Quality of care for pancreatic cancer patients, with focus on the elderly

Lydia van der Geest

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PhD thesis, University of Amsterdam, The Netherlands

ISBN: 978-94-6375-239-8
Cover design and layout: Marlies van Hoof | www.madebymarlies.nl
Printed by: Ridderprint BV | www.ridderprint.nl

The printing of this thesis is financially supported by:
Netherlands Comprehensive Cancer Organisation (IKNL), University of Amsterdam (UvA), Dutch Pancreatic Cancer Group (DPCG)

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus

Prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 15 februari 2019, te 10.00 uur

door Leboeria Gijsbertha Maria van der Geest
geboren te Woubrugge

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Chapter 1

General introduction

The pancreas

The pancreas is an organ of about 15 cm long and located in the retroperitoneum behind the stomach in the upper abdomen. The head of the pancreas is located next to the first part of the small intestine (duodenum). The central section of the pancreas is called the neck or body whereas the thin end is called the tail, which extends towards the spleen on the far left side of the abdomen. Several major blood vessels towards the liver and bowels are located directly behind the pancreas. The pancreas has two main functions: an exocrine function in which enzymes are produced and released into the duodenum to help digest fats, carbohydrates, and proteins, and an endocrine function that regulates blood sugar level. Most common disorders affecting the exocrine pancreas include pancreatitis, premalignant conditions (such as pancreatic intraepithelial neoplasia [PanIN] and intraductal papillary mucinous neoplasm [IPMN]), and pancreatic cancer.

An aging population

In many Western countries, a so-called 'double aging' is taking place; people are getting older due to improved health care and living conditions. As well as that the post-war born baby boom generation is currently reaching an older age. In the next three decades, the proportion and absolute number of older persons in the Dutch population will continue to rise. For example, the proportion of persons aged 70 years or older in the general population will increase from 10% in 2015 to 20% in 2045 in men and from 13% to 22% in women. The absolute number of octogenarians (aged 80 years and older) in the Netherlands will increase by 2.5-3 times from approximately 730,000 persons in 2015 to 2,000,000 at its' top in 2055 (**Figure 1**) [1].

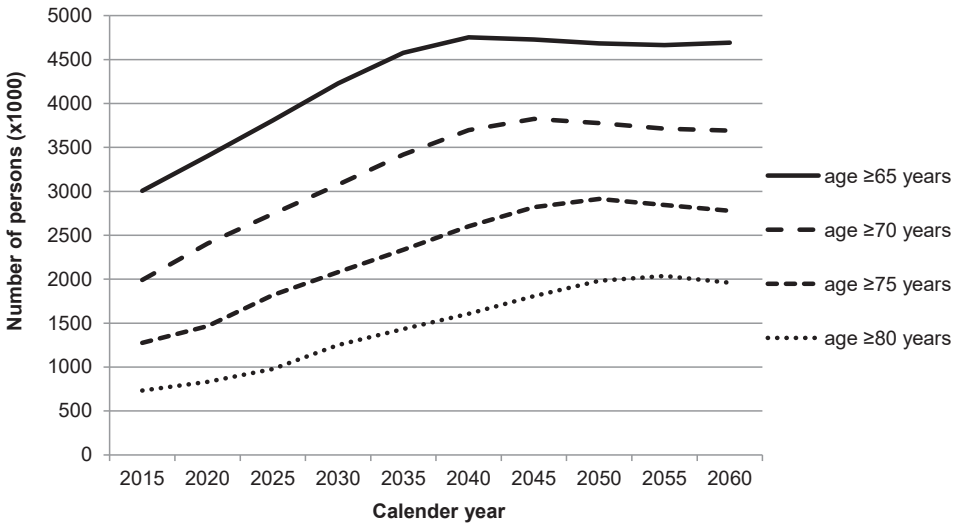

Figure 1. Projection of elderly persons in the next decades in the Netherlands.

In the past decades in the Netherlands, the remaining life expectancy at advanced age has gradually increased. At the age of 70, the remaining life expectancy in 1985 was 12 years in men and 16 years in women, in 2017 this had been increased to 16 years and 18 years respectively [1]. Elderly persons who reach the age of 80 in 2017, still exhibit a remaining life expectancy of 9 years in men and 10 years in women.

Pancreatic cancer epidemiology

Incidence, mortality, survival

Pancreatic cancer is a less common type of cancer. With 2.3% of all cancer diagnoses in the Netherlands, pancreatic cancer is the 10th leading type of cancer in males and the 8th type of cancer in females [2]. In the past decade, the absolute number of newly diagnosed patients with pancreatic cancer in the Netherlands has increased from about 1,700 in 2005 to at least 2,400 patients in 2017.

Pancreatic cancer is a highly fatal cancer accounting for 5.8% of cancer deaths in the Netherlands. It was the 7th and 6th most common cause of death from cancer in males and females respectively in 2017 [1]. The prognosis after a pancreatic cancer diagnosis is extremely poor, with 1- and 5-year relative survival rates of 20% and 6% respectively in the Netherlands [2].

Risk factors

Older age is the most important risk factor for developing pancreatic cancer, while the leading (avoidable) risk factor is cigarette smoking. Other known risk factors are chronic pancreatitis, overweight and obesity, diabetes mellitus, diet features, and family history of pancreatic cancer. Known genetic syndromes with an elevated risk of pancreatic cancer are BRCA2, familial atypical multiple mole melanoma syndrome (FAMMM), Lynch syndrome (also known as hereditary non-polyposis colorectal cancer syndrome HNPCC), and the Peutz-Jeghers syndrome [3]. Although alcohol is not a risk factor for developing pancreatic cancer, (excessive) alcohol use is a known risk factor for pancreatitis and thereby indirectly related to cancer.

Pancreatic carcinoma

Pancreatic cancer is often used synonymously to exocrine pancreatic cancer (approx. 95% of all cases) or invasive pancreatic ductal adenocarcinoma (PDAC, approx. 90% of all histological verified cases, 8500, including subtypes 8020, 8035, 8154, 8480, 8490, 8560/3) [4]. The second most common type of pancreatic cancer, pancreatic neuroendocrine tumours (NET), represent less than 5% of all cases and have a less poor prognosis compared with adenocarcinoma. Other epithelial pancreatic cancers are rare, for example cystic carcinoma (serous cystadenocarcinoma 8441/3, mucinous cystadenocarcinoma 8470/3), invasive intraductal papillary-mucinous carcinoma (8453/3), acinar cell carcinoma (8550/3, 8551/3, 8154/3), pancreatoblastoma (8971/3, young age), and solid-pseudopapillary carcinoma (8452/3) [4]. Cases without histological verification generally are considered pancreatic adenocarcinoma.

Symptoms
About two-third of pancreatic cancers are located in the pancreatic head. Common symptoms of pancreatic cancer include yellow-coloured skin (jaundice) and light-coloured stools due to obstruction of the bile duct in patients with pancreatic head cancer. Pain, particularly epigastric pain that radiates to the back, is the main symptom in patients with pancreatic tail cancer. Other symptoms are unintended weight loss, loss of appetite, fatty faeces and or nausea. At an early stage of the disease, usually no or only nonspecific symptoms are present. As a result, most patients with pancreatic cancer are not diagnosed until the cancer has spread to adjacent structures or distant organs [3, 5].

Quality of care concepts

More than 15 years have passed since the USA Institute of Medicine published their reports "To err is human: building a safer health system" (2000) and "Crossing the quality chasm: a new health care system for the 21st century" (2001) [6, 7]. These landmark reports were followed by many efforts to improve safety and quality in health care. Delivered care should be safe, effective, patient-centered, timely, efficient and equitable. Measurement is central to the concept of quality improvement. To identify opportunities for improvement, health care providers need to know what they actually do in clinical practice (in Dutch: "meten is weten").

The most commonly used classification of quality indicators is the structure - process – outcome classification by Donabedian [8, 9]. Preferably, quality indicators are evidence-based and derived from the academic literature (e.g. Cochrane Collaboration literature syntheses, meta-analyses, or randomised controlled trials). The scientific evidence needs to be transformed into concrete recommendations (specification). However, when scientific evidence is weak or even lacking or impossible to obtain, quality indicators are often determined by an expert panel of health professionals and patients in a consensus process [9]. For example, quality indicators covering timeliness and patient-centeredness of care often miss a strong evidence-base. Quality indicators that focus on provider volume are proxy measures [10]. Evidence suggests that hospitals (and physicians) achieve better outcomes when they perform more of intensive, highly complex, or high-technology procedures a year. Not surprisingly, volume standards especially apply to surgical procedures.

Guidelines are aimed at improving outcome of care by optimizing knowledge on evidence-based management of care processes. The development of evidence-based guidelines is performed by (temporary) multidisciplinary collaboration of clinicians who are mandated by their professional society. In the Netherlands, these collaborations were supported by the Netherlands Comprehensive Cancer Organisation (IKNL). The RAND-modified Delphi-method is a frequently used method to prioritise guideline recommendations or quality indicators on relevance for health outcomes (effectiveness, safety, costs) and applicability (acceptable, measurable, improvable), and combines both anonymous surveys and panel discussions of experts. Further operationalisation results in a specified population and detailed definition for each quality indicator [11].

Pancreatic cancer care

Diagnosis
Several radiologic techniques can be used to diagnose a suspected pancreatic tumour, such as multidetector computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS). CT and MRI have comparable sensitivities and specificities, and both can also be used to evaluate distant metastases and to make 3-dimensional reconstructions on the relationship of the tumour to nearby large blood vessels [3, 12]. The gold standard for establishing any cancer diagnosis is pathology. Particularly before starting chemotherapy or chemoradiotherapy, either neoadjuvant or palliative, confirmation of the malignancy is mandatory [13]. Microscopic confirmation is obtained by puncture of a liver metastasis, by fine needle aspiration at the time of Endoscopic UltraSound (EUS-FNA), or by brush cytology or intraductal biopsy at the time of Endoscopic Retrograde Cholangio Pancreaticography (ERCP). Diagnostic results should be discussed by a multidisciplinary tumour board (MTB) with adequate pancreatic cancer expertise to determine resectability and optimal treatment [14].

Treatment
Only 10-20% of patients diagnosed with pancreatic cancer has a resectable tumour [5]. A pancreatoduodenectomy (PD) is the most commonly performed pancreatic resection (Kausch-Whipple or pylorus-preserving). A PD is performed for cancer located in the head of the pancreas or in the periampullary region (ampulla of Vater, distal bile duct, duodenum). A distal pancreatectomy is performed for cancers in the body or tail of the pancreas and includes the spleen to obtain adequate lymphadenectomy. Sporadically, a total pancreatectomy is performed. Following several randomised studies published between 2007 and 2010 [15-17], adjuvant chemotherapy with gemcitabine has become standard of care for pancreatic cancer patients in the Netherlands [14].

In 50-60% of pancreatic cancer patients, distant metastases are found at time of diagnosis [18]. From 1997 onwards, gemcitabine monotherapy has been the cornerstone of systemic treatment for metastatic pancreatic cancer [14, 19, 20]. In recent years, a substantial survival advantage was found by two new treatment regimens, namely FOLFIRINOX [21] and gemcitabine combined with nab-paclitaxel [22]. The remaining patients (approximately 30-40% of all patients) have non-metastatic but irresectable pancreatic cancer (locally advanced pancreatic cancer, LAPC) [23-25]. Palliative treatment using chemotherapy or chemoradiotherapy were the main treatment options for patients with LAPC [14]. In recent years, some of these patients have undergone a resection or a focal ablation (radiofrequency ablation, irreversible electroporation), mostly within studies and following several months of chemotherapy.

Objective and outline of this thesis

The double aging of the Dutch population, together with the fact that pancreatic cancer is primarily a disease of older age, will generate a significant increase of the numbers of elderly pancreatic cancer patients in the next decades. Although epidemiological information on

pancreatic cancer incidence and survival is publicly available on the website of the NCR [2], little was known about treatment and treatment outcomes of various groups of pancreatic cancer patients in the Netherlands. In 2011, the evidence-based guideline on pancreatic and periampullary carcinoma was published[14]. In the same year, a minimum volume standard of 20 pancreatoduodenectomy (PD) was set [26]. These quality initiatives may have affected elderly patients differently than younger patients.

Objective

This thesis evaluates quality of care for patients diagnosed with pancreatic (or periampullary) carcinoma in the Netherlands, and particularly whether elderly patients received similar quality of care compared to younger patients.

Part I National quality assessment and improvement

In the first part of this thesis (**chapters 2, 3, 4, 5**) national quality assessment and quality improvement of pancreatic cancer care are studied. More specifically, we evaluate guideline adherence and centralisation of pancreatic cancer surgery in the Netherlands.

Chapter 2 studies compliance with the Dutch multidisciplinary evidence-based guideline on pancreatic and periampullary carcinoma (2011), more specifically adherence to three quality indicators one year before and one year after publication of the guideline. One of the quality indicators, the administration of adjuvant chemotherapy, is studied in more detail in **chapter 3**. Of patients who were alive 90-days after tumour resection in one of the 19 centres for pancreatic surgery, we assess which factors determine the use of adjuvant chemotherapy and its effect on overall survival.

A couple of years before the introduction of the national volume standard, centralisation of pancreatic surgery was initiated in some cancer regions in the Netherlands. In **chapter 4** we evaluate one example of this voluntary centralisation process in the Leiden region. Ongoing centralisation of pancreatic cancer surgery in the Netherlands is studied in **chapter 5** to determine whether a minimal volume plateau can be identified.

Part II Pancreatic cancer care for elderly patients

The second part of this thesis (**chapters 6, 7, 8, 9, 10**) focuses on quality of care for elderly patients with pancreatic cancer. In many studies a single age cut-off at 70, 75 or 80 years is used to define elderly patients. Since marked treatment or outcome differences may exist between elderly age groups, we distinguish multiple elderly age groups above 70 years of age.

For example, it is unknown to what degree elderly patients benefit from recent quality initiatives in pancreatic surgery (guideline and volume standard in 2011). The Dutch guideline stated that high age alone should not be a contraindication for pancreatic surgery. Therefore, **chapter 6** studies time trends in resection rates, as well as short-term and long-term outcomes of elderly patients who underwent resection for primary pancreatic or periampullary cancer. Supplementary, in **chapter 7** postoperative mortality and overall survival of elderly patients are studied in hospital volume tertiles.

Pancreatic surgery starts with thoroughly exploration of the abdomen to detect unforeseen small metastases (i.c. liver, peritoneal) and to evaluate involvement of the major blood vessels

that can make a radical resection impossible. Although a decision to refrain from resection seems solely based on tumour characteristics, age and hospital volume may also be important factors in decision making and outcomes after non-resection surgery (**chapter 8**).
In the remaining **chapters 9 and 10**, non-surgical treatment (e.g. chemotherapy) is studied in elderly patients with advanced pancreatic cancer. **Chapter 9** studies time trends in chemotherapy use for patients with metastatic pancreatic carcinoma (>50% of all patients), and survival of elderly patients who received chemotherapy. The administration of systemic chemotherapy in the intermediate group of patients with non-resected non-metastatic disease (30-40% of patients) is studied in **chapter 10**.

