The recommendation of 12 ELNs was close to the suggestion by the AJCC/UICC which emphasized stage migration only. Although mostly slightly, the recommendation could vary with different demographic, clinical, and pathologic characteristics as shown in the stratified analyses. For some stratifications, associations were less uniform across cohorts, most likely due to the paucity of cases or because node status did not influence treatment. Notably, it was further found that younger patients achieved these thresholds in higher proportions in both cohorts (data not shown).

Notably, in the Netherlands, ≥19 ELNs were not associated with higher survival in node-negative disease, which was different from the case in the US. While this could be partly due to the much smaller proportion of patients with ≥19 ELNs among those with declared "N0" disease in the Netherlands compared to the US (8% *vs.* 23%), for early-stage lesions, limited resection might already provide sufficient favorable benefits, and it remains uncertain whether the stage migration benefit could be translated directly into improved patient outcomes. Attention should be exerted when applying the 19-ELN threshold to node-negative disease, for which the threshold could be lower. Notably, accuracy of a declared node-negative disease could also be affected by other factors beyond ELN count, and could vary across countries. It has always been difficult to identify the real "N0" disease before resection. More efficacious approaches to pre- or intra-operatively predict LN metastasis (*e.g.*, laparoscopic ultrasound) could be preferred.

Results from earlier randomized studies suggested that compared to standard lymphadenectomy, extended lymphadenectomy with largely varying ELNs and definitions was not associated with improved survival overall. Most of these studies were, however, insufficiently powerful due to immature survival data and/or small case number (Michalski *et al.*, 2007; Pedrazzoli *et al.*, 1998; Riall *et al.*, 2005; Sun *et al.*, 2014; Tol *et al.*, 2014b; Yeo *et al.*, 2002; Yeo *et al.*, 1999). While extended lymphadenectomy did not increase postoperative mortality, it tended to increase morbidity (Michalski *et al.*, 2007; Pedrazzoli *et al.*, 1998; Riall *et al.*, 2005; Sun *et al.*, 2014; Tol *et al.*, 2014b; Yeo *et al.*, 2002; Yeo *et al.*, 1999). Extended lymphadenectomy has thus not been recommended by the NCCN, ESMO, or ISGPS as a routine procedure, while it has been commonly performed in the US (Ducreux *et al.*, 2015b; Tempero *et al.*, 2017; Tol *et al.*, 2014b). A randomized controlled trial (RCT) (Pedrazzoli *et al.*, 1998) reported that compared to standard lymphadenectomy (mean ELN=13), extended lymphadenectomy (mean ELN=20) prolonged survival in node-positive but not in node-negative disease. Another RCT (Riall *et al.*, 2005; Yeo *et al.*, 2002; Yeo *et al.*, 1999) comparing extended (mean ELN=29) with standard lymphadenectomy (mean ELN=17) showed a trend toward overall higher 5-year survival in pancreatic adenocarcinoma patients undergoing extended lymphadenectomy (29%

vs. 13%). A later RCT (Farnell *et al.*, 2005) with a mean of 36 nodes resected during extended lymphadenectomy showed no survival difference. Notably, the mean ELN number would be too large in the extended group in most previous studies (Michalski *et al.*, 2007; Pedrazzoli *et al.*, 1998; Riall *et al.*, 2005; Sun *et al.*, 2014; Tol *et al.*, 2014b; Yeo *et al.*, 2002; Yeo *et al.*, 1999), compared to the thresholds determined. Excessive ELNs might even reduce survival, and there could be an upper threshold for ELN number after which the HR might markedly increase. However, this could not be determined in this study because of the small number of patients with relatively large ELN numbers. Further prospective/randomized studies on the extent of lymphadenectomy with more adequate ELN number and with nodal status-stratified analyses might be warranted, and the increase in morbidity and potential survival benefits should be well-balanced.

This study is limited by its observational nature. Data from observational studies can only detect associations, but cannot infer causality, and it cannot be concluded that examination or dissection of more LNs improves survival. The ultimate ELN number results from a collaboration between surgeons responsible for LN dissection and pathologists responsible for specimen examination and node identification. The reported ELN number might also be impacted by other confounders not available and not accounted for in this study, such as patient body mass index, immune status, surgical standards, difficulty in separating individual LN in dissected specimens, evaluators' expertise, and tumor biologic behaviors. Notably, reaching the threshold might not be possible for some patients with specific features, despite optimal surgery and pathologic assessment.

While clinical practice might have changed during the investigation period, year of diagnosis was included in multivariable analyses and subgroup analyses by limiting patients to those diagnosed in 2010 or later was performed, revealing very similar results. Multivariable analyses by accounting for every additional LN would reduce the impact of varying clinical practice. Multiple cancer histology types were initially included, considering the real-world practice and the consensus by the ISGPS that, in the presence of a solid mass suspicious for malignancy, biopsy proof has not been and is not required before proceeding with resection (Asbun et al., 2014). Subgroup analyses according to tumor histology were further performed. Since it is hardly possible to fully confirm an N0 disease before resection, patients regardless of LN status were initially included, with further subgroup analyses according to N stage conducted.

Other important aspects including LN station and location could not be investigated, the understanding of which might contribute to precise LN dissection. The ELN number is determined by both the stations and extent of LNs dissected. It needs to be further investigated whether the number of ELNs or the distribution of dissected LN stations is more prognostically significant in specific patient populations. While there was no information on dissected nodal stations, it would be difficult to incorporate this information into the models as an independent variable, given its strong correlation with nodal yield.