Data source

All studies in this thesis are conducted with data from the nationwide population-based Netherlands Cancer Registry (NCR), which was established in 1989 [27, 28]. The NCR includes all newly diagnosed malignancies of Dutch inhabitants. Several sources of notification are used to strive for completeness of the NCR. Notification of the majority of newly diagnosed malignancies is obtained from the automated pathological archive (PALGA), the nationwide network and registry of histopathology and cytopathology in the Netherlands. Additional sources of notification comprise the national registry of hospital discharge diagnoses (LBZ) and - in a minority of cases - haematology departments, radiotherapy institutions and hospital reimbursement data (DBC) [2]. The use of additional sources of notification is very important for pancreatic cancers in the NCR. In about one third of registered new pancreatic malignancies no histological or cytological verification was obtained [29, 30].

At first notification, general patient (e.g. sex, date of birth) and tumour characteristics (e.g. date of diagnosis, (sub)location, histological group code) are registered in the NCR. Approximately nine months after diagnosis, trained registrars evaluate the first notification data and collect additional tumour (e.g. stage, grade) and treatment characteristics (e.g. local and systemic cancer treatment, multimodality of initial treatment) from the medical records of patients in all hospitals in the Netherlands.
Tumour location (topography) and tumour type (morphology) are coded according to the International Classification of Diseases for Oncology (ICD-O-3) [31]. The three-dimensional Tumor-Node-Metastasis (TNM) classification by the Union for International Cancer Control (UICC) is used to classify the clinical and – if applicable - pathological tumour stage [32].
When microscopic verification of cancer is lacking, a one-dimensional Extent of Disease (EoD) is recorded in the NCR. Both types of staging information can be combined into one summary stage variable (**Box 1 and Figure 2**).

Box 1. Definitions of Tumour-Node-Metastasis (TNM) and Extent of Disease (EoD)

TNM 6th and 7th edition [a]	EoD	TNM and EoD combined (summary stage)
I = T1-2, N0, M0	Tumour confined to the organ of origin	Localised (within pancreas)
II = T3, N0, M0 or T1-2-3, N1, M0 III = T4, any N, M0	Direct extension in adjacent organs or tissues Metastasised in regional lymph nodes Both	Non-localised (beyond pancreas)
IV = any T, any N, M1	Distant metastasis	Metastasis
X = TX N0 M0	Unknown	Unknown

[a] 2003-2009 TNM 6th edition, 2010-2016 TNM 7th edition
T1=tumour limited to pancreas, 2 cm or less in greatest dimension
T2=tumour limited to pancreas, more than 2 cm in greatest dimension
T3=tumour extends beyond pancreas, but without involvement of coeliac axis or superior mesenteric artery
T4=tumour involves coeliac axis or superior mesenteric artery
N1=regional lymph node metastasis
M1=distant metastasis

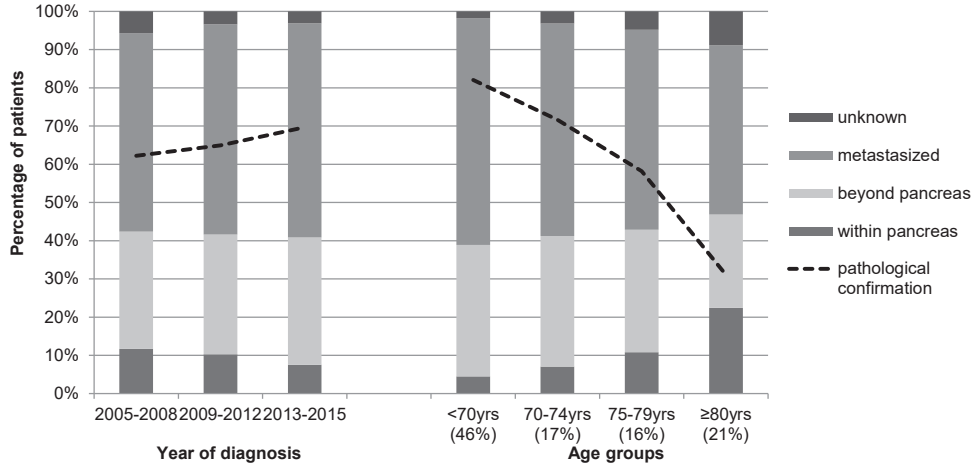

Figure 2. Distribution of tumour stage (bars) and pathological confirmation (line) of patients diagnosed with pancreatic (adeno)carcinoma in the Netherlands, in the course of time and according to age.

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PART I

National quality assessment and improvement

Chapter 2

National compliance to an evidence-based multidisciplinary guideline on pancreatic and periampullary carcinoma

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Pancreatology. 2016 Jan-Feb;16(1):133-7.

Abstract

Background
We evaluated national compliance to selected quality indicators from the Dutch multidisciplinary evidence-based guideline on pancreatic and periampullary carcinoma and identified areas for improvement.

Methods
Compliance to 3 selected quality indicators from the guideline was evaluated before and after implementation of the guideline in 2011: 1) adjuvant chemotherapy after tumor resection for pancreatic carcinoma, 2) discussion of the patient within a multidisciplinary team (MDT) meeting and 3) a maximum 3-week interval between final MDT meeting and start of treatment.

Results
In total 5,086 patients with pancreatic or periampullary carcinoma were included. In 2010, 2,522 patients were included and in 2012, 2,564 patients. 1) Use of adjuvant chemotherapy following resection for pancreatic carcinoma increased significantly from 45% (120 out of 268) in 2010 to 54% (182 out of 336) in 2012 which was mainly caused by an increase in patients aged <75 years. 2) In 2012, 64% (896 of 1396) of patients suspected of a pancreatic or periampullary carcinoma was discussed within a MDT meeting which was higher in patients aged <75 years and patients starting treatment with curative intent. 3) In 2012, the recommended 3 weeks between final MDT meeting and start of treatment was met in 39% (141 of 363) of patients which was not influenced by patient and tumor characteristics.

Conclusion
Compliance to three selected quality indicators in pancreatic cancer care was low in 2012. Areas for improvement were identified. Future compliance will be investigated through structured audit and feedback from the Dutch Pancreatic Cancer Audit.

Introduction

Pancreatic cancer is a devastating disease affecting approximately 10-12 per 100,000 persons per year [1-3]. Only around one in every five patients presents with resectable disease, surgical resection being the only curative treatment option [4,5]. Palliative treatment offers a limited survival benefit and some improvement in quality-of-life [6]. Total 5-year survival rates are as low as 3-6% [1,7,8].

Both national and international developments regarding diagnostic strategies and treatment options, and the participation of various medical disciplines mandate uniform evidence-based guidelines on pancreatic and periampullary cancer. Quality indicators in pancreatic cancer care are scarce and mainly focus on pancreatectomy case volume [9]. However, guideline compliance in the management of pancreatic cancer has been associated with improved survival [10]. The Dutch National Working Group on Gastrointestinal Tumors (LWGIT) therefore developed a multidisciplinary evidence-based guideline which was guided and financed by the Netherlands Comprehensive Cancer Organisation [11]. The guideline was implemented in The Netherlands in 2011 and comprises both pancreatic and periampullary carcinomas [12].

The aim of this study was to evaluate national compliance to 3 selected quality indicators from the guideline and to identify areas for improvement of compliance. The 3 quality indicators were selected based on their relevance and potential benefit. Selected quality indicators were the use of adjuvant chemotherapy following tumor resection for pancreatic carcinoma, the discussion of a patient with a suspected pancreatic or periampullary carcinoma within a multidisciplinary team (MDT) meeting, and a maximum transit time of 3 weeks between final MDT meeting and the start of potentially curative treatment.

Methods

Patient selection
Patients diagnosed with an invasive pancreatic or periampullary carcinoma in The Netherlands between 2010 and 2012were selected fromthe database of the DutchNational Cancer Registry (NCR),which covers nearly 17 million inhabitants. Patients diagnosed at autopsy, <18 years old at diagnosis, with a non-invasive tumor or diagnosed abroad were excluded. Patients receiving surgery abroad were excluded from the analyses of compliance to the selected indicators.

Data acquisition
Specially trained registration-employees of the NCR gather data on patient (age, sex), tumor (date of diagnosis, morphology, topography, stage) and treatment (tumor resection, surgical exploration, chemotherapy) characteristics from medical files in all Dutch hospitals. Data were not regularly available on the occurrence of MDT meetings and on time intervals between MDT meetings and the start of treatment. These were therefore additionally collected for patients diagnosed between May 1st and December 31st of 2012.

Conforming to guideline recommendations, the use of adjuvant chemotherapy was evaluated only for patients with a pancreatic carcinoma. Discussion of a patient within a MDT meeting was evaluated for all patients diagnosed with a pancreatic or periampullary carcinoma. Only patients who started potentially curative treatment for pancreatic or periampullary carcinoma were selected in the evaluation of the time interval between the final MDT meeting and the start of (neoadjuvant) treatment.

Hospitals were divided into academic, top-clinical and general hospitals (in 2012 respectively 8, 28 and 57 hospitals). Hospital volume was calculated based on respectively the true number of resections and the number of planned resections. Regions were divided based on (previous) NCR regions. For one region in The Netherlands no data on the occurrence or dates of a MDT was available.

Statistical analysis
Data were analyzed using STATA/SE (version 13.0; STATA Corp., College Station, Texas, USA). Populations were compared using Chi-square tests. Case-mix corrected data were compared using likelihood ratio test. Differences between hospitals and regions were corrected for sex, age (<60, 60-74, ≥75 years), tumor location and TNM stage. Results were considered statistically significant at a p-value below 0.05. For the analysis of variation between hospitals patients who initiated tumor-directed treatment (resection or chemo(radio)therapy) were classified based on the hospital of treatment and the remainder of patients were classified based on the hospital of clinical diagnosis.

Results

In total 5,086 patients with a pancreatic or periampullary carcinoma were included. In 2010, in total 2,522 patients were included of which 2,159 (86%) patients had a pancreatic carcinoma. Of these patients, 685 (27%) patients underwent surgical exploration. In 2012, 2564 patients with a pancreatic or periampullary (of which 83% with pancreatic carcinoma) were included, of which 765 (30%) patients underwent surgical exploration. **Table 1** depicts patient and tumor characteristics. Neoadjuvant therapy was only administered sporadically during the study period (1.6% of all patients with pancreatic carcinoma that underwent surgical exploration in 2012).

Table 1. Patient and tumor characteristics of patients diagnosed in 2010 and 2012 with a pancreatic or periampullary carcinoma, or only a pancreatic carcinoma, respectively.

	Pancreatic- and periampullary carcinoma			Pancreatic carcinoma		
	2010	2012	Chi2	2010	2012	Chi2
	N=2522 (%)	N=2564 (%)	p-value	N=2159 (%)	N=2122 (%)	p-value
Sex			0.77			0.80
Male	1276 (51)	1308 (51)		1074 (50)	1064 (50)	
Female	1246 (49)	1256 (49)		1085 (50)	1058 (50)	

Table 1 continues on next page

Continuation of table 1

	Pancreatic- and periampullary carcinoma			Pancreatic carcinoma		
	2010	2012	Chi2	2010	2012	Chi2
	N=2522 (%)	N=2564 (%)	p-value	N=2159 (%)	N=2122 (%)	p-value
Age			0.44			0.47
< 60 years	431 (17)	431 (17)		374 (18)	354 (17)	
60-74 years	1142 (45)	1206 (47)		988 (46)	1011 (48)	
≥75 years	949 (38)	927 (36)		797 (37)	757 (36)	
Stage [a]			n.a.			n.a.
TNM – I (T1-2N0M0)	136 (5)	236 (9)		75 (3)	168 (8)	
TNM – II (T3N0M0, T1-2-3N1M0)	425 (17)	606 (24)		319 (15)	459 (22)	
TNM – III (T4M0)	214 (9)	312 (12)		179 (8)	265 (13)	
TNM – IV (M1)	887 (35)	1260 (49)		804 (37)	1154 (54)	
TNM - X	82 (3)	115 (5)		35 (2)	47 (2)	
No TNM-info (diagnosis 2010)	779 (31)	35 (1)		747 (35)	29 (1)	
Hospital of 1st visit			<0.001			0.001
Academic	311 (12)	238 (9)		256 (12)	195 (9)	
Top-clinical	1171 (46)	1137 (44)		1007 (47)	943 (44)	
General	1040 (41)	1189 (46)		896 (42)	984 (46)	
Hospital of pathological diagnosis [b]			0.05			0.01
Academic	450 (18)	523 (20)		361 (17)	426 (20)	
Top-clinical	1199 (48)	1159 (45)		1033 (48)	955 (45)	
General	873 (35)	882 (34)		765 (35)	741 (35)	
Treatment			0.01			0.02
Curative intent [c]	685 (27)	765 (30)		483 (22)	506 (24)	
Other tumor-directed treatments [d]	405 (16)	450 (18)		379 (18)	426 (20)	
No tumor-directed treatment	1432 (57)	1349 (53)		1297 (60)	1190 (56)	

n.a. not applicable.

[a] Based on pTNM supplemented with cTNM. NX and MX were classified as N0 and M0.

[b] When no pathological diagnosis was available, hospital of clinical diagnosis was selected.

[c] Curative intent: surgical exploration with curative intent with or without tumor resection, neo-adjuvant chemo(radio) therapy before surgical exploration with curative intent.

[d] Other tumor-directed treatments: chemo(radio)therapy not followed by surgery, radiotherapy for metastases and sporadically radio frequent ablation (RFA) or irreversible electroporation (IRE). No tumor-directed treatment: no treatment or symptom-relief only.

First indicator: use of adjuvant chemotherapy

The use of adjuvant chemotherapy following resection of a pancreatic carcinoma increased significantly from 44% (121 of 275 patients) in 2010 to 54% (182 of 336 patients) in 2012 (p = 0.02, **Table 2**). This was mainly caused by an increase in patients aged younger than 75 years, where the use of adjuvant chemotherapy increased from 51% to 63% (p = 0.008). In patients aged 75 years or older there was a non-significant increase (10%-16%). In 2010, in hospitals with lower resection volumes fewer patients received adjuvant chemotherapy compared to hospitals with higher resection volumes (28-52%, p = 0.02). In 2012 these differences were non-significant (25-59%, p = 0.13). In 2010 and 2012 there were no significant differences between academic, top-clinical or general hospitals.

Table 2. Use of adjuvant chemotherapy following resection of pancreatic carcinoma.

	2010		2012		Increase?
	Numerator / denominator [b]	Indicator value	Numerator / denominator	Indicator value	Chi2 p-value
All patients	120 / 268	45%	182 / 329	54%	0.02
Age		<0.001		<0.001	
< 60 years	43 / 64	67%	48 / 67	72%	0.58
60-74 years	73 / 162	45%	123 / 204	60%	0.004
≥ 75 years	4 / 42	10%	9 / 58	16%	0.38
Stage [a]		0.43		<0.001	
TNM – I (T1-2N0M0)	16 / 46	35%	10 / 42	24%	0.26
TNM – II (T3N0M0, T1-2-3N1M0)	95 / 203	47%	163 / 276	59%	0.008
TNM – III (T4M0)	7 / 16	44%	7 / 11	64%	0.31
TNM - X	2 / 3	67%	-	-	n.a.
Radicality of resection		0.15		0.77	
R0	90 / 188	48%	118 / 217	54%	0.19
R1-2	28 / 70	40%	56 / 103	54%	0.06
RX	2 / 10	20%	6 / 9	67%	0.04

[a] Based on pTNM. NX and MX were classified as N0 and M0.