This study is the largest on the clinical significance and cut-point determination of ELNs in PaC

using multinational real-world cohorts with robust statistics and representative and generalizable results. The ELN number could be one of the quality assessment criteria and metrics. The recommendation potentially contributes to the consensus between surgeons and pathologists, especially regarding the degree of *en bloc* resection. *The results should NOT encourage surgeons to do more extended lymphadenectomies.*

4.2 Gastric cancer

This part of the large international population-based study reported the patient and tumor characteristics, resection trends, and treatment-associated factors for GC across Europe and the US in the early 21st century. Surprisingly, resection rates decreased for both non-metastatic and metastatic cancers. In non-metastatic cancers, for which resection remains the only curative treatment, this decreasing trend was consistently seen in various subgroups and could not be explained by several tumor and patient characteristics. Notably, overall patients were not less frequently treated in most countries, with increasing rates of non-surgical therapies.

The observed decreasing trends are consistent with some previous national studies from the US and the Netherlands in earlier periods. In the US, 63% of patients with non-cardia GC underwent resection during 1983-2002. During that period, resection rates declined by 6% units in all stages, and by even 20% units in local stages (Le *et al.*, 2007; McGhan *et al.*, 2012). Using the Nationwide Inpatient Sample in 1988-2000, a 20% stratified random sample representative of all US hospitals, gastric resection rate showed a 20% decline (Wainess *et al.*, 2003); however, rates of reduction operations for GC increased from 5% to 34% during 1990-2001 (Espat *et al.*, 2004). In the Netherlands, resection rates for stage I-III non-cardia cancer decreased from 71% (1989-1992) to 62% (2005-2008), while rates for cardia cancer remained relatively stable during that period (Dassen *et al.*, 2013); palliative resection rates for patients <70 (25% to 3%) and ≥70 years (26%-5%) both decreased from 1989-1993 to 2009-2013 (Nelen *et al.*, 2017). Resection trends in the other European countries have been rarely reported.

In Western countries, there is consensus that medically fit patients with non-metastatic resectable GC should undergo standardized resection in specialized, high-volume centers with appropriate surgical expertise and perioperative care (Begg *et al.*, 1998; Birkmeyer *et al.*, 2002; Dikken *et al.*, 2013). Volume-outcome associations have motivated centralization of surgical care worldwide (Coupland *et al.*, 2013), and morbidity and mortality have markedly decreased after GC resection (Lepage *et al.*, 2010). Still, many Western surgeons do not see sufficient GC patients to improve the surgical skills, and are more often faced with hurdles including more challenging body habitus, more comorbidities, and older ages (Bunt *et al.*, 1995). While the degree and the start time vary across countries, GC surgery has shown increasing trends towards centralization to high-volume specialized unites. It was found that the proportions of patients managed and of resections performed in academic

hospitals increased moderately in the Netherlands (2005-2014: 14%-22% and 17%-34%) and Belgium (2004-2013: 38%-43% and 40%-47%), and strongly in Sweden (2006-2016: 34%-70% and 38%-84%). In the US, proportions of gastrectomies performed at centers with ≥9 resections per year increased from 43% in 1988-1989 to 48% in 1999-2000 (Wainess *et al.*, 2003), although the number of gastric surgery per chief resident decreased from 12 in 1990 to 11 in 2001 (Espat *et al.*, 2004). It was found that the proportions of patients managed (27%-29%) and of resections performed (33%-33%) in hospitals with ≥20 annual gastric/esophageal resections remained relatively stable during 2005-2014 in the Netherlands, where centralization of GC surgery has essentially been imposed since 2012 only (Claassen *et al.*, 2018a; Claassen *et al.*, 2018b). Proportions of resections done in hospitals with ≥20 yearly resections increased moderately in Belgium (2004-2013: 18%-28%). In Sweden, proportions of patients treated (30%-72%) and of resections (32%-68%) performed in hospitals with ≥20 resections per year increased strongly in 2006-2016. It is expected that further centralization might retard or even reverse the decreasing trends in the years to come.

Palliative (R1/2) resection might not bring any benefit compared with exclusive medical treatment, but only increase posttreatment morbidity and mortality (Ajani *et al.*, 2016; Japanese Gastric Cancer, 2017; Smyth *et al.*, 2016). The fear of margin-positive resection might impede more and more surgeons from conducting resection especially in challenging situations. Increasing clear-margin (R0) resection rates have been observed among all resections for non-metastatic cancer in the Netherlands (2005-2014: 83%-88%) and Sweden (2006-2016: 83%-92%). Furthermore, proportions of resections with ≥15 examined lymph nodes for non-metastatic disease increased in the US (2004-2014: 36%-51%), the Netherlands (2005-2014: 32%-67%), and Sweden (2006-2016: 42%-82%). While these trends could partly reflect the surgical advances, they might also indicate the increasingly stricter selection criteria of resection candidates.

Some patients with metastatic GC underwent resection, albeit with decreasing trends observed in most countries. Patients with metastatic cancers are typically not suitable for curative surgical treatment (Thrumurthy *et al.*, 2013). The role of gastrectomy remains unclear in patients with technically operable metastatic GC (Japanese Gastric Cancer, 2017). Recent advances in chemotherapy have resulted in considerable tumor regression in many cases of inoperable GC, and might render them operable (Bouche *et al.*, 2004; Wagner *et al.*, 2010). Observational studies (de Gara *et al.*, 2003; Zhang *et al.*, 2011) showed that palliative resection might improve survival and quality of life in selected patients with advanced GC. There might be a subgroup of patients with metastatic GC for whom primary tumor resection with chemotherapy might improve survival (Warschkow *et al.*, 2018). In particular, selected patients with peritoneal carcinomatosis or positive peritoneal cytology might benefit from aggressive surgery in expert centers. A meta-analysis (Coccolini *et al.*, 2014) of 20 randomized trials suggested that cytoreductive surgery for GC with peritoneal carcinomatosis was associated with improved survival up to 3 years, but not at 5 years. Notably, no evidence in support of reduction gastrectomy for patients with limited metastatic disease, which aims to enhance survival by

reducing tumor volume, was found in the international REGATTA randomized trial (D'Ugo *et al.*, 2016; Fujitani *et al.*, 2016). However, in the phase II AIO-FLOT3 trial (Al-Batran *et al.*, 2017), patients with limited metastasis receiving neoadjuvant chemotherapy and proceeding to resection showed favorable survival. Until further evidence is presented, resection should be considered only experimental for metastatic GC patients or for palliative reasons in gastric outlet-obstructive tumors.

It was found that GC was most commonly diagnosed in patients ≥70 years and at stomach cardia, two factors that were associated with significantly less frequent resection. For elderly patients who are generally more frail the resection-upfront approach might be suboptimal unless specifically tailored (Cunningham and Chua, 2007). Geriatric evaluation would be helpful before initiating treatment for older patients. However, GC patients were getting increasingly younger in the investigated period. Cardia cancer often requires total gastrectomy and might be more surgically challenging (Sasako *et al.*, 2006). While its recent increasing incidence potentially impedes resection (Colquhoun *et al.*, 2015; Smyth *et al.*, 2016), resection rates for non-cardia cancer were also decreasing. Interestingly, compared to those with non-cardia cancers, the magnitude of decrease in resection rates with increasing age was markedly greater in patients with cardia cancers. Within non-metastatic tumors, cancers invading adjacent structures had lower R0 resection rates, which potentially bars resection. Recent advances in diagnostics have made the detection of patients with incurable advanced disease more efficient and thus made them less often referred for aggressive treatment (Ajani *et al.*, 2016; Kwee and Kwee, 2007). Patients with SRC GC, who are a rapidly increasing population and have a poor prognosis, have been shown to be inherently more resistant to chemotherapy, and might even be harmed by the delay in resection (Charalampakis *et al.*, 2016; Heger *et al.*, 2014; Messager *et al.*, 2011). Total gastrectomy is often required for SRC carcinoma (Sasako *et al.*, 2006). Notably, non-metastatic SRC cancers were less often surgically managed in some countries, and the differences between countries could be biased by differences in classification of SRC across countries. The different patterns and strengths of associations of resection with patient and tumor characteristics across countries and between non-metastatic and metastatic cancers highlight the variation in clinical practice and the need for standardization. The aforementioned factors could not fully explain the decreasing trends as indicated by multivariable analyses.

The rates of non-surgical therapies were further explored, which were increasing compared to the declining resection rates. Overall, patients did not receive markedly less frequent management. Following the pivotal MAGIC trial (Cunningham *et al.*, 2006), perioperative therapy is recommended as standard of care for most resectable GC planned for resection throughout many parts of Europe, and is increasingly favored over adjuvant treatment (Cunningham *et al.*, 2006; Ychou *et al.*, 2011). It is especially recommended for cardia cancer with invasion of serosa and/or adjacent structures and/or with positive nodes (Cunningham *et al.*, 2006; Ychou *et al.*, 2011). Two subsequent multicenter randomized trials (2008 (Cunningham *et al.*, 2008) and 2011 (Ychou *et al.*, 2011)) further reported benefits from perioperative chemotherapy and potentially resulted in wider application of neoadjuvant

treatment. While the preoperative approach might enhance resectability by down-staging tumor, it also allows substantial time for further growth of advanced cancers or metastases, which potentially impeded the application of resection. Greater access to and wider use of non-surgical care and pre-surgical chemotherapy-associated toxicity might also preclude some patients from receiving further resection (Macdonald, 2004; Stahl *et al.*, 2009). These factors may have implicated an overall increasingly less aggressive approach toward GC. However, it is unclear whether this change is due to a superior patient selection strategy, and the associated survival warrants further investigation.

Proper patient selection for treatment is paramount. Physician recommendation and expertise, and patient preference and adherence importantly impact treatment choice. In patients with unresected non-metastatic GC in the SEER-18, the proportion of those recommended for surgery decreased from 12% in 2004 to 11% in 2014. The aggressive nature of GC and historically poor outcomes even in the setting of operable disease should be discussed with patients before treatment. Patient performance, nutrition, and psychosocial statuses, organ function, medical history, tolerability, therapeutic burden especially cost, potential benefit from resection, postoperative morbidity and mortality, and quality of life should also be factored into treatment decisions. Combined modality therapy optimized by multidisciplinary teams is effective and essential for GC patients (Brar *et al.*, 2014; Cunningham *et al.*, 2006; Macdonald *et al.*, 2001).