[b] All patients that received resection of pancreatic (adeno)carcinoma.

Second indicator: discussion of a patient within a MDT meeting

Of all patients diagnosed with pancreatic or periampullary carcinoma in 2012, 64% (896 of 1,396 patients) had been discussed within a MDT meeting (**Table 3**). Patients aged 75 years and older were significantly less often discussed (51%) within a MDT meeting compared to patients younger than 75 years (72%, p < 0.001).

Of all patients who initiated tumor-directed treatment, 22% had not been discussed within a MDT. In patients who underwent surgical exploration this percentage was lower (15%) compared to patients receiving palliative chemo(radio)therapy (33%, p < 0.001). Of patients not receiving treatment, 50% had not been discussed within a MDT.

Both patients receiving tumor-directed treatment and patients not receiving tumor-directed treatment were less often discussed within a MDT in a general hospital compared to patients in an academic or top-clinical hospital (p < 0.001 for both groups).

Table 3. Frequency of discussion of patients with pancreatic or periampullary carcinoma within multidisciplinary team meeting.

	Numerator / denominator [c]	Indicator value	p-value	Numerator / denominator [d]	Indicator value	p-value
All patients [a]	543 / 694	78%		353 / 702	50%	
Start treatment with			<0.001			
Curative intent	375 / 442	85%				
Other tumor-directed treatments	168 / 252	67%				
No tumor-directed treatment				353 / 702	50%	
Age			0.44			<0.001
< 60 years	123 / 163	75%		44 / 70	63%	
60-74 years	326 / 408	80%		149 / 255	58%	
≥ 75 years	94 / 123	76%		169 / 337	42%	
Tumor location			0.05			0.86
Pancreas	412 / 538	77%		311 / 617	50%	
Periampullary	131 / 156	84%		43 / 85	49%	
Stage [b]			<0.001			<0.001
TNM – I (T1-2N0M0)	40 / 53	75%		38 / 73	52%	
TNM – II (T3N0M0, T1-2-3N1M0)	237 / 270	88%		52 / 82	63%	
TNM – III (T4M0)	81 / 97	84%		51 / 65	78%	
TNM – IV (M1)	181 / 270	67%		192 / 424	45%	
TNM - X	4 / 4	100%		20 / 58	34%	

[a] Excluding 86 patients in which information on dates was absent (6% of selection period and regions).
[b] Based on pTNM, supplemented with cTNM. NX and MX were classified as N0 and M0.
[c] All patients suspected of a pancreatic or periampullary carcinoma that received tumor-directed treatment (i.e. surgical exploration or chemo(radio)therapy).
[d] All patients suspected of a pancreatic or periampullary carcinoma, that did not receive tumor-directed therapy.

Third indicator: time interval between final MDT meeting and start of treatment

Of all patients receiving potentially curative surgery in 2012, 39% (141 of 363 patients) underwent surgical exploration or started neoadjuvant treatment within 3 weeks following the final MDT meeting. Patient and tumor characteristics did not influence this result (**Table 4**).

In academic hospitals fewer patients (33%) started potentially curative treatment within 3weeks following the final MDT meeting compared to top-clinical (47%) and general hospitals (45%, p = 0.02).

Table 4. Percentage of patients with maximum transit time of 3 weeks between final MDT meeting and the start of potentially curative treatment.

	Start treatment with curative intent (2012)				
	Numerator / denominatior [c]	Indicator value	p-value	Mean (SD), in days	Median (p25-p75), in days
All patients	141 / 363	39%		30 (21)	28 (15-39)
Start treatment type [a]			0,97		
Resection	107 / 270	39%		30 (21)	28 (15-39)
Surgical bypass	22 / 56	39%		33 (21)	28 (14-39)
Exploration only ('open-close')	11 / 32	34%		28 (15)	26.5 (13.5-37)
Neoadjuvant treatment	1 / 5	20%		38 (19)	41 (26-46)
Age			0,1		
< 60 years	31 / 66	47%		24 (14)	25 (12-32)
60-74 years	89 / 228	39%		30 (22)	28 (15-39)
≥ 75 years	21 / 72	29%		34 (20)	32.5 (20-42)
Tumor location			0,76		
Pancreas	95 / 250	38%		32 (14)	31 (24-37)
Periampullary	46 / 116	40%		30 (21)	28 (14-39)
Stage [b]			0,93		
TNM – I (T1-2N0M0)	12 / 37	32%		35 (29)	28 (19-42)
TNM – II (T3N0M0, T1-2-3N1M0)	88 / 222	40%		30 (20)	28 (15-39)
TNM – III (T4M0)	19 / 47	40%		26 (17)	26 (13-35)
TNM – IV (M1)	21 / 57	37%		28 (19)	27 (14-39)
TNM – X	1 / 3	33%		46 (45)	23 (17-97)

[a] Excluding patients where date of start of treatment was not available.
[b] Based on pTNM, supplemented with cTNM. NX and MX classified as N0 and M0.
[c] All patients with a malignant pancreatic or periampullary tumor that underwent surgical exploration following multidisciplinary team meeting.

Discussion

National compliance to 3 selected quality indicators from the Dutch evidence-based guideline on pancreatic carcinoma was low in 2012. Following resection of a pancreatic carcinoma, patients in adequate clinical condition should receive adjuvant chemotherapy [13,14]. However, in total only 54% of patients received adjuvant chemotherapy in 2012. Use of adjuvant chemotherapy significantly increased following implementation of the guideline in 2011 which was mainly caused by an increase in patients younger than 75 years old. Possibly, adjuvant chemotherapy is precluded in older patients due to a consequently worse performance status or increased comorbidity compared to younger patients, however we had no data available on this issue. With the exception of a hospital volume category of less than 10 resections per year, the number of patients receiving adjuvant chemotherapy increased in each higher hospital volume category. Possibly low volume hospitals are less aware of guideline recommendations. Many studies have already demonstrated improved postoperative and long-term survival following pancreatic surgery in hospitals with higher procedural volumes as compared to low volume hospitals [15-

18]. Over the past decade, centralization of pancreatic surgery has also been observed in The Netherlands which was accompanied by a decrease in postoperative mortality [19-21].

Due to an increasing number of available treatment options, MDT meetings are considered essential for each patient and not only to discuss possible surgical treatment. In 2012 this was not yet evident in The Netherlands. As the survival of older patients is similar to younger patients following surgery, age should not preclude surgery [22]. However, patients older than 75 years were less often discussed in a MDT compared to patients younger than 75 years old. Possibly it is anticipated that there is a worse preoperative condition of the patient to be eligible for surgery, however these aspects should be weighed during the MDT meeting itself. Indeed, perhaps older patients should even be more often discussed within a MDT meeting because of co-morbid diseases and relatively poor performance status. Possibly, some elderly patients may have refused to undergo high-risk pancreatic surgery. Patients that underwent surgical exploration were more often discussed within a MDT compared to patients who did not. Possibly more patients would be eligible for curative treatment if they had been discussed within a MDT. However, in multiple hospitals MDT meetings seem to be selectively utilized.

Due to the participation of patient organizations in the development of the guideline there has been an increased attention for shorter transit times. A maximum time interval of three weeks between the final MDT meeting and the start of potentially curative treatment was chosen by the guideline committee as this was considered feasible for all hospitals to perform additional diagnostics if necessary, and to plan the operation. Various factors such as a patient's preoperative condition and the need for preoperative biliary drainage may slow transit times. Preoperative biliary drainage may increase the rate of postoperative complications, as was demonstrated in patients undergoing surgery for pancreatic head cancer [23]. However, the maximum time interval of 3 weeks following MDT meeting to surgery or neoadjuvant treatment is an important quality indicator and was most often achieved in top-clinical and general hospitals. Improved hospital logistics, collaborations or tumor-specific MDT's may increase compliance to this quality indicator.

It was challenging in which hospital a MDT meeting should be registered. Many patients start a diagnostic pathway in hospital A but are consequently referred to hospital B where pathological diagnosis, MDT meeting and possibly treatment are performed. Registering the MDT meeting in hospital B probably fails many referring hospitals. However, registering the MDT meeting in hospital A - as the hospital responsible for adequate referral of potentially curable patients - does not reflect the true situation. We therefore chose a partition. For the analysis of variation between hospitals, patients who initiated tumor-directed treatment (resection or chemo(radio) therapy) were classified based on the hospital of treatment and the remainder of patients were classified based on the hospital of clinical diagnosis. With the exception of a few general hospitals, data on MDT meetings was available in all (digital) medical files used by registration employees. Therefore only a slight under-registration in general hospitals on the number of patients discussed within MDT meetings is possible.

In order to stimulate and monitor further compliance to the guideline, continuous audit and feedback at a hospital level is recommended, with attention to 'best practices'. Examples include the recently started audit systems in the Netherlands by the Dutch Institute for Clinical Auditing (DICA), which also include an audit for pancreatic carcinoma [24]. In the Dutch Pancreatic Cancer Audit (DPCA) patient-, tumor- and surgical characteristics are registered, as are the treatment results of patients receiving a pancreatic resection [25]. In the future these data will be shared with both health care providers and patients, so that transparency may contribute to improvement in the quality of care with adequate case-mix correction. Furthermore, the Netherlands Comprehensive Cancer Organisation reports periodically to all hospitals on all patients diagnosed with a pancreatic or periampullary carcinoma.

Based on a nationwide evaluation, compliance to a multidisciplinary evidence-based guideline on pancreatic and periampullary carcinoma was low. A significantly increased amount of patients should receive adjuvant chemotherapy. Non-compliance to this quality indicator seems to be mainly affected by older age. Although a slight improvement was seen before and after implementation of the guideline, a longer study period is needed to evaluate compliance changes. The percentage of patients discussed within a MDT should approach 100% and non-compliance seems to be affected by a patient's older age and not starting treatment with curative intent. A significantly increased amount of patients should experience faster transit times between the final MDT meeting and start of treatment. Better hospital logistics, collaborations or tumorspecific MDT's between hospitals within regions may here contribute to improvement.

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Chapter 3

The use of adjuvant chemotherapy for pancreatic cancer varies widely between hospitals: a nationwide population-based analysis

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Cancer Med. 2017 Dec;6(12):2840-2849.

Abstract

Background
Adjuvant chemotherapy after pancreatoduodenectomy for pancreatic cancer is currently considered standard of care. In this nationwide study, we investigated which characteristics determine the likelihood of receiving adjuvant chemotherapy and its effect on overall survival.

Methods
The data were obtained from the Netherlands Cancer Registry. All patients alive 90 days after pancreatoduodenectomy for M0-pancreatic cancer between 2008 and 2013 in the Netherlands were included in this study. The likelihood to receive adjuvant chemotherapy was analysed by multilevel logistic regression analysis and differences in time-to-first-chemotherapy were tested for significance by Mann–Whitney U test. Overall survival was assessed by Kaplan–Meier method and Cox regression analysis.

Results
Of the 1,195 patients undergoing a pancreatoduodenectomy for pancreatic cancer, 642 (54%) patients received adjuvant chemotherapy. Proportions differed significantly between the 19 pancreatic centers, ranging from 26% to 74% ($p < 0.001$). Median time-to-first-chemotherapy was 6.7 weeks and did not differ between centers. Patients with a higher tumor stage, younger age, and diagnosed more recently were more likely to receive adjuvant treatment. The 5-year overall survival was significantly prolonged in patients treated with adjuvant chemotherapy: 23% versus 17%, $p = 0.01$. In Cox regression analysis, treatment with adjuvant chemotherapy significantly prolonged survival compared with treatment without adjuvant chemotherapy.

Conclusion
The finding that elderly patients and patients with a low tumor stage are less likely to undergo treatment needs further attention, especially since adjuvant treatment is known to prolong survival in most of these patients.

Introduction

Pancreatic cancer has a very poor prognosis. Currently, surgical resection is the only possible treatment to obtain long-term survival [1]. The recent CONKO-001 randomized clinical trial has demonstrated an additional benefit of adjuvant chemotherapy on disease-free and overall survival for pancreatic cancer [2]. These results were obtained in all age groups, for both sexes and independent of tumor stage [2]. Given these results, adjuvant chemotherapy is now considered standard of care in most countries including the Netherlands, where adjuvant chemotherapy (Gemcitabine) has been recommended by the Dutch society of Medical Oncology (NVMO) since 2008 [3].

In the Netherlands, surgery for pancreatic cancer is only performed in centers performing at least 20 pancreatoduodenectomies (PD) annually. This centralization significantly improved outcomes of pancreatic surgery in terms of postoperative morbidity and mortality [4,5]. In contrast, systemic treatment of pancreatic cancer patients, including adjuvant chemotherapy in operated patients is given in almost all hospitals in the Netherlands. Previous studies have shown that a considerable amount of patients do not receive adjuvant chemotherapy after recovery from a pancreatoduodenectomy [6–8]. It is currently unknown which factors determine the likelihood for receiving adjuvant chemotherapy.

Therefore, this nationwide study investigated the variation between pancreatic centers in adjuvant treatment and which characteristics determine the likelihood of receiving adjuvant chemotherapy in the Netherlands. By doing so, correctable reasons for underutilization of adjuvant chemotherapy may be identified, thereby raising the possibility to further improve the treatment of pancreatic cancer patients.

Methods

Data collection

Data were obtained from the nationwide Netherlands Cancer Registry (NCR). This registry contains data of all newly diagnosed cancer patients in the Netherlands (approximately 16.8 million inhabitants in 2013), which is routinely extracted from the medical records in all hospitals and registered by specially trained, independent administrators. The NCR contains patient, tumor, and treatment characteristics. The extent of disease was defined by pathological findings, and was staged using the TNM classification or pathologic extent of disease (pEoD). pEoD classifications were converted to TNM classification [9, 10]. In pEoD classification, tumor involvement of the truncus coeliacus or arteria mesenterica superior (AMS) is not specified. Therefore, no differentiation between TNM stage II or III could be made, and these patients were categorized as TNM II/III.

Patient selection

All nonmetastatic (M0) patients diagnosed with adenocarcinoma of the pancreas (ICD C25) [11] between 1 January 2008 and 31 December 2013 in the Netherlands and surgically treated

by PD in a pancreatic center were included in this study. Patients diagnosed with carcinoma-in-situ (Tis), neuroendocrine tumors, patients with missing data on tumor stage, and patients deceased within 90 days after surgical treatment were excluded from further analysis (n = 218). This landmark at 90 days, postoperative, was chosen to minimize the possible effect of postoperative complications on the administration of adjuvant chemotherapy and to deal with immortal time bias of patients receiving chemotherapy. Adjuvant chemotherapy was defined as any chemotherapeutical treatment starting within 16 weeks after surgery.

Pancreatic center
In the Netherlands, a minimum of 20 PDs per year is currently required to be considered as a pancreatic center. This resulted in 19 pancreatic centers in the Netherlands in 2013, including eight university hospitals.

Statistical analysis
Differences in patient-and tumor characteristics between patients who underwent adjuvant chemotherapy and patients who did not were compared with chi-square tests. To analyze the hierarchically structured data of patients nested within pancreatic centers, a multilevel logistic regression analysis was used. Multilevel regression analyses provide more accurate estimates when dealing with hierarchically structured data than traditional regression analyses as they account for dependency of patients within pancreatic centers [12,13]. The outcome variable was adjuvant chemotherapy (0, no; 1, yes). Patient-and tumor-related variables (sex, age, TNM stage, year of diagnosis) were added to the multivariable multilevel model. The effect of a variable on the likelihood of adjuvant chemotherapy was expressed as an odds ratio (OR) with 95% Confidence Interval (CI).