This study was firstly limited by its observational nature. Some important variables were not recorded in certain countries, and the quality of registration might vary. While variables included in the main models were complete, some variables were not included in modeling due to the relatively high proportions of missing values (*e.g.*, differentiation). Proportions of unknown metastasis were particularly high in Belgium (22%) compared to the other countries (4%-10%). *Data were not pooled or compared between countries, considering the potential heterogeneity, but were analyzed, presented, and interpreted for each country separately.* It is noteworthy that in non-metastatic cancers the proportion of cardia cancer was very low in Slovenia (27%) and Estonia (12%), and SRC carcinoma was very often diagnosed in Estonia (28%). While this could be partly explained by differences in dietary and obesity patterns and the prevalence of *Helicobacter pylori* infection, potential variation in clinical and registry practice might also play a role which underlines the importance of further standardization. The investigated time periods were not totally identical. Nevertheless, they mostly covered the period 2003/2004-2013/2014, and year of diagnosis was adjusted for in all multivariable models.

Nevertheless, the largest sample size ever investigated, uniformly defined variables across nationwide population-based registries from multiple countries with potentially different health care systmes, careful case selection and quality control, and valid statistical methods enabled this report to show important results regarding treatment for GC that warrants clinicians' and policymakers' attention.

4.3 Conclusions

These large international population-based cohort study series in this dissertation/thesis show that:

4.3.1 Pancreatic cancer

The resection rates for PaC are generally low in Europe and the US with large international variations. Further investigations are warranted to further explore the reasons for these variations. Although the role of chemotherapy has been well established, its use remained very heterogeneous and of mostly low rates for both resected and unresected PaCs in Europe, despite major increases especially for resected tumors from 2003-2005 to 2012-2014. The benefit remaining controversial, radiotherapy was rarely administered, and its role needs to be clarified in further RCTs.

Comprehensive data on survival expectations of patients with resected PaCs are then provided, which are substantially higher than the widely available and known dismal survival of overall patients. Benefits of resection cannot be concluded from the observational study. However, the cancer TNM stage- and patient age group-stratified survival might be of help for clinical counselling. The estimated survival for advanced-stage cancers should be interpreted with caution due to potential underreporting. Patients with advanced stage and/or old age should undergo careful assessment before treatment. Limited but encouraging survival improvement is observed.

Independent factors associated and not associated with survival in patients with resected stage I-II PaC receiving chemotherapy are further revealed, with country-specific association patterns and strengths. A novel, robust, and reliable survival-predicting model was further established and internationally validated, which may provide the basis for more precise individualized survival estimation and which could be useful for clinical counselling for both doctors and patients. While with very good calibration, this nomogram together with all known models predicting survival in resected PaC performs modestly.

More ELNs are associated with more accurate nodal staging, which might to a great extent explain the association with higher survival in resected PaC in the observational study, and no definitive conclusions on causality or benefits should be drawn. The analysis suggests 12 and 19 ELNs as potential minimal and optimal cut-points for the overall quality assessment regarding LN examination in clinical practice and for postoperative prognosis stratification especially in node-positive disease. These findings should be further validated in prospective studies.

4.3.2 Gastric cancer

Both non-metastatic and metastatic GCs were less frequently surgically managed in Europe and the US in the early 21st century. While the decreasing trends could not be explained by various variables associated with resection, they were accompanied by increasing non-surgical therapy use. Since

resection remains the only potentially curative treatment for most non-metastatic resectable GCs, the appropriateness of such trends warrants further investigation. Further centralization might be needed to weaken or reverse the decreasing resection trends.

5 SUMMARY

In this dissertation large international population-based cohorts of pancreatic cancer (PaC) and gastric cancer (GC) patients registered in multiple European national population-based cancer registries from the Netherlands, Belgium, Norway, Denmark, Sweden, Slovenia, and Estonia and the US Surveillance, Epidemiology, and End Results (SEER-18) Program database in the early 21st century were analyzed.

For pancreatic cancer:

Resection can potentially cure resectable PaC and significantly prolong survival in some patients. The role of chemotherapy in the management of PaC has been well established, while radiotherapy plays ambiguous roles. The prognosis of resected and overall (resected and unresected) PaC varies strongly across different stages and age groups. Prognostic factors for resected PaC receiving chemotherapy at the population level remains largely unexplored, and there lacks a corresponding population-based tool to predict survival. Examined lymph node (ELN) number is an important quality metric in cancer care.

The PaC part of this thesis aimed to investigate the variations in resection for PaC, the real-world use of chemotherapy and radiotherapy for resected and unresected PaC, and the determinants for the use of the treatment modalities, to provide TNM stage- and age group-specific survival estimates and trends in resected and overall PaC, to explore factors associated with survival in patients with resected TNM stage I-II PaC receiving chemotherapy, to develop and internationally validate a population-based survival-predicting model for this patient group, to investigate the associations of ELN number with accurate staging and long-term survival, and to determine the ELN thresholds.

In 2012-2014, age-standardized resection rates ranged from 13.2% (Estonia) to 21.2% (Slovenia) overall and from 34.8% (Norway) to 68.7% (Denmark) for stage I-II cancers, with large international variations. During 2003-2014, resection rates only increased in the US, the Netherlands, and Denmark. Using multivariable logistic regression, resection was found to be significantly less frequently performed with more advanced tumor stage and increasing age. Patients with stage III-IV tumors and aged ≥70 years comprised the majority. Performance status, location, and size were also associated with resection use.

From 2003 to 2014, age-standardized chemotherapy use rates increased in most countries and more strongly for resected patients, while radiotherapy use was generally rare with a slight decline or no obvious trend. In 2012-2014, 12.5% (Estonia) to 61.7% (Belgium) of resected and 17.1% (Slovenia) to 56.9% (Belgium) of unresected patients received chemotherapy. Radiotherapy was used for 2.6% (the Netherlands) to 32.6% (the US) of resected and 1.0% (the US) to 6.0% (Belgium) of unresected patients. Strong temporal and geographical variations were observed. Patterns and strengths of associations of treatment use with various demographic and clinical factors differed substantially between resected and unresected cancers and varied greatly across countries.

Overall, age-stratified 3-year survival was 20%-34% (<60 years), 14%-25% (60-69 years), and 9%-13% (≥70 years) in stage I-II PaC, and 2%-5% (<60 years), 1%-2% (60-69 years), and <1%-1% (≥70 years) in stage III-IV cancer. Operated patients had higher 3-year survival in each stage and age group (stage I-II: 23%-39% (<60 years), 16%-31% (60-69 years), and 17%-30% (≥70 years); stage III-IV: 5%-19% (<70 years) and 2%-14% (≥70 years)). Perioperative survival also decreased with advancing stage and older age. In 2003-2011, for overall PaC, both short-term and long-term survival improvements were observed in all countries except Belgium; for resected disease, short-term improvements were present only in the US and Slovenia, but long-term improvements in all countries except Slovenia, with stage-specific variations.

In patients with resected stage I-II PaC receiving chemotherapy, the median survival time was 18-23

months with 3-year survival rates of 21%-31%. In the main analysis, patient age, tumor T stage, N stage, and differentiation were independently associated with survival across most countries, with country-specific patterns and strengths. Resection margin, hospital type, tumor size, positive and harvested lymph node number, lymph node ratio, and comorbidity number were associated with survival in countries with available information. A median survival time- and 1- to 5-year survival probability-predictive nomogram incorporating the backward-selected prognostic variables in the main analysis of SEER-18 was built. It fits the European cohorts similarly well. Calibration curves showed very good agreement between nomogram-prediction and actual observation. The concordance-index of the nomogram was significantly higher than that of the T and N stage-based model for predicting survival. It was validated both internally using bootstrap and externally in the European datasets.

In patients with resected stage I-II PaC registered in the US SEER-18 Program and the Netherlands National Cancer Registry (NCR), with increasing ELN number, both cohorts exhibited significant proportional increases from node-negative to node-positive disease and serial improvements in survival after controlling for confounders, in both overall and most stratified analyses. Cut-point analyses of the series of the odds ratios for stage migration and the hazard ratios for survival with more ELNs in the derivation SEER-18 cohort suggested a minimal threshold ELN number of 12 and an optimal number of 19, respectively, which were validated both internally and externally.

In conclusion, in Europe and the US in the early 21st century, rates of PaC resection remain low with large international variations. Use of chemotherapy but not radiotherapy increased, but treatment rates were low and the uptake varied strongly across countries. These highlight the need for standardization in PaC treatment to improve patient care, and further studies are warranted to explore reasons for these variations. TNM stage- and age-specific population-based survival in overall and resected PaC are further provided, which will facilitate clinical counseling. Patients with advanced-stage disease and/or older age should undergo careful risk assessment before treatment. Some limited but encouraging improvement in survival was observed. Resected PaC patients receiving chemotherapy have distinct characteristics independently associated with survival, with country-specific patterns and strengths. A robust benchmark population-based personalized survival-predicting model was established and internationally validated, which would be easy-to-use, practical, and helpful clinically and aid to patient allocation in international studies. More ELNs are associated with more precise nodal staging, which might largely explain the survival association. 12 and 19 ELNs are suggested as the minimal and optimal cut-points, respectively, for evaluating quality of lymph node examination and possibly for stratifying postoperative prognosis.

For gastric cancer:

Resection is potentially curative for many resectable non-metastatic GCs, and some metastatic GCs are technically resectable. The GC part of this thesis aimed at investigating the resection trends for non-metastatic and metastatic GCs and at exploring the underlying reasons for the trends.

Resection rates significantly decreased in all countries for non-metastatic cancers and in all countries except the Netherlands, Slovenia, and Estonia for metastatic cancers. Patients with increasing ages, cardia cancers, or cancers invading adjacent structure were significantly less often resected. Resection was also associated with patient sex, performance status, comorbidities, tumor histology, size, hospital type and volume. Association patterns and strengths varied across countries. After adjusting for the associated factors, resection rates remained decreasing for both non-metastatic and metastatic cancers. Rates of non-surgical therapies increased, making the overall treatment rates mostly stable or slightly increasing.

In conclusion, both non-metastatic and metastatic GCs were less frequently surgically managed in Europe and the US in the early 21st century. While the decreasing trends could not be explained by various variables associated with resection, they were accompanied by increasing non-surgical therapy use. The survival relevance of such trends warrants further investigation.