Each patient's adjusted chance to undergo adjuvant chemotherapy was given by the following formula: $P = eL/(1 + eL)$, where L is the calculated value from the logistic regression for that particular patient. The mean adjusted probability to undergo adjuvant chemotherapy for each pancreatic center was defined as the mean adjusted surgical probability of the patients within that pancreatic center. This resulted in a range of probabilities to undergo adjuvant chemotherapy adjusted for differences in patient- and tumor characteristics between pancreatic centers. The variation in adjuvant chemotherapy probabilities between pancreatic centers was tested for statistical significance by means of ANOVA with Bonferroni correction.

The differences in comparisons made for the time period between surgery and start of adjuvant chemotherapy, defined as time to adjuvant chemotherapy in weeks, were tested for significance using the nonparametric Mann–Whitney U test.

Conditional survival
Data retrieved from the Municipal Personal Records Database (BRP) were used to calculate survival. In the BRP, all deaths or emigrations of Dutch inhabitants are registered. Survival time was defined as time from diagnosis to death, or until 1 January 2015 for patients who were still alive. The Kaplan–Meier method was used to determine 5-year survival. The effect of the time

to adjuvant chemotherapy on the overall survival was assessed by log-rank test. Multivariable Cox regression analysis was undertaken to investigate the prognostic impact of adjuvant chemotherapy on overall survival, after adjustment for patient characteristics. Results from survival analyses using Cox regression analysis were reported as hazard ratios (HR) with 95% CI. All analyses were performed using Statistical Analysis Software (SAS) version 9.4, North Carolina, USA and a $p < 0.05$ was considered statistically significant.

Results

Patients

Between 2008 and 2013, 5,846 patients were diagnosed with M0-pancreatic cancer in the Netherlands of whom 1,413 (24%) underwent PD in a pancreatic center. In total, 218 patients were excluded. The main reasons for exclusion were diagnosis of a neuroendocrine tumor (n = 78) and death within 90 days after surgery (n = 84). The remaining 1,195 patients were included in this study. Adjuvant chemotherapy was administered to 642 (54%) of these patients, either in the pancreatic center where the surgery was performed (56%) or in the referring hospital (44%). Baseline characteristics differed between patients treated with and without adjuvant chemotherapy, with patients receiving chemotherapy being younger (median 64 vs. 70 years, respectively, $p < 0.001$) and being diagnosed with a higher TNM tumor stage (**Table 1**).

Table 1. Baseline characteristics of M0-pancreatic cancer patients treated by pancreatoduodenectomy between 2008 and 2013 in the Netherlands.

	All patients	Adjuvant chemotherapy	No adjuvant chemotherapy	Chi2
	N=1,195	N=642 (54%)	N=553 (46%)	p-value
Sex				0.871
Male	615 (51%)	329 (51%)	286 (52%)	
Female	580 (49%)	313 (49%)	267 (48%)	
Age				<0.001
<60 years	285 (24%)	201 (31%)	84 (15%)	
60-74 years	715 (60%)	409 (64%)	306 (55%)	
≥75 years	195 (16%)	32 (5%)	163 (30%)	
TNM Stage				<0.001
I	157 (13%)	54 (8%)	103 (19%)	
II / III	1,038 (87%)	588 (92%)	450 (81%)	
Year of diagnosis				<0.001
2008	129 (11%)	42 (7%)	87 (16%)	
2009	162 (14%)	87 (13%)	75 (13%)	
2010	162 (14%)	84 (13%)	78 (14%)	
2011	188 (15%)	98 (15%)	90 (16%)	
2012	278 (23%)	164 (26%)	114 (21%)	
2013	276 (23%)	167 (26%)	109 (20%)	

Center of surgery

The observed proportion of patients receiving adjuvant chemotherapy differed significantly between the 19 pancreatic centers in the Netherlands and ranged from 26% to 74%, $p < 0.001$ (**Figure 1**). Multilevel logistic regression confirmed the effect of the pancreatic center on the probability to undergo adjuvant chemotherapy. The case-mix adjusted probability for adjuvant chemotherapy treatment ranged between 35% and 68% according to the pancreatic centers (**Figure 2**; $p < 0.001$).

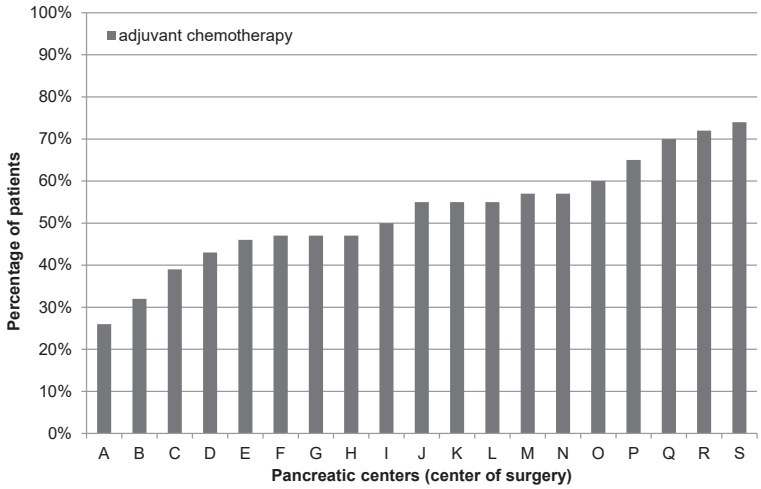

Figure 1. Observed percentage of adjuvant chemotherapy treatment in pancreatic cancer patients undergoing pancreatoduodenectomy in pancreatic centers between 2008 and 2013 in the Netherlands.

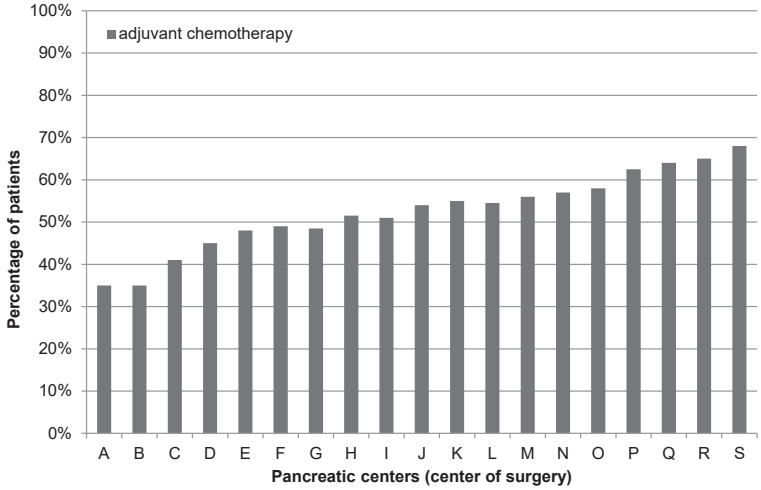

Figure 2. Multilevel case-mix adjusted probability for adjuvant chemotherapy treatment for pancreatic centers in the Netherlands between 2008 and 2013.

No significant difference was found in the observed treatment percentages between university pancreatic centers and nonuniversity pancreatic centers (55% vs. 52%, p = 0.245).

Variables influencing the likelihood of receiving adjuvant chemotherapy are presented in **Table 2**. Multilevel logistic regression model showed that an increased likelihood of adjuvant treatment was observed in patients with a TNM tumor stage II or III compared to TNM stage I (respectively, 57% vs. 34%, OR = 2.71, 95% CI 1.77–4.15). Furthermore, patients older than 60 years were less likely to undergo adjuvant chemotherapy (70% <60 years vs. 57% 60–75 years, OR = 0.48, 95% CI 0.34–0.67). Patients older than 75 years were the least likely to receive chemotherapy (16%, OR = 0.06, 95% CI 0.04–0.10).

Over time, the use of adjuvant chemotherapy increased from 33% in 2008 to 61% in 2013. Patients diagnosed in the year 2013 were more likely to undergo adjuvant treatment compared to patients diagnosed in 2008 (OR = 4.63, 95% CI 2.73–7.87).

Table 2. Multilevel logistic regression analyses for the likelihood of adjuvant chemotherapy treatment among M0-pancreatic cancer patients diagnosed between 2008 and 2013 and surgically treated by pancreatoduodenectomy in the Netherlands.

	Adjuvant chemotherapy	OR (95% CI)
All patients	N=642 (54%)	
Sex		
Male	329 (54%)	1.00
Female	313 (54%)	1.06 (0.81 – 1.40)
Age		
<60 years	201 (71%)	1.00
60-74 years	409 (57%)	0.48 (0.34 – 0.67) *
≥75 years	32 (16%)	0.06 (0.04 – 0.10) *
TNM Stage		
I	54 (34%)	1.00
II / III	588 (57%)	2.71 (1.77 – 4.15) *
Year of diagnosis		
2008	42 (33%)	1.00
2009	87 (54%)	2.83 (1.61 – 4.98) *
2010	84 (52%)	2.85 (1.61 – 5.05) *
2011	98 (52%)	3.42 (1.96 – 5.99) *
2012	164 (59%)	4.39 (2.59 – 7.46) *
2013	167 (61%)	4.63 (2.73 – 7.87) *

Corrected for pancreatic center, intercept 0.275, SE 0.127.
OR Odds ratio, CI Confidence Interval
*Significantly different

Time to adjuvant chemotherapy

In 400 (62%) patients, adjuvant chemotherapy was initiated within 8 weeks after PD, in 134 (21%) patients, between 8 and 12 weeks postoperatively, and in 23 (4%) patients, treatment was started more than 12 weeks after PD. In 85 (13%) patients, information on time to adjuvant chemotherapy was missing. Median time to adjuvant chemotherapy was 6.6 weeks (Interquartile range [IQR]: 2.9). The time to adjuvant chemotherapy did not significantly differ between patients resected in university centers versus nonuniversity centers, p = 0.803 (respectively, median 6.7, IQR: 2.7 vs. median: 6.4, IQR: 3.3). Furthermore, no difference in time to adjuvant chemotherapy was found for patients treated in a pancreatic center versus patients referred to a nonpancreatic center for receiving adjuvant chemotherapy, p = 0.194 (respectively, median: 6.3, IQR: 2.9 vs. median: 7.0, IQR: 3.4).

Conditional survival

Kaplan–Meier analysis (**Figure 3**) revealed a significant difference in 5-year overall survival rates based on whether patients were treated by adjuvant chemotherapy: 23% versus 17% if not treated by adjuvant chemotherapy (Log-rank p < 0.001). Patients treated with adjuvant chemotherapy had a 5-year survival rate of 22% if time to adjuvant chemotherapy was ≤6 weeks versus 21% for time to adjuvant chemotherapy >6 weeks. In Cox regression analyses (**Table 3**), adjuvant chemotherapy treatment was a significant predictor of prolonged survival for both adjuvant chemotherapy within 6 weeks as well as for adjuvant chemotherapy after 6 weeks compared with no adjuvant chemotherapy (HR=0.68, 95% CI 0.56–0.82 vs. HR=0.79, 95% CI 0.66–0.95). A tumor stage TNM II/III was a significant variable for shortened survival (HR=1.97 95% CI 1.58–2.47).

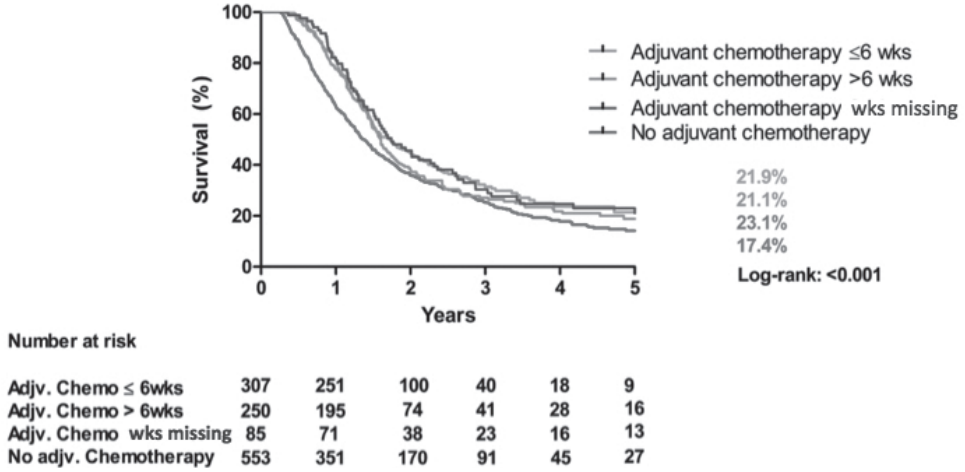

Figure 3. Kaplan–Meier, 5-year overall survival adjuvant chemotherapy versus no adjuvant chemotherapy after pancreatoduodenectomy in pancreatic cancer patients in the Netherlands between 2008 and 2013.

Table 3. Multivariable Cox regression analyses among M0-pancreatic cancer patients diagnosed between 2008 and 2013 in the Netherlands and surgically treated by pancreatoduodenectomy.

	HR (95% CI)
Sex	
Male	Ref
Female	0.93 (0.82 – 1.07)
Age	
<60 years	Ref
60-74 years	1.06 (0.90 – 1.26)
≥75 years	1.16 (0.92 – 1.47)
TNM Stage	
I	Ref
II / III	1.97 (1.58 – 2.47)
Year of diagnosis	
2008	Ref
2009	0.70 (0.54 – 0.91)
2010	0.90 (0.69 – 1.16)
2011	0.87 (0.67 – 1.12)
2012	0.93 (0.72 – 1.18)
2013	1.10 (0.85 – 1.43)
Adjuvant chemotherapy	
No	Ref
Yes (started ≤6 weeks postoperative)	0.68 (0.56 – 0.82)
Yes (started >6 weeks postoperative)	0.79 (0.67 – 0.95)
Yes (date of start missing)	0.71 (0.54 – 0.93)

HR hazard ratio, CI confidence interval

Discussion

The current population-based study revealed that 54% of the pancreatic cancer patients received adjuvant chemotherapy following PD. Elderly patients were less likely to undergo adjuvant chemotherapy. Interestingly, the likelihood of receiving adjuvant chemotherapy treatment varied significantly between pancreatic centers. Survival analyses showed that the addition of adjuvant chemotherapy was associated with a prolonged survival. This was seen in patients receiving adjuvant chemotherapy within 6 weeks postoperatively but also in patients receiving chemotherapy more than 6 weeks after PD.

Our findings on overall survival are in line with a recent RCT (randomized clinical trial) and a previous population-based study in the USA showing a positive influence of adjuvant chemotherapy on overall survival [2,6]. This again stresses the beneficial effect of treating patients with adjuvant chemotherapy, if possible. A recent study in the Netherlands showed limited compliance to quality indicators in pancreatic cancer care based on the Dutch guideline. The administration of adjuvant chemotherapy increased from 45% of patients in 2010 to 54%

in 2012 [14]. Nevertheless, the proportion of patients treated by adjuvant chemotherapy in this study is comparable to percentages described in literature. Mayo et al. [6] reported adjuvant treatment in 51% of patients undergoing any type of surgery for pancreatic adenocarcinoma in Medicare beneficiaries in the USA. A multicenter study in Japan demonstrated that 66% of the pancreatic cancer patients received adjuvant chemotherapy [15]. Finally, a study by Aloia et al. [7] showed the highest percentage: 74% of patients received adjuvant therapy after PD. However, in spite of this high percentage, the authors suggested that at least 90% of patients with localized pancreatic adenocarcinoma and good pretreatment performance status would have been candidates for postoperative adjuvant therapy.