6 ZUSAMMENFASSUNG

In dieser Dissertation wurden große internationale bevölkerungsbezogene Kohorten von Bauchspeicheldrüsenkrebs- (PaC) und Magenkrebspatienten (GC), die in europäischen nationalen bevölkerungsbezogenen Krebsregistern aus den Niederlanden, Belgien, Norwegen, Dänemark, Schweden, Slowenien und Estland sowie der SEER-18 (US Surveillance, Epidemiology, and End Results) Datenbank aus der USA im frühen 21. Jahrhundert registriert wurden, analysiert.

Für Bauchspeicheldrüsenkrebs (PaC):

Eine Resektion hat das Potenzial, resezierbare PaC zu heilen und bei einigen Patienten das Überleben signifikant zu verlängern. Die Rolle der Chemotherapie bei der Behandlung von PaC ist gut belegt, während die Strahlentherapie eine unklare Rolle spielt. Die Prognose nach resezierten PaC und nach PaC ingesamt (reseziert und nicht-reseziert) variiert stark zwischen den verschiedenen Stadien- und Altersgruppen. Auf Bevölkerungsebene sind prognostischen Faktoren bei resezierten PaC nach Erhalt einer Chemotherapie noch weitgehend unerforscht, und es fehlt ein entsprechendes populationsbasiertes Werkzeug zur Vorhersage des Überlebens. Die Zahl der untersuchten Lymphknoten (ELN) ist eine wichtige Qualitätskennzahl in der Krebsbehandlung.

Der Abschnitt dieser Arbeit zu PaC zielte darauf ab, zeitliche und regionale Unterschiede der Nutzung einer Resektion bei PaC und der Administration von Chemotherapie und Strahlentherapie für resezierte und nicht-resezierte PaC zu beschreiben. Darüber hinaus wurden Determinanten für die Verwendung dieser Behandlungsmodalitäten untersucht. Auch wurden Stadien- und altersspezifische Überlebensschätzer und Trends bei resezierten PaC und der Gesamtgruppe von PaC Patienten berechnet. Es wurden Faktoren untersucht, die potentiell mit dem Überleben in Stadium I-II PaC Patienten, die eine Chemotherapie erhalten haben, assoziiert sind. Ein weiteres Ziel war die Entwicklung und internationale Validierung eines bevölkerungsbezogenen Modells zur Vorhersage des Langzeitüberlebens in dieser Patientengruppe. Außerdem wurde die Assoziation zwischen der Anzahl der ELN und einer akkuraten Stadienvergabe und dem Langzeitüberleben untersucht und ein Schwellenwert für die Anzahl der ELN ermittelt.

Im Zeitraum 2012-2014 schwankten die altersstandardisierten Resektionsraten von 13,2% (Estland) bis 21,2% (Slowenien) insgesamt und von 34,8% (Norwegen) bis 68,7% (Dänemark) für Stadium I-II PaC. Steigende Resektionsraten im Zeitraum 2003-2014 waren nur in den USA, den Niederlanden und Dänemark sichtbar. Mit Hilfe der multivariablen logistischen Regression wurde gezeigt, dass eine Resektion signifikant seltener mit fortgeschrittenem Tumorstadium und steigendem Alter durchgeführt wurde. Die meisten Patienten hatten Tumoren im Stadium III-IV und waren ≥70 Jahren. Performancestatus, Lokalisation und Tumorgröße waren auch mit der Durchführung einer Resektion assoziiert.

Von 2003 bis 2014 stieg die altersstandardisierte Nutzungsrate der Chemotherapie in den meisten Ländern an, mit größten Steigerungen bei resezierten Patienten, während die Strahlentherapie im Allgemeinen selten durchgeführt wurde, mit einem leichten Rückgang oder keinem offensichtlichen Trend. Im Zeitraum 2012-2014 erhielten 12,5% (Estland) bis 61,7% (Belgien) der resezierten und 17,1% (Slowenien) bis 56,9% (Belgien) der nicht resezierten Patienten eine Chemotherapie. Die Strahlentherapie wurde bei 2,6% (Niederlande) bis 32,6% (USA) der resezierten und 1,0% (USA) bis 6,0% (Belgien) der nicht resezierten Patienten eingesetzt. Starke zeitliche und geografische Unterschiede wurden beobachtet. Die Muster und Stärken der Assoziationen zwischen der Durchführung dieser Behandlungen und verschiedenen demographischen und klinischen Faktoren unterschieden sich erheblich zwischen resezierten und nicht resezierten PaC und waren in den einzelnen Ländern sehr unterschiedlich.

Insgesamt betrug das altersstandardisierte 3-Jahres-Überleben 20%-34% (<60 Jahre), 14%-25% (60-69 Jahre) und 9%-13% (≥ Jahre) in Stadium I-II PaC, und 2%-5% (<60 Jahre), 1%-2% (60-69 Jahre) und <1%-1% (≥ Jahre) in Stadium III-IV PaC. Die operierten Patienten hatten in jeder Phase und Altersgruppe eine höhere 3-Jahres-Überlebensrate (Stadium I-II: 23%-39% (<60 Jahre), 16%-31% (60-69 Jahre) und 17%-30% (≥70 Jahre); Stadium III-IV: 5%-19% (<70 Jahre) und 2%-14% (≥70 Jahre)). Das perioperative Überleben nahm mit fortschreitendem Stadium und höherem Alter ebenfalls ab. Im Zeitraum 2003-2011 wurden in allen Ländern mit Ausnahme Belgiens Verbesserungen im Kurz- und Langzeitüberleben beobachtet; bei resezierten PaC hat sich das Kurzzeitüberleben nur in den USA und Slowenien verbessert, wogegen das Langzeitüberleben in allen Ländern mit Ausnahme Sloweniens anstieg, wobei es unterschiedliche Trends in den einzelnen Stadiengruppen gab.

Bei Patienten mit reseziertem Stadium I-II PaC, die eine Chemotherapie erhalten haben, betrug die mediane

Überlebenszeit 18-23 Monate mit 3-Jahres-Überlebensraten von 21%-31%. In der Hauptanalyse waren Patientenalter, Tumor-T-Stadium, N-Stadium und Differenzierung unabhängig voneinander in den meisten Ländern mit dem Überleben assoziiert, wobei es Unterschiede zwischen den Ländern gab. Resektionsrand, Krankenhaustyp, Tumorgröße, Anzahl der positiven und entnommenen Lymphknoten und die Anzahl der Komorbiditäten waren in Ländern mit verfügbaren Informationen mit dem Überleben assoziiert. Es wurde ein Nomogramm zur Vorhersage der medianen Überlebenszeit und der 1- bis 5-Jahres-Überlebenswahrscheinlichkeit auf den SEER-18 Daten erstellt, welches auf prognostischen Faktoren beruht, die mithilfe von backward-selection ausgewählt wurden. Dieses Nomogramm erreichte auch gute Vorhersagen in anderen europäischen Kohorten. Die Kalibrierungskurven zeigten eine sehr gute Übereinstimmung zwischen Nomogramm-Vorhersage und tatsächlicher Beobachtung. Der Konkordanzindex des Nomogramms war signifikant höher als bei einer Vorhersage basierend auf T- und N-Stadium. Das Nomogramm wurde sowohl intern mittels Bootstrap als auch extern in den europäischen Datensätzen validiert.

Bei Patienten mit reseziertem Stadium I-II PaC, die im SEER-18 Programm oder im nationalen niederländischen Krebsregister registriert wurden, zeigte sich nach Adjustierung für Störfaktoren mit steigender ELN-Zahl signifikante Erhöhungen von dem Anteil Lymphknoten-negativer zu Lymphknoten-positiver Erkrankung und kontinuierliche Überlebenszeitverbesserungen, sowohl in der Gesamtgruppe als auch in den meisten Subgruppen. Analysen der SEER-19 Daten zur Bestimmung der optimalen Anzahl der ELN im Hinblick auf die Stadienvergabe und des Überlebens ergaben einen minimalen Schwellenwert von 12 und einen optimalen Schwellenwert von 19 ELN. Diese Schwellenwerte wurden sowohl intern als auch extern validiert.

Zusammenfassend lässt sich sagen, dass in Europa und den USA zu Beginn des 21. Jahrhunderts die Rate der PaC-Resektion niedrig bleibt und große internationale Unterschiede aufweist. Der Einsatz von Chemotherapie (aber nicht der Radiotherapie) nahm zu, aber die Behandlungsraten waren niedrig und sehr unterschiedlich in den einzelnen Ländern. Diese Ergebnisse zeigen die Notwendigkeit einer Standardisierung der PaC-Behandlung zur Verbesserung der Patientenversorgung. Außerdem sollten in weiteren Studien die Gründe für diese Unterschiede im Detail untersucht werden. Die Bereitstellung von Stadien- und altersspezifischen bevölkerungsbezogenen Überlebensraten für PaC insgesamt und reseziertes PaC wird die klinische Beratung erleichtern. Bei Patienten mit Erkrankungen im fortgeschrittenen Stadium und/oder im höheren Lebensalter sollte vor der Behandlung eine sorgfältigen Risikobewertung durchgeführt werden. Kleine aber vielversprechende Verbesserungen des Überlebens wurden beobachtet. Bei resezierten PaC-Patienten, die eine Chemotherapie erhalten haben, sind spezielle Faktoren mit dem Überleben assoziiert, aber die Assoziationen unterscheiden sich zwischen den Ländern. Ein robustes Modell zur populationsbasierten personalisierten Überlebensvorhersage, das einfach zu nutzen ist und die Patientenauswahl für internationalen Studien erleichtert, wurde mit dieser Arbeit erstellt und international validiert. Mehr ELNs sind mit einer präziseren Lymphknoten-Stadienvergabe assoziiert, was die Überlebensassoziation weitgehend erklären könnte. 12 und 19 ELNs werden als minimale bzw. optimale Schwellenwerte vorgeschlagen, um die Qualität der Lymphknotenuntersuchung zu bewerten und eventuell die postoperative Prognose zu stratifizieren.

Für Magenkrebs (GC):

Bei resektablen nicht-metastasierten GCs ist eine Resektion potenziell heilend. Einige metastatische GCs sind technisch resektabel. Der GC-Teil dieser Arbeit zielte auf die Untersuchung der Trends in den Resektionsraten bei nicht-metastasierte und metastasierte GCs und auf die Erforschung der zugrundeliegenden Gründe für die Trends ab.