A similar limited use of adjuvant chemotherapy has been shown in other tumors. For instance, only 60% patients with colon cancer and lymph node metastases received adjuvant chemotherapy in the Netherlands [16]. Remarkably, the proportion of patients receiving adjuvant chemotherapy varied significantly between pancreatic centers in this study. This finding was not in line with expectations, as all pancreatic centers are supposed to have expert knowledge in the treatment of pancreatic cancer and to adhere to the national guidelines. The differences in the probability to receive adjuvant chemotherapy remained present after adjustment for available case-mix variables; sex, age, TNM stage, year of diagnosis. There may be various explanations for this phenomenon. First of all, the multidisciplinary tumor boards (MDTB) in the 19 pancreatic centers may have various attitudes toward the guideline recommendations, resulting in a different tendency to advice adjuvant chemotherapy. Since a significant proportion of the patients (44%) were not treated in the pancreatic center but in the referring hospital, medical oncologists from referring hospitals may choose to react differently on the advice of the MDTB. Furthermore, it should be acknowledged that in some cases, patients choose to not undergo adjuvant chemotherapy. This decision-making process will be the subject of further research.

In this study, age was an important variable in selecting patients with older patients being less likely to receive adjuvant chemotherapy. Previous retrospective studies have reported also an effect of age on the selection of patients for adjuvant chemotherapy [8,17]. However, it was shown in the CONKO-001 trial that the beneficial effects of adjuvant chemotherapy were obtained regardless of age [2]. Also in the cohort study by Nagrial et al., [17] it was demonstrated that adjuvant chemotherapy in elderly patients was associated with an improved survival to at least a similar degree as for younger patients. Furthermore, it is known that PDs can be safely performed in elderly patients with good postoperative outcomes [18,19]. Therefore, physicians may be too reluctant in prescribing adjuvant chemotherapy to elderly patients.

Patients diagnosed with a tumor stage TNM II or III, were more likely to receive adjuvant chemotherapy treatment as compared to patients with stage I disease. Given the worse prognosis in stage TNM II or III patients, especially in the case of lymph node metastases, treating physicians may be more willing to administer adjuvant chemotherapy in these patients. However, as was shown by Oettle and colleagues, the beneficial results of adjuvant chemotherapy were not only achieved in high-staged tumors but also in low-staged tumors [2]. Therefore, adjuvant chemotherapy treatment of patients with stage I disease needs further attention.

This study had some limitations. Although the NCR registry is a reliable and complete database, data like resection status (R0/R1), postoperative complications, comorbidities, and performance status are lacking. These factors may have influenced the likelihood of receiving adjuvant chemotherapy treatment. Insurance status is not likely to affect the likelihood for adjuvant chemotherapy because of the equally accessible health care system in the Netherlands. Data on type of chemotherapy and completion rates in patients undergoing adjuvant chemotherapy were not registered. In our study, an effort to minimize the possible effect of postoperative complications on the administration of adjuvant chemotherapy was undertaken by excluding patients deceased within 90 days. A correlation between severe complications and omission of adjuvant treatment was reported earlier by Wu et al., [8]. Furthermore, they described a decreased likelihood for adjuvant chemotherapy if the length of postoperative stay exceeded 9 days [8]. The results of that study showed that withdrawal of adjuvant chemotherapy in some cases could be explained by a prolonged postoperative recovery where early initiation of adjuvant chemotherapy could not be achieved caused by postoperative complications [6–8]. However, recently, Valle et al. [20] reported that survival following start of adjuvant chemotherapy treatment within 8-12 weeks postoperatively did not differ from initiation within 8 weeks postoperatively. Completion of the full course of the treatment was a more important factor determining outcomes. Likelihood of completion of the full course was maximized by an adequate postoperative recovery. Consequently, an inability of administering adjuvant chemotherapy prior to 8 weeks postoperatively does not eliminate the beneficial effect of chemotherapy, as was confirmed by our study [20]. The observed median time of 6.6 weeks between PD and initiation of adjuvant chemotherapy, however, suggests that there might have been a nihilistic approach to a late start of adjuvant chemotherapy.

In summary, there is an underuse of adjuvant chemotherapy for pancreatic cancer in the Netherlands. Even in the last year of this study, only 61% of the patients received adjuvant treatment. Elderly patients were less likely to undergo adjuvant chemotherapy, despite the beneficial effect of such treatment also in this age group. Interestingly, the likelihood of receiving adjuvant chemotherapy treatment varied significantly between pancreatic centers, a finding that may not be explained by case-mix alone. This finding clearly needs further attention and more research, especially since in this study, treatment with adjuvant chemotherapy resulted in a significantly prolonged overall survival. The Dutch Pancreatic Cancer Project (PACAP) including prospective audit, are used for improvements in the use of adjuvant chemotherapy and other relevant factors in survival for pancreatic cancer care in the Netherlands.

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Chapter 4

Quality improvement of pancreatic surgery by centralization in the western part of the Netherlands

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Ann Surg Oncol (2011) 18:1821–1829.

Abstract

Background
Centralization of pancreatic surgery in high-volume hospitals is under debate in many countries. In the western part of the Netherlands, the professional network of surgical oncologists agreed to centralize all pancreatic surgery from 2006 in two high-volume hospitals. Our aim is to evaluate whether centralization of pancreatic surgery has improved clinical outcomes and has changed referral patterns.

Materials and Methods
Data of the Comprehensive Cancer Centre West (CCCW) of all 249 patients who had a resection for suspected pancreatic cancer between 1996 and 2008 in the western part of the Netherlands were analyzed. Multivariable modelling was used to evaluate survival for 3 time periods; 1996–2000, 2001–2005 (introduction of quality standards), and 2006–2008 (after centralization). In addition, the differences in referral pattern were analyzed.

Results
From 2006, all pancreatic surgery was centralized in 2 hospitals. The 2-year survival rate increased after centralization from 39% to 55% ($p = 0.09$) for all patients who had a pancreatic resection for pancreatic cancer. After adjustment for age, tumor location, stage, histology, and adjuvant treatment, the latter period was significantly associated with improved survival (hazard ratio [HR]=0.50; 95% confidence interval [95% CI] 0.34–0.73).

Conclusions
Centralization of pancreatic surgery was successful and has resulted in improved clinical outcomes in the western part of the Netherlands, demonstrating the effectiveness of centralization.

Introduction

In many countries, the question whether high-risk surgery should be centralized in high-volume centers is prominent in the quality of healthcare debate. The association between high procedural volume and improved outcomes is generally accepted, and the strongest association is seen with high-risk, low volume procedures, such as pancreatic or esophageal surgery [1–8]. Authors suggest that especially these high-risk procedures can benefit from concentration in high-volume centers [9]. However, translating these results into practice is challenging.

In the Netherlands, the annual incidence of pancreatic cancer is around 1,700 new cases of pancreatic cancer and around 440 cases of extra hepatic bile duct cancer (source: Netherlands Cancer Registry). A resection is done in approximately 15% of the cases, resulting in 300 pancreatic resections for malignant disease each year. For more than a decade, there is an ongoing debate for minimal volume standards for pancreatic resections. However, despite the plea for centralization, little had changed in referral patterns or postoperative mortality in the period 1994–2004 [10].

The Dutch Healthcare Inspectorate considers a minimal volume standard for pancreatic resections, but already does demand a minimal volume for esophageal resections. Recently, Wouters et al. showed a reduction of postoperative morbidity and length of stay after centralization of esophageal resections in the Netherlands [11]. The postoperative mortality fell from 12% to 4%. However, although many studies on the volume outcome relationship for pancreatic surgery exist, reports showing actual improvement of quality of care after centralization have only been scarce.

In the western part of the Netherlands, 9 hospitals are affiliated with the Comprehensive Cancer Centre West (CCCW), 1 of the 8 comprehensive cancer centers in the country. In 2001 the professional network of surgical oncologists (PNSO) in the region formulated quality standards for hospitals performing pancreatic surgery (**shown in the frame**). Furthermore, they declared the intention to centralize pancreatic surgery after a period of monitoring. In 2005 the PNSO agreed to centralize all pancreatic surgery in 2 centers from January 1, 2006.
In this study the outcomes of the centralization process in the western part of the Netherlands are reported.

Quality criteria for pancreatic surgery formulated by the PNSO of the CCCW in the Netherlands include:

1. new patients are preoperatively and postoperatively discussed in a multidisciplinary board with a gastroenterologist and a radiologist;
2. all patients are operated on by an experienced surgeon;
3. the hospital has an intensive care unit, intervention radiology, and gastroenterology department; and
4. all patients are operated on by two surgeons together.

Methods

Hospitals and centralization
From 1996 until 2005 the CCCW comprised 11 affiliated hospitals. After 2 mergers in 2006, 9 affiliated hospitals were left: 1 academic center, 6 teaching hospitals, and 2 nonteaching hospitals. All are located in the Midwestern part of the Netherlands and fully cover the region West. This area is mainly urban with 1.7 million inhabitants. Traveling distances between hospitals are 45 km (30 miles) maximum.

From 1996 until 2005 all hospitals performed pancreatic surgery. Since 2006 pancreatic surgery was centralized in 2 hospitals: the Leiden University Medical Centre (LUMC), an academic center, and the Reinier de Graaf Hospital (RdGG), a teaching hospital.

Data source
In the Netherlands, the nationwide population based Netherlands Cancer Registry (NCR) registers all newly diagnosed malignancies. Independently trained data managers from the NCR collect data from original patient files, after receiving an automatic report from the Dutch pathology reporting system PALGA. Completeness of the cancer registry is cross-checked by linking with the Dutch National Registry of Hospital Discharge Diagnosis, which is a near-complete registry of hospital discharge data for all in-hospital treatments. Information on patient characteristics, tumor characteristics, treatment, hospital of diagnosis, hospital of treatment, and follow-up is recorded. For coding tumor site and morphology the International Classification of Diseases for Oncology (ICD-0) is used [12]. Cancers are staged according the TNM classification (TNM classification of Malignant Tumors, 6th edition) [13]. The quality of the data is high, and completeness is estimated to be at least 95% [14]. Vital status of all patients was obtained actively on a regular basis through linkage of the cancer registry data with the integrated database of the municipal registry. The Leiden cancer registry (part of the NCR), collects data of all patients who are diagnosed for a new malignancy in 1 of the affiliated hospitals in the CCCW region. All hospitals gave formal consent to participate.

In addition, after centralization, operating surgeons register all patients who undergo pancreatic surgery (both for malignant and benign diagnoses) in an electronically shared database to monitor the results. Completeness of the data was further cross-checked with linking of the shared database to the cancer registry.

Patient groups
Patients with pancreatic surgery for cancer in the region of the CCCW from January 1, 1996 to December 31, 2008 were identified from the NCR, which covered surgically treated malignancies of pancreas (C25), duodenum (C17.0), ampulla of Vater (C24.1), and the hepatic bile duct (C24.0). Patient demographics, pathological notes TNM staging, and data on surgical and (neo-) adjuvant treatments were collected. Additional data on comorbidities, detailed postoperative complications, length of stay, and margin status of all patients who underwent pancreatic surgery between 2006 and 2008 for both malignant and benign diagnoses were collected from the shared database.

Outcomes
Outcomes of pancreatic resections in 3 time periods were compared: 1996–2000, 2001–2005, and 2006–2008. In the first period from 1996 till 2000, no quality control for pancreatic surgery was performed in the region. In 2001, quality standards were implemented and from 2006 pancreatic surgery was centralized in 2 hospitals. Outcome was assessed using 30-day mortality, 90-day survival, 1-year survival, and 2-year survival and the number of evaluated lymph nodes. Survival was calculated as the difference between date of surgery, or —if not available— the date of confirmed diagnosis (which is usually the same as the date of surgery), and, either the date of death, or the date of last patient follow-up. Follow-up of patients was completed until January 1, 2010.

For the period 2006–2008, postoperative complications, length of stay, length of ICU admission, and margin status were also analyzed.

Statistical methods
Descriptive statistics were calculated for all variables. Differences in patient, tumor, and treatment characteristics between the 3 time periods as well as outcome measurements were assessed using the Kruskal–Wallis test (for continuous variables) and Chi-square test (for categorical variables).

Observed survival rates were estimated with the Kaplan–Meier method. Differences in survival between the 3 time periods were assessed with the log-rank test. The multivariable Cox proportional hazard model was used to identify factors associated with improved survival after surgery. Period of diagnosis, age, tumor location, histology, stage, and adjuvant chemotherapy and radiotherapy were entered in the multivariable model as prognostic factors. All analyses were conducted with SPSS version 15 (SPSS Inc, Chicago, IL).

Results

Centralization and referral pattern
From 1996 until 2005 pancreatic surgery was performed in all CCCW-affiliated hospitals. The mean annual hospital volume of oncologic pancreatic resections was 1.7 in 1996–2000 and 2.0 in 2001–2005. Since January 1, 2006 all pancreatic surgery was centralized in 2 hospitals. The mean annual hospital volume increased to 23.

After centralization, the percentage of patients receiving surgical treatment for pancreatic cancer, increased from 14.3% to 18.4% ($p = 0.08$). The proportion of patients who are living in the CCCW region and had surgery within the region increased from 55% to 69% ($p = 0.085$).

Characteristics and crude outcomes
Table 1 shows the characteristics of 249 patients who underwent pancreatic surgery for a malignancy from 1996 to 2008 in the CCCW region, stratified by the period of diagnosis. There were no significant differences in patient age, tumor stage, and histology. In the latter period,

more patients had a tumor located in the pancreas and chemotherapy use increased from 2.4% in 1996–2000, to 23.6% in 2006–2008. **Table 2** shows the crude outcomes. The 30-day mortality fell from 8% in the first period to 0% and 2% in the latter periods. Testing of statistical significance was not feasible because of low numbers. Of all patients with a malignant tumor, the observed 90-day survival improved from 88% to 96% (p = 0.03), and the 2-year survival from 39% to 55% (p = 0.09). The 2-year survival of patients with pancreatic adenocarcinoma first dropped from 38% to 28% in the first two time periods and then improved to 49% in the latest period (p = 0.04). The median number of evaluated lymph nodes increased significantly from median 2 to median 7 lymph nodes examined. There was no significant change in observed overall survival (p = 0.106, **Figure 1**).

Table 1. Characteristics of 249 patients with pancreatic surgery for a malignancy in the western part of the Netherlands between 1996 and 2008.