Die Resektionsraten sind bei nicht-metastasierende GC in allen Ländern und bei metastasierende GC in allen Ländern mit Ausnahme der Niederlande, Sloweniens und Estlands deutlich gesunken. Patienten mit zunehmendem Alter, mit Kardiakrebs oder GC, der in die angrenzende Struktur eingedrungen ist, wurden deutlich seltener operiert. Die Resektion war auch mit dem Geschlecht des Patienten, dem Leistungsstatus, den Komorbiditäten, der Tumorhistologie, der Tumorgröße, dem Krankenhaustyp und dem Krankenhausvolumen assoziiert. Die Assoziationsmuster und -stärken waren in den einzelnen Ländern unterschiedlich. Nach Adjustierung für diese Faktoren blieben die Resektionsraten sowohl bei nicht-metastasierenden als auch bei metastasierenden GC jährlich rückläufig. Die Rate der nicht-chirurgischen Therapien stieg, so dass die Gesamtbehandlungsraten weitgehend stabil oder leicht ansteigend waren.

Zusammenfassend lässt sich sagen, dass sowohl nicht-metastasierte als auch metastasierte GCs im frühen 21. Jahrhundert in Europa und den USA weniger häufig operativ behandelt wurden. Während die rückläufigen Trends nicht durch die mit der Resektionsdurchführung assoziierten Variablen erklärt werden konnten, gingen sie mit einer Zunahme der nicht-chirurgischen Therapien einher. Der Einfluss dieser Trends auf Überleben muss in weiteren Studien untersucht werden.

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8 OWN PARTICIPATION IN DATA COLLECTION AND ANALYSES AND LIST OF OWN PUBLICATIONS

The requested population-based data were collected and delivered by the respective included registries, following uniform standardized variable lists created by me. The data collection was coordinated by me. All the data analyses in this thesis/dissertation were completely done by me myself, and were then checked and validated by the statistician Dr. Yesilda Balavarca.

Some parts of the present work have been published in the following articles:

1 **Huang, L.**, Jansen, L., Balavarca, Y., Molina-Montes, E., Babaei, M., van der Geest, L., Lemmens, V., Van Eycken, L., De Schutter, H., Johannesen, T. B., Fristrup, C. W., Mortensen, M. B., Primic-Žakelj, M., Zadnik, V., Becker, N., Hackert, T., Mägi, M., Cassetti, T., Sassatelli, R., Grützmann, R., Merkel, S., Goncalves, A. F., Bento, M. J., Hegyi, P., Lakatos, G., Szentesi, A., Moreau, M., van de Velde, T., Broeks, A., Sant, M., Minicozzi, P., Mazzaferro, V., Real, F. X., Carrato, A., Molero, X., Besselink, M. G., Malats, N., Buchler, M. W., Schrotz-King, P. and Brenner, H. (2017). **Resection of pancreatic cancer in Europe and the US: an international large-scale study highlighting large variations**. Gut, doi: 10.1136/gutjnl-2017-314828.

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3 **Huang, L.**, Jansen, L., Balavarca, Y., van der Geest, L., Lemmens, V., Van Eycken, L., De Schutter, H., Johannesen, T. B., Primic-Žakelj, M., Zadnik, V., Mägi, M., Pulte, D., Schrotz-King, P. and Brenner, H. (2018b). **Nonsurgical therapies for resected and unresected pancreatic cancer in Europe and USA in 2003-2014: a large international population-based study**. Int J Cancer, doi: 10.1002/ijc.31628.

Chapters 1.1.1, 1.1.2 (except the last two paragraphs), 2.1.1, 2.2.1, and 2.2.2 are covered in part by

Publication 1, **2**, and/or **3**. **Publication 1** covers Chapters 2.1.2, 2.2.3, 3.1.1, and 4.1.1 in this dissertation; **Publication 2** covers Chapters 2.2.4, 3.1.2, and 4.1.2 in this dissertation; **Publication 3** covers 2.2.5, 3.1.3, and 4.1.3 in this dissertation. Permissions and licenses to reuse the figures, tables, and texts of the published articles in this dissertation/thesis have been obtained from the publishers. **Publication 2** is an open access article, which is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

My contributions to all the publications include literature review, study conception, design, and full coordination, proposal and protocol writing, application for ethics approval, registry search and contact, establishment of common standardized databases, acquisition, harmonization, analyses, and interpretation of all data, drafting, writing, revision, and finalizing of all manuscripts, and approval of all the final versions.

Meeting abstracts:

1 **Huang, L.**, Jansen, L., Balavarca, Y., Babaei, M., van der Geest, L., Lemmens, V., Van Eycken, L., De Schutter, H., Johannesen, T. B., Primic-Žakelj, M., Zadnik, V., Besselink, M. G., Schrotz-King, P. and Brenner, H. (2018). **Survival of resected and overall pancreatic cancer patients in Europe and the US in 2003-2014: An international large-scale population-based investigation**. Journal of Clinical Oncology *36(15_suppl)*, doi: 10.1200/JCO.2018.36.15_suppl.e16251.

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EIDESSTATTLICHE VERSICHERUNG

1. Bei der eingereichten Dissertation zu dem Thema
   Investigation of treatment modalities and outcomes concerning pancreatic and gastric cancer patients in Europe and the US
   handelt es sich um meine eigenständig erbrachte Leistung.

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Ort und Datum Unterschrift

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