	1996-2000	2001-2005	2006-2008	Chi-square
	N (%)	N (%)	N (%)	p-value
Total nr of patients	85	89	110	
Sex				0.572
Male	40 (47.1)	48 (53.9)	52 (47.3)	
Female	45 (52.9)	41 (46.1)	58 (52.7)	
Age				0.218
< 50 year	13 (15.3)	16 (18.0)	9 (8.2)	
50-74 year	60 (70.6)	64 (71.9)	82 (74.5)	
≥ 75 year	12 (14.1)	9 (10.1)	19 (17.3)	
Tumour location				0.046
Pancreas	45 (52.9)	60 (67.4)	78 (70.9)	
Extrahepatic bile duct	29 (34.1)	16 (18.0)	22 (20.0)	
Duodenum	11 (12.9)	13 (14.6)	10 (9.1)	
Histology				0.190
Adenocarcinoma	72 (84.7)	71 (79.8)	98 (89.1)	
Other [a]	13 (15.3)	18 (20.2)	12 (10.9)	
Stage (pTNM)				0.073
I-II	41 (48.2)	38 (42.7)	40 (36.4)	
III-IV	33 (38.8)	31 (34.8)	56 (50.9)	
Other	11 (12.9)	20 (22.5)	14 (12.7)	
Chemotherapy				0.000
No	83 (97.6)	84 (94.4)	84 (76.4)	
Yes	2 (2.4)	5 (5.6)	26 (23.6)	
Radiotherapy				[b]
No	80 (94.1)	86 (96.6)	110 (100)	
Yes	5 (5.9)	3 (3.4)	0	

[a] Other histology includes (neuro)endocrine tumors, carcinoid tumors, and unspecified histology.
[b] not feasible to calculate significance.

Table 2. Crude outcomes of all patients who had pancreatic surgery for a malignancy or adenocarcinoma of the pancreas

All pancreatic malignancies	1996-2000	2001-2005	2006-2008	p-value
	N=85	N=89	N=110	
30 day mortality	7 (8%)	0	2 (2%)	[a]
90 day survival	75 (88%)	86 (97%)	106 (96%)	0.03
1 year survival	55 (65%)	58 (65%)	81 (74%)	0.31
2 year survival	33 (39%)	36 (40%)	36 (55%)	0.09
Lymph nodes (median)	2	4	7	<0.001
Pancreatic adenocarcinoma	1996-2000	2001-2005	2006-2008	p-value
	N=72	N=71	N=98	
30 day mortality	5 (7%)	0	2 (2%)	[a]
90 day survival	64 (89%)	68 (96%)	94 (96%)	0.12
1 year survival	46 (64%)	46 (64%)	70 (71%)	0.13
2 year survival	27 (38%)	20 (28%)	29 (49%)	0.04
Lymph nodes (median)	2	4	7	<0.001

[a] not feasible to calculate significance

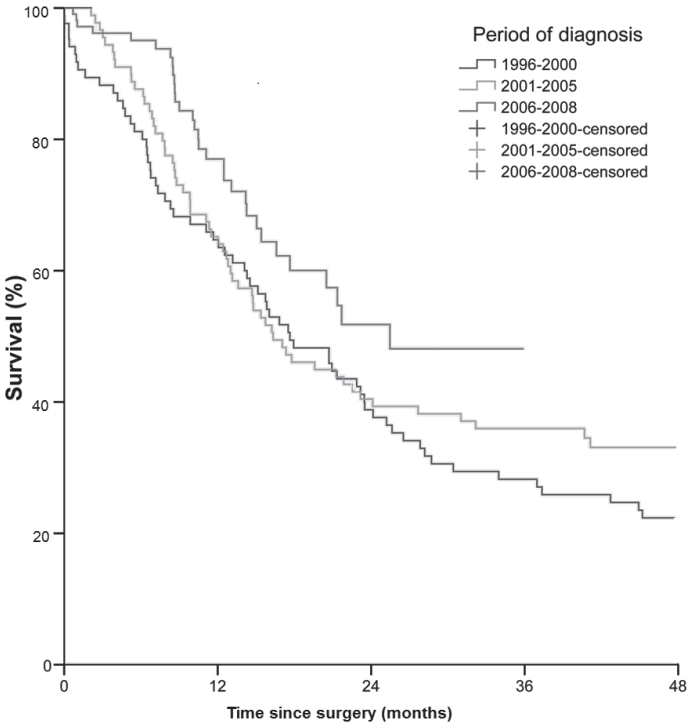

Figure 1. Observed survival after pancreatic surgery for malignant diagnosis, for the periods 1996–2000, 2001–2005, and 2006–2008 (calculated with log-rank test; p = 0.106).

Univariable and multivariable analysis of survival

In univariable analysis, risk of death was associated with higher age, a tumor located in the pancreas, stage III and IV, adenocarcinoma of the pancreas, and diagnosis in the early periods (**Table 3**). After adjustment for age, tumor location, histology, stage, and adjuvant therapy, a significant association between the latest period of diagnosis and a lower risk of death was seen (hazard ratio [HR] = 0.50; 95% confidence interval [95% CI] 0.34–0.73). **Figure 2** shows that after risk adjustment patients diagnosed in the latest period had a significantly better survival compared with patients diagnosed before centralization.

Table 3. Univariate and multivariate Cox regression analysis of overall survival in n = 274 patients with pancreatic surgery following diagnosis of cancer in pancreas, ampulla of Vater, extrahepatic bile duct, or duodenum. The risk of dying is presented as hazard ratio (HR) with the 95% confidence interval (95% CI).

	Univariable		Multivariable	
Characteristics	HR (95% CI)	p-value	HR (95% CI)	p-value
Period of diagnosis		0.11		0.001
1996-2000	1.00		1.00	
2001-2005	0.79 (0.56-1.11)		0.94 (0.67-1.33)	
2006-2008	0.69 (0.49-0.98)		0.50 (0.34-0.73)	
Age		0.008		0.17
<50 years	1.00		1.00	
50-74 years	2.13 (1.32-3.44)		1.49 (0.90-2.46)	
≥ 75 years	1.99 (1.11-3.58)		1.76 (0.96-3.22)	
Gender		0.84		
Male	1.00			
Female	1.03 (0.78-1.36)			
Tumour location		<0.001		<0.001
Pancreas (C25)	1.00		1.00	
Other (C24, C17.1)	0.52 (0.38-0.71)		0.48 (0.35-0.67)	
Histology		<0.001		0.001
Adenocarcinoma	1.00		1.00	
Other	0.29 (0.18-0.49)		0.31 (0.15-0.61)	
Stage (pTNM)		<0.001		<0.001
I-II	1.00		1.00	
III-IV	2.26 (1.65-3.08)		2.46 (1.78-3.42)	
Unknown / no TNM	0.60 (0.37-0.99)		1.38 (0.73-2.60)	
Chemotherapy		0.42		0.81
No	1.00		1.00	
Yes	1.20 (0.77-1.86)		1.07 (0.63-1.80)	
Radiotherapy		0.09		0.76
No	1.00		1.00	
Yes	1.84 (0.91-3.73)		1.14 (0.50-2.59)	

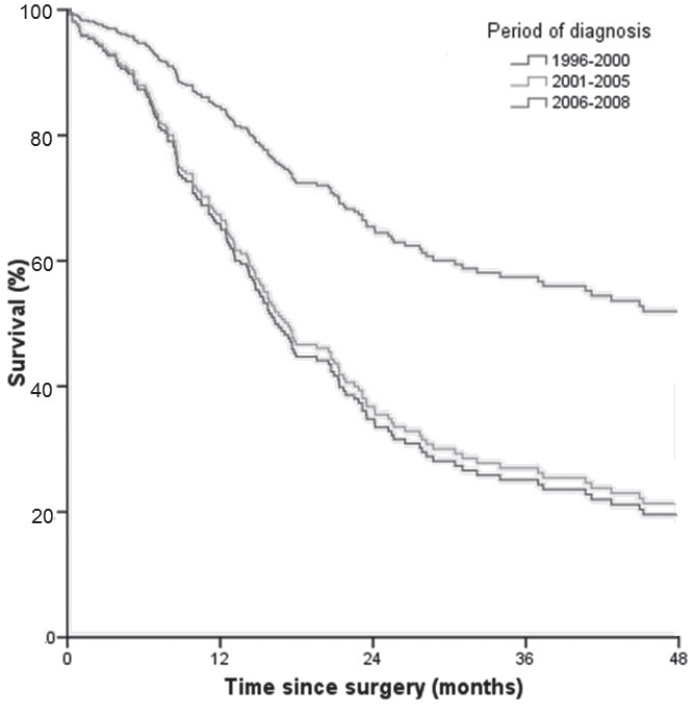

Figure 2. Survival curves for patients with pancreatic surgery for a malignant diagnosis, after adjustment for age, tumor location, histology, and stage, in the western part of the Netherlands, for the periods 1996–2000, 2001–2005, and 2006–2008.

Additional characteristics and outcomes 2006–2009

In the period 2006–2009, in total 213 patients underwent pancreatic surgery in the 2 high-volume hospitals. Almost 25% of all pancreatic surgery was done for benign diagnosis (53 of 213). Most patients had comorbidity (63%) and were classified as ASA II (62%) or higher (15%). The Whipple and the PPPD procedure were the most performed procedures (49%).

The postoperative mortality was 3.3% (7 of 213) and 38% (82 of 213) had postoperative complications. Reintervention was carried out in (18 of 213) 8.6% of all patients. The median length of stay was 10 days, and the median stay at the ICU was 1 day. The median interval between first contact and surgery was 22 days. Of all patients who had pancreatic surgery for a malignant diagnosis, 115 of 160 (72%) had tumor-free margins (R0), 29 of 160 (18%) had microscopic margin involvement (R1), and 1 patient had macroscopic margin involvement (R2). From 15 of 160 (10%) the margin status was unknown.

Discussion

The present study shows that after centralization of pancreatic surgery, the survival of patients with pancreatic malignancies actually improved. After adjusting for differences in age, tumor stage, location, histology, and adjuvant treatment, a strong association between surgery after centralization and improved survival was shown (HR 0.50; 95% CI 0.34–0.73). In addition, after centralization a higher proportion of patients with pancreatic cancer received surgery.

To date there are 9 studies, reporting the association of concentration of pancreatic care and clinical outcomes (**Table 4**) [15–23]. Most did not evaluate centralization as an intervention, but described the concentration of care over time. All studies were based on large administrative databases. In-hospital mortality was the outcome parameter in all studies, and only 4 were risk adjusted. None provided information on survival.

Most previous studies showed a beneficial effect of centralization on in-hospital mortality with mortality reductions varying from 12% to 0.5%. Rosemurgy et al. observed an increased mortality, despite fewer surgeons carried out more pancreatic resections [21]. This was attributed to the fact that most pancreatic surgery was still done by low-volume surgeons and the mortality rate for surgeons in the lowest volume category increased significantly.

This study shows that centralization in the CCCW region was successful. The centralization was based on regional agreement; thus, the regional availability of surgical care was ensured. A frequently mentioned argument against centralization is the concern that the travel burden is too demanding for patients and their family [24]. Our results show an increase of patients operated on within their own region. However, travel distances between the nine affiliated hospitals did not exceed 45 km, so the benefit is limited.

The increased burden of pancreatic surgery in the 2 centers did not result in increased waiting times. The percentage of patients who received surgical treatment for pancreatic cancer increased from 14% to 18%. Because surgical treatment remains the only potential for curing pancreatic cancer, this can potentially benefit the survival of more patients.

The additional outcomes from the period 2006–2009 of all pancreatic surgery were comparable to reported outcomes of other high-volume centers. The number of evaluated lymph nodes increased significantly (from median 2 to median 7 examined lymph nodes) [25]. The complication rate and the rate of involved margins were acceptable and comparable to previously described rates [26,27]. The median length of stay of 10 days, is shorter than previously reported [28].

The present study has several strengths. The NCR provides clinical, population-based data, which are reliable and complete. In addition, a multivariable analysis was performed to adjust for confounding factors, which could be responsible for the improved survival after centralization. However, also several limitations to our data exist.

Table 4. Outcomes reported in previous studies evaluating centralization of pancreatic surgery

Author	Year	Country	Unit	Period	% HVH	No. hospitals/ surgeons[c]	Inhospital mortality	p-value	OR (CI)	RR (CI)
Gordon [15]	1998	USA	Hospital	1984	21		17.2			1.00
				1995[a]	59		4.9			0.92 (0.86-0.99)
Ho [16]	2006	USA	Hospital	1988–1991	2.6[b]		11.4		1.00	
				1992–1996	3.1[b]		10.0		0.97 (0.76-1.23)	
				1997–2000	4b		8.3		0.91 (0.71-1.17)	
Riall [17]	2007	USA	Hospital	1999	54.5		6.6	0.01		
				2004[a]	63.3		3.9			
McPhee [18]	2007	USA	Hospital	1988	30		7.8		1.49 (1.04-2.13)	
				2003[a]	39		4.6		1.00	
Langer [19]	2007	Canada	Hospital	1988–1996	18	72	10.2			
				2002–2004	61	28	4.5	Not reported		
Pal [20]	2008	UK	Hospital	1999–2002		101	6.2			
				2002–2005		73	5.7	Not reported		
Rosemurgy [21]	2008	USA	Surgeon	1995–1997		266	5.1			
				2003–2005		282	5.9	0.45		
Stitzenberg [22]	2009	USA	Hospital	1996	35		7.3			
				2006[a]	70		3.8	0.001		
Gasper [23]	2009	USA	Hospitals	1990–1994	28		9.9			
				1995–1999	37		7.1			
				2000–2004	58		6.0	Not significant		

OR odds ratio, RR relative risk, CI 95% confidence interval.

[a] Not two separate periods compared but a gradual trend over time between the 2 noted years

[b] Mean annual hospital volume

[c] No. of hospitals or surgeons performing pancreatic surgery

First, the cancer registration only collects data of malignant diagnosis. However, pancreatic surgery for benign pathology does contribute to the experience of the surgeon and the hospital. In the latest period, pancreatic surgery was performed in 25% of the cases because of benign diagnoses. It is expected that including benign diagnosis could have had an additional effect on the effect of centralization.

In addition, we had no data on comorbid diseases until 2006. Consequently, risk adjustment for comorbidity, an important determinant of clinical outcome, was not possible [29]. Differences in comorbidity could have influenced our results. In the latest period, 64% of all patients had comorbid disease and the majority was classified as ASA II or higher. We expect that this was not higher in the previous periods because no increase of age occurred and therefore will not have influenced the survival analysis.

Also, we had no detailed information about structural changes in the management of pancreatic cancer. After centralization, a higher proportion of patients received chemotherapy, which could have explained the better survival. However, the univariable and multivariable analysis did not show a significant effect of chemotherapy. We expect that since centralization, more patients who had tumor invasion in the venal portal wall had more extensive resections, including resection of the vessel wall. However, this improvement can be attributed to the centralization: more experienced surgeons could also have more experience with more extensive resections.

Awareness on quality assurance could have had an intrinsic effect on the practice patterns and the dedication of the surgeons and thus have impact on the quality of care, which is known as the Hawthorne effect [30]. However, quality standards were already introduced in 2001 and no differences were detected between the first period and the period after the quality initiatives were started.

The improved survival can also be explained by better patient selection for surgery. In the last period the resection rate increased and the majority of the resected patients was classified as ASA II or higher. The primary tumor was more often located in the pancreas and the extrahepatic bile ducts and less in the duodenum. This suggests that more patients were eligible for a resection after centralization.

At last, the improved survival could have been the result of other improvements in the diagnosis, surgical technique, or postoperative care. However, at a national level, no improvement in overall survival of pancreatic cancer during our study period was observed in the Netherlands (source Netherlands Cancer Registry, available at www.cijfersoverkanker.nl). Although this includes both resected and unresected patients, it can be expected that general improvements in the management of pancreatic cancer would have led to an improved survival at a national level. Nevertheless, progress in techniques could have interfered with our findings.

It is suggested that the beneficial effect of centralization can be explained by better facilities in high-volume centers and more experience of the surgical team, leading to fewer complications,

and better treatment adjusted to the patient [31]. These facilities include specialized diagnostic procedures, anesthetic and postoperative care, radiologic and endoscopic interventions, early recognition and treatment of complications, multidisciplinary teams, knowledge of nutrition, and so forth. It is challenging to identify essential structural characteristics for good quality [32]. Bilimoria showed differences in the utilization of multimodality therapy between low- and high-volume providers [33]. Patients with localized pancreatic cancer were more likely to receive pancreatectomy and adjuvant chemoradiation at academic and high-volume centers. This suggests that more frequent use of surgery and chemoradiation may be one of the underlying reasons of improved outcomes in high-volume centers. Our data show an increased utilization of surgery and adjuvant chemotherapy after centralization as well. Nevertheless, after adjusting for adjuvant chemotherapy, survival was still higher after centralization.

Volume Standards

The evidence for better outcome of complex, low-volume surgical procedures in high-volume centers and the large disparities in quality of care between high- and low-volume centers have fueled the discussion about centralization. Volume is considered a proxy for high quality of care, and volume standards are recommended to improve patient outcomes. However, a minimum volume standard cannot be identified.

In the region of the CCCW in the Netherlands, centralization was based on mutual agreement to assign each complex, low-volume procedure to a different affiliated hospital. The pancreatic procedures were centralized in 2 hospitals with proven high quality of care and the required facilities to perform pancreatic surgery. In this way, the availability of good care in the region was ensured. This can be an example for future centralization initiatives. However, bottom-up centralization initiatives are lacking. Despite the plea for centralization, the referral patterns did not change in the Netherlands in the period 1994–2003, and only slight changes were seen in the United States in the period 1998–2003 [10,18]. Therefore, a top-down introduction of minimal volume standards might be necessary to improve the outcomes of pancreatic surgery. In the United States, the Leapfrog Group, a coalition of large employers and public and private purchasers of health care, introduced a volume standard for pancreatic resections of 11 procedures per year [34]. In Europe, minimal volume standards are currently under consideration.

In conclusion, our study shows that centralization has resulted in improved clinical outcomes of patients who underwent pancreatic surgery for a malignancy. Centralization was realized by agreement of the regional network of surgical oncologists and did not require major structural changes in organization, nor did it affect the accessibility of the health care. These results are encouraging and show how centralization initiatives can actually improve quality of care in a straightforward way. Since regional centralization initiatives are lacking, a top-down introduction of minimal volume standards might be an effective approach to improve the quality of care.

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Chapter 5

Volume–outcome relationships in pancreatoduodenectomy for cancer

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HPB (Oxford). 2016 Apr;18(4):317-24.

Abstract

Background
Volume–outcome relationships in pancreatic surgery are well established, but an optimal volume remains to be determined. Studies analyzing outcomes in volume categories exceeding 20 procedures annually are lacking.

Study design
A consecutive 3,420 patients underwent PD for primary pancreatic or periampullary carcinoma (2005–2013) and were registered in the Netherlands Cancer Registry. Relationships between hospital volume (<5, 5–19, 20–39 and ≥40 PDs/year) and mortality and survival were explored.

Results
There was a non-significant decrease in 90-day mortality from 8.1 to 6.7% during the study period (p = 0.23). Ninety-day mortality was 9.7% in centers performing <5 PDs/year (n = 185 patients), 8.9% for 5–19 PDs/year (n = 1432), 7.3% for 20–39 PDs/year (n = 240) and 4.3% for ≥40 PDs/year (n = 562, p = 0.004). Within volume categories, 90-day mortality did not change over time. After adjustment for confounding factors, significantly lower mortality was found in the ≥40 category compared to 20–39 PDs/year (OR = 1.72, 95% CI 1.08–2.74). Overall survival adjusted for confounding factors was better in the ≥40 category compared to categories under 20 PDs/year: HR (≥40 vs 5–19/year) = 1.24, 95%CI 1.09–1.42. In the ≥40 category significantly more patients received adjuvant chemotherapy and had >10 lymph nodes retrieved compared to lower volume categories.

Conclusions
Volume–outcome relationships in pancreatic surgery persist in centers performing ≥40 PDs annually, regarding both mortality and survival. The volume plateau for pancreatic surgery has yet to be determined.

Introduction

Pancreatic carcinoma affects 10 per 100,000 persons annually [1]. Resection offers the only chance for cure in patients with pancreatic or periampullary (duodenum, ampulla, distal bile duct) carcinoma. Pancreatic surgery is traditionally regarded as low-volume, high-complex surgery. Many studies have clearly demonstrated improved postoperative outcomes following pancreatoduodenectomy (PD) in centers with higher procedural volumes compared to low volume hospitals. However, most studies examine volume–outcome relationships up to more than 20 procedures per year, and an optimal volume cut-off level is currently unknown [2–5].

Over the past decade, centralization of pancreatic surgery has occurred in The Netherlands which was accompanied by improved postoperative and long-term survival [6–9]. Nationwide minimum volumes have been set for various procedures and are reviewed periodically. For PD, in 2011 the Dutch Society for Surgery has set a minimum volume level of 20 procedures per center annually [10]. The question was raised whether further increasing the volume cut-off for PD from 20 to 40 could further improve outcomes.

The aim of this study was to examine postoperative mortality and long-term survival in patients who underwent PD for primary pancreatic or periampullary malignancy in The Netherlands with hospital volume categories higher than previously examined.

Methods

Patient selection

This study was approved by the review board of the Netherlands Comprehensive Cancer Organization (IKNL), which was established to protect the privacy rights of patients and hospitals in the Netherlands Cancer Registry (NCR). Newly diagnosed malignancies in The Netherlands are registered in the population-based NCR, covering 17 million inhabitants. Completeness is estimated to be at least 95%. Topography and morphology are coded according to the international Classification of Diseases for Oncology (ICD-O) [11]. The tumor – lymph node – metastasis (TNM) classification was used to record tumor stage at diagnosis [12]. Survival data was obtained from the Municipal Personal Records Database.

All patients who underwent a PD (either pylorus-preserving or Whipple-Kausch) for primary pancreatic (C25), ampulla of Vater (C24.1), extrahepatic bile duct (C24.0) or duodenal (C17.0) adenocarcinoma between 2005 and 2013 were selected from the NCR. Patients residing or resected abroad, other (pancreatic) resections and age under 18 years old were excluded. Tumor location was categorized as pancreas or periampullary (ampulla, distal bile duct and duodenum). Tumor stage (TNM 6th (2005–2009) and 7th (2010–2013) edition) was based on pathological TNM. Socioeconomic status (SES) was based on The Netherlands Institute for Social Research and deciles were collapsed into three categories (high: 1st–3rd, intermediate: 4th–7th, low: 8th–10th deciles).

Hospital volume and outcome measures

Hospital volume was categorized as <5, 5–19, 20–39 and ≥40 PDs per year. The highest volume category was based on doubling of the current volume cut-off of 20 PDs per year [6, 9]. Hospital volume classification was based on the number of PDs for primary malignancies. The volume category per hospital was calculated for each years separately. For each hospital, the volume category could vary per year. To account for late fatal outcomes of postoperative complications, postoperative mortality was defined as death from any cause within 90 days postoperatively. Patients with metastatic disease undergoing PD (n = 61) were excluded from the analysis of survival. Overall survival (OS) was defined as the time between PD and death Patients alive after December 31st, 2014 were censored. To minimize the influence of postoperative mortality on results of long-term survival, patients alive at 90 days postoperatively were included in the analysis of conditional survival (CS).

Statistical analysis

Baseline patient characteristics (gender, age, prior cancer, SES), tumor characteristics (location, stage, grade) and treatment characteristics (margin status, lymph nodes, chemotherapy) were compared between hospital volume categories using Pearson's chi-square tests. A p-value <0.05 was considered statistically significant. The chi-square test was used to investigate the association between hospital volume and postoperative outcomes. Univariable and multivariable logistic regression analyses were performed to investigate hospital volume and the influence of patient and tumor characteristics on 90-day postoperative mortality. Supplementary multilevel analysis did not reveal relevant clustering within hospitals (likelihood ratio test, p = 0.14) and was discarded. Cox proportional hazard regression analysis was used to evaluate the relation between hospital volume and (conditional) survival. Characteristics with a p < 0.10 in univariable analysis were entered into multivariable models, as well as period of surgery to adjust for possible time effects of (high) hospital volumes. Hospital volume was entered in all models. Analyses were performed using STATA/SE (version 13.0; STATA Corp., College Station, Texas, USA).

Results

Patient and hospital characteristics

In total 3,420 patients were included. The nationwide total volume of PDs for primary pancreatic or periampullary carcinoma doubled from 270 patients in 2005 to 538 patients in 2013. Between 2005 and 2013, an increase was found in the proportion of patients receiving PD aged 65 years or older (from 54 to 64%, p = 0.003) and the proportion of stage II pancreatic carcinoma (T3 or N1, 66–73%, p < 0.001). Patient and hospital characteristics are shown in **Table 1**. Patients in high volume centers more often had high SES (37 vs 24–30%, p = 0.002). In the lowest volume category the tumor was more often located in the periampullary region (50 vs 40–44%, p = 0.012).

Between 2005 and 2013, the number of hospitals performing PD for pancreatic or periampullary carcinoma halved from 42 to 21. The median annual number of PDs per hospital increased from 4 (interquartile range [IQR] 2–7) to 23 (IQR 20–32). The highest volume category of ≥40

procedures per year contained 4% of all hospital-years (5 different hospitals), while the lowest volume category consisted of 30% of all hospital-years. The highest annual number of PD's performed for pancreas or periampullary carcinoma by a single center was 57 in 2013. The number of patients undergoing surgery in a >40 PDs/year center increased from 14% in 2009 to 36% in 2013 ($p < 0.001$).

Table 1. Baseline characteristics of patients who underwent pancreatoduodenectomy (PD) for primary pancreatic or periampullary carcinoma between 2005 and 2013 based on volume of PDs/year.

	All	<5 /year	5-19 /year	20-39 /year	≥40 /year	P-value
Hospital-years n=	286	87	139	48	12	-
Patients n=	3,420	185	1,432	1,241	562	-
	N (%)	%	%	%	%	
Patient						
Sex						0.459
Male	1,929 (56)	58	57	57	53	
Female	1,491 (44)	42	43	43	47	
Age						0.085
<65 years	1,426 (42)	49	43	40	40	
65-74 years	1,385 (41)	40	39	42	42	
≥75 years	609 (18)	11	18	18	18	
History of cancer						0.025
No	2,873 (84)	90	85	82	85	
Yes	547 (16)	10	15	18	15	
SES						0.002
High	1,026 (30)	24	30	28	37	
Medium	1,371 (40)	40	41	40	38	
Low	1,023 (30)	36	30	32	25	
Tumor						
Location of primary tumor						0.012
Pancreas	1,960 (57)	50	60	56	56	
Periampulary	1,460 (43)	50	40	44	44	
Tumor invasion (T)						<0.001
T1-2	1,185(35)	43	39	31	29	
T3-4	2,205(64)	56	60	69	70	
TX	30(0.9)	1	1	1	1	
Lymph node status (N)						<0.001
N0-X	1,376(40)	48	44	38	34	
N1	2,044(60)	52	56	62	66	
Distant metastasis (M)						0.36
M0-X	3,359(98)	99	98	98	98	
M1	61(1.8)	1	2	2	2	

Table 1 continues on next page

Continuation of table 1

Tumor grade						<0.001
Moderate/well diff.	1,835 (54)	64	56	50	51	
Poor diff.	1,041 (30)	26	26	35	33	
Unknown	544 (16)	9.2	18	15	15	
Treatment characteristics						
Lymph nodes [1]	1,660 (49)	23	39	55	66	<0.001
Margin status [2]	2,270 (75)	69	74	78	77	0.024
Chemotherapy [3]	810 (41)	15	30	50	61	<0.001

SES socioeconomic status. Diff differentiation. [1] per cent 10 or more examined. [2] per cent R0, T1-2-3N0-1M0 only.
[3] per cent chemotherapy in patients with pancreatic carcinoma only.

Postoperative mortality

Between 2005 and 2013, no significant decrease in 90-day mortality was found (8.1–6.7%, p = 0.23). The 90-day mortality was 9.7% in centers performing <5 resections annually (n = 185 patients), 8.9% for 5–19 resections (n = 1432), 7.3% for 20–39 resections (n = 1240) and 4.3% for ≥40 resections (n = 562, p = 0.004).Within volume categories, 90-day mortality did not change over time. After adjustment for confounding factors including period of surgery (**Table 2**), significantly worse 90-day mortality was found in each volume category compared to the highest (≥40) volume category: OR = 2.59 (95% CI 1.32–5.09) for the <5 category, OR = 2.11 (95% CI 1.32–3.38) for the 5–19 category and OR = 1.72 (95% CI 1.08–2.74) for the 20–39 category, respectively.

Table 2. Univariable and multivariable analyses predicting 90-day postoperative mortality following PD for pancreatic or periampullary carcinoma between 2005 and 2013.

		Univariable		Multivariable	
Characteristics	N (%)	OR (95%CI)	p-value	OR (95%CI)	p-value
	3,419 (100) [a]				
Hospital volume			0.002		
<5 / year	185 (5)	2.41 (1.28-4.56)		2.59 (1.32-5.09)	0.006
5-19 / year	1,432 (42)	2.18 (1.39-3.41)		2.11 (1.32-3.38)	0.002
20-39 / year	1,240 (36)	1.75 (1.11-2.78)		1.72 (1.08-2.74)	0.023
≥40 / year	562 (16)	1.00		1.00	
Period of surgery			0.232		
2005-2007	853 (25)	1.00		1.00	
2008-2010	1,075 (31)	1.04 (0.75-1.44)		1.08 (0.77-1.52)	0.646
2011-2013	1,491 (44)	0.82 (0.59-1.12)		0.93 (0.65-1.33)	0.695
Sex			0.006		
Male	1,929 (56)	1.00		1.00	
Female	1,490 (44)	0.69 (0.53-0.90)		0.69 (0.53-0.90)	0.006

Table 2 continues on next page

Continuation of table 2

		Univariable		Multivariable	
Characteristics	N (%)	OR (95%CI)	p-value	OR (95%CI)	p-value
	3,419 (100) [a]				
Age			<0.001		
<65 years	1,425 (42)	1.00		1.00	
65-74 years	1,385 (41)	2.07 (1.51-2.83)		2.14 (1.56-2.93)	<0.001
≥75 years	609 (18)	3.03 (2.14-4.31)		3.17 (2.23-4.52)	<0.001
History of cancer			0.921		
No	2,872 (84)	1.00			
Yes	547 (16)	1.02 (0.72-1.44)			
SES			0.378		
High	1,026 (30)	1.00			
Medium	1,370 (40)	1.07 (0.78-1.47)			
Low	1,023 (30)	1.25 (0.90-1.73)			
Location of primary tumor			0.566		
Pancreas	1,959 (57)	1.00			
Periampullary	1,460 (43)	1.08 (0.84-1.39)			
Tumor invasion (T)			0.082		
T1-2	1,185(35)	1.00		1.00	
T3-4	2,204(64)	1.07 (0.81-1.40)		1.12 (0.85-1.48)	0.422
TX	30(0.9)	3.24 (1.29-8.13)		3.47 (1.34-8.98)	0.010
Lymph node status (N)			0.912		
N0-X	1,375(40)	1.00			
N1	2,044(60)	0.99 (0.76-1.28)			
Distant metastasis (M)			0.277		
M0-X	3,358(98)	1.00			
M1	61(1.8)	1.60 (0.72-3.55)			
Tumor grade			0.150		
Moderate/well diff.	1,834 (54)	1.00			
Poor diff.	1,041 (30)	1.09 (0.82-1.46)			
Unknown	544 (16)	1.41 (1.00-1.97)			

SES socioeconomic status. Diff differentiation. OR odds ratio. CI confidence interval.
[a] N=1 lost to follow up due to emigration before 90 days postoperatively.

Treatment characteristics

With increasing hospital volume, there were significant differences in treatment characteristics (**Table 1**). Following adjustment for period of surgery, age, SES, prior cancer, tumor location, stage and grade, and excluding metastatic disease, in the ≥40 category significantly more often 10 or more lymph nodes were found at pathological analysis compared to each lower volume category: OR = 0.22 (95% CI 0.15–0.33) compared to the <5 category, OR = 0.41 (95% CI 0.33–0.51) compared to the 5–19 category, and OR = 0.66 (95% CI 0.54–0.82) compared

to the 20–39 category. Also, significantly more patients received adjuvant chemotherapy in the highest volume category compared to each lower category: OR = 0.22 (95% CI 0.11–0.43) compared to the <5 category, OR = 0.45 (95% CI 0.32–0.60) compared to the 5–19 category, and OR = 0.70 (95% CI 0.52–0.95) compared to the 20–39 category. Furthermore, a radical resection (R0) was achieved significantly more often in the highest volume category compared to the <5 category but not to respective higher categories: OR = 0.62 (95% CI 0.41–0.93) compared to the <5 category, OR = 0.89 (95% CI 0.69–1.15) compared to the 5–19 category, and OR = 1.12 (95% CI 0.87–1.43) compared to the 20–39 category.

Overall survival and conditional survival

Median OS was 16.8 months for patients undergoing resection for pancreatic carcinoma, and 31.9 months for patients with periampullary carcinoma. Older age, pancreatic tumors, advanced tumor stage, poor differentiation, and positive margins were associated with worse OS. After adjustment for confounding factors including the period of surgery, OS was better in the ≥40 volume category compared to hospital volumes under 20 procedures per year: HR = 1.34 (95% CI 1.09–1.65) compared to the <5 category, HR = 1.24 (95% CI 1.09–1.42) compared to the 5–19 category, and HR = 1.10 (95% CI 0.97–1.26) compared to the 20–39 category (**Table 3**). When using the 20–39 volume category as reference category, significantly better OS was found in this reference category compared to volumes under 20 procedures per year: HR = 1.21 (95% CI 1.01–1.46) compared to the <5 category and HR = 1.13 (95% CI 1.02–1.24) compared to the 5–19 category.

Besides aforementioned confounding factors, in CS (n = 3,160), the use of adjuvant chemotherapy was associated with improved survival. In a multivariable model predicting CS, survival of patients alive at 90 days after resection was significantly better in the ≥40 volume category compared to hospital volumes under 20 procedures per year: HR = 1.30 (95% CI 1.04–1.61) compared to the <5 category and HR = 1.19 (95% CI 1.04–1.37) compared to the 5–19 category. No significant difference was found compared to the 20–39 hospital volume category: HR = 1.06 (95% CI 0.93–1.22). When using the 20–39 volume category as reference category, significantly better CS was found in this reference category compared to volumes under 20 procedures per year: HR = 1.22 (95% CI 1.01–1.49) compared to the <5 category and HR = 1.12 (95% CI 1.01–1.25) compared to the 5–19 category.

Table 3. Univariable and multivariable proportional hazard (Cox) regression analyses predicting overall survival following PD for primary pancreatic or periampullary carcinoma between 2005 and 2013.

		Univariable		Multivariable	
Characteristics	N=3,359 [a]	HR (95%CI)	p-value	HR (95%CI)	p-value
Hospital volume			0.002		
<5 / year	184	1.31 (1.08-1.59)		1.34 (1.09-1.65)	0.006
5-19 / year	1,404	1.23 (1.09-1.40)		1.24 (1.09-1.42)	0.002
20-39 / year	1,222	1.10 (0.97-1.26)		1.10 (0.97-1.26)	0.14
≥40 / year	549	Ref		Ref	
Period of surgery			0.320		
2005-2007	843	Ref		Ref	
2008-2010	1,051	0.93 (0.84-1.03)		1.02 (0.92-1.14)	0.70
2011-2013	1,465	0·94 (0.84-1.04)		1.03 (0.91-1.15)	0.68
Sex			0.208		
Male	1,898	Ref			
Female	1,461	0.95 (0.87-1.03)			
Age			<0.001		
<65 years	1,396	Ref		Ref	
65-74 years	1,362	1.17 (1.07-1.28)		1.16 (1.06-1.27)	0.001
≥75 years	601	1.35 (1.21-1.51)		1.31 (1.16-1.47)	<0.001
History of cancer			0.551		
No	2,824	Ref			
Yes	535	1.03 (0.93-1.16)			
SES			0.314		
High	1,006	Ref			
Medium	1,345	1.05 (0.95-1.16)			
Low	1,008	0.98 (0.88-1.09)			
Location of primary tumor			<0.001		
Pancreas	1,921	Ref		Ref	
Periampullary	1,438	0.55 (0.50-0.60)		0.60 (0.55-0.66)	<0.001
Tumor invasion (T)			<0.001		
T1-2	1,174	Ref		Ref	
T3-4	2,157	1.51 (1.38-1.65)		1.20 (1.09-1.32)	<0.001
TX	28	1.32 0.85-2.06		1.60 1.01-2.52	0.04
Lymph node status (N)			<0.001		
N0-X	1,363	Ref		Ref	
N1	1,996	2.11 (1.93-2.30)		1.92 (1.75-2.11)	<0.001
Tumor grade			<0.001		
Moderate/well diff.	1,801	Ref		Ref	
Poorly diff.	1,022	1.53 (1.40-1.67)		1.52 (1.39-1.66)	<0.001
Unknown	536	0.94 (0.83-1.06)		0.99 (0.88-1.12)	0.90

Table 3 continues on next page

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Chemotherapy			0.78		
No	2,399	Ref		Ref	
Yes	960	0.99 (0.90-1.08)		0.70 (0.66-0.81)	<0.001
Radical resection			<0.001		
Yes (R0)	2,481	Ref		Ref	
No	756	2.07 (1.89-2.28)		1.54 (1.49-1.82)	<0.001
Unknown	122	1.80 (1.48-2.20)		1.26 (1.13-1.69)	0.002
≥10 LN examined			0.67		
No	1,621	Ref		Ref	
Yes	1,623	1.03 (0.95-1.12)		0.89 (0.81-0.97)	0.008
Unknown	115	1.08 (0.87-1.34)		1.09 (0.87-1.36)	0.46

SES socioeconomic status. Diff differentiation. LN lymph nodes. HR hazard ratio. CI confidence interval.
[a] Excluding patients with metastatic disease (n=61).

Discussion

In this nationwide population-based study including over 3,400 PDs for primary pancreatic and periampullary carcinoma, an improved postoperative mortality, increased use of adjuvant chemotherapy and higher number of retrieved lymph nodes was observed in centers performing >40 PDs/year, compared to each lower volume category. Significantly favorable OS and CS were found in centers performing 20 or more procedures annually. These results were not confounded by time periods of surgery.

Our findings regarding 90-day mortality are consistent with a recent study using the National Cancer Data Base, in which the unadjusted 90-day mortality rate for PD was 7.4%. Similarly, also in our study 90-day mortality was significantly lower in each higher hospital volume category, up to a category of more than 40 procedures annually [5]. The US study did not report survival outcomes. To our knowledge, this study is the first to examine long-term (survival) volume–outcome relationships including hospitals performing >40 PDs annually. A long-term volume-outcome effect may reflect better quality of surgery (e.g. high percentage R0 resection is associated with lower local recurrence rate), but also better management of late-follow up events (e.g. late postoperative morbidity, disease progression).

Conditional survival reflects the probability of surviving an additional period of time, based on a specific length of time already survived. For patients with pancreatic carcinoma it was previously demonstrated that CS is a better estimator of survival compared to traditional survival estimates [13]. In our study, CS reflects the survival of patients following the initial short-term mortality zone of 90 days and was significantly improved in both volume categories beyond 20 procedures per year compared to lower hospital volumes, and no statistically significant difference was found in volume categories beyond 40 procedures per year compared to a 20–39 hospital volume category. As such, in the present study improved long-term outcomes required

a lower threshold than improved short-term outcomes. Long-term outcomes are influenced by more factors than just short-term postoperative complications. Many patients undergoing surgery in high volume hospitals will receive both adjuvant therapy and management of follow-up events in their referring hospitals. Therefore, to provide high-quality care pathways to all patients centralization of surgical treatment should be accompanied by close collaboration between pancreatic (surgery) centers and referring hospitals.

Patient (SES), tumor and prognostic treatment characteristics differed between hospital volume categories. Although higher volume hospitals resected less patients with TNM Stage I disease, patient SES was higher. Possibly, patients with a higher SES prefer surgery in higher volume, mainly academic centers. Furthermore, with increasing hospital volume, more favorable margin status (R0), number of examined lymph nodes and use of adjuvant chemotherapy were found. More experience with the disease in higher volumes centers might be associated with this finding [14]. However, differences between hospital volumes regarding these important prognostic treatment features did not explain the hospital volume effect in long-term survival.

Increasing capabilities to support patients with postoperative complications may delay some postoperative mortality beyond the 30-day period [15, 16]. Hospitals may differ in their capability to timely recognize and adequately manage severe complications after pancreatic surgery ('failure-to-rescue') [17]. In a previous study, doubled mortality rates at 90- compared to 30-postoperative days following resection for pancreatic carcinoma were found in all hospital volume categories.5 In our study, the most favorable 90-day mortality was found in >40 PDs/year centers. There was non-significant improvement in mortality during the study period. However, as was previously demonstrated, during the study period there was an increase in the number of T3 and N1 patients being resected and an increasing age of resected patients [9, 18]. Especially elderly patients were at increased risk of postoperative mortality.

Due to an almost doubling of pancreatic resections in the Netherlands within eight years, hospital volumes in our study automatically increased over time ('volume creep') [19]. However, a further decrease in the number of hospitals performing pancreatic surgery in most recent years indicates an ongoing centralization of pancreatic surgery in the Netherlands [4, 6, 9]. Based on the current data a volume-plateau for 90-day mortality and overall survival cannot yet be determined. Furthermore, learning curves of hospitals with still increasing volumes could influence outcomes.

This study has some limitations mainly related to the available data in the NCR-database. First, no comorbidity data were available. Negative impacts of comorbid conditions on outcomes following pancreatic surgery have been described and may differ between hospital volume categories [16, 20, 21]. Second, a hospital volume classification based on the number of PDs for primary malignancies was used while the actual volume standard in the Netherlands is based on PD for benign and malignant diagnoses. Therefore, volume categories of hospitals might be slightly underestimated. However, the vast majority of PDs are performed for pancreatic malignancy [7]. With ongoing centralization, future registry studies can investigate the

association between outcomes of PD and hospital volumes at still higher cutoffs. Based on the current data we cannot determine whether the plateau for 90-day mortality and overall survival has been reached with 40 PDs annually.

Concluding, the volume–outcome relationship for PD persists also in centers who perform ≥40 procedures annually, both for lower 90-day mortality rate and overall survival, as compared to lower volume categories. The volume plateau for pancreatic surgery has yet to be determined. Ultimately, research should extend beyond solely hospital volume numbers. Including adequate case-mix correction, surgeon volume, completeness of multidisciplinary care, traveling distances, patient preferences, and other factors all contribute to a more nuanced but complex discussion regarding the volume–outcome relationship in pancreatic surgery.

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PART II

Pancreatic cancer care for elderly patients

Chapter 6

Pancreatic cancer surgery in elderly patients: balancing between short-term harm and long-term benefit, a population-based study in the Netherlands

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Acta Oncol. 2016;55(3):278-85.

Abstract

Background
At a national level, it is unknown to what degree elderly patients with pancreatic or periampullary carcinoma benefit from surgical treatment compared to their younger counterparts. We investigated resection rates and outcomes after surgical treatment among elderly patients.

Methods
From the Netherlands Cancer Registry, 20,005 patients diagnosed with primary pancreatic or periampullary cancer in 2005–2013 were selected. The associations between age (<70, 70–74, 75–79, ≥80 years) and resection rates were investigated using Chi-square tests, and surgical outcomes (30-, 90-day mortality) were evaluated using logistic regression analysis. Overall survival after resection was investigated by means of Kaplan-Meier and Cox proportional hazard regression analysis.

Results
During the study period, resection rates increased in all age groups (<70 years: 20–30%, $p < 0.001$; ≥80 years: 2–8%, $p < 0.001$). Of 3,845 patients who underwent tumour resection for pancreatic or periampullary carcinoma, the proportion of octogenarians increased from 3.5% to 5.5% ($p = 0.03$), whereas postoperative mortality did not increase (30-day: 6–3%, $p = 0.06$; 90-day: 9–8%, $p = 0.21$). With rising age, 30-day postoperative mortality increased (4–5–7–8%, respectively, $p < 0.001$), while 90-day mortality was 6–10–13–12% ($p < 0.001$) and three-year overall survival rates after surgery were 35–33–28–31%, respectively ($p < 0.001$). After adjustment for confounding factors, octogenarians who survived 90 days postoperative exhibited an overall survival close to younger patients (hazard ratio (80 vs.<70 years) = 1.21, 95% confidence interval 0.99–1.47, $p = 0.070$).

Conclusion
Despite higher short-term mortality, octogenarians who underwent pancreatic resection showed long-term survival similar to younger patients. With careful patient screening and counselling of elderly patients, a further increase of resection rates may be combined with improved outcomes.

Introduction

Pancreatic cancer is one of the most fatal types of cancer, with both incidence and mortality rates close to 10 cases per 100 000 European inhabitants [1]. Incidence rates rise with increasing age from less than one case per 100 000 Dutch inhabitants under 40 years of age up to 70 cases per 100 000 inhabitants aged 75 years or older. At time of diagnosis, over half of patients diagnosed with pancreatic cancer are aged 70 years or older.

For pancreatic and periampullary carcinoma, tumour resection is the only treatment option with a curative intent. Unfortunately, tumour resection is possible in only 15–20% of patients due to locally advanced or metastatic disease at time of diagnosis. Pancreatic surgery is considered highly complex due to relatively high morbidity and mortality rates. Therefore, in the past this type of surgery was restricted to relatively young patients. Together with centralisation of pancreatic surgery, postoperative mortality after pancreatic surgery has decreased; with in-hospital and 30-day mortality rates reported under 5% [2,3]. With improving postoperative mortality risk, more elderly patients, including fit octogenarians, may be offered pancreatic surgery [4]. Although several specialised institutions reported an absence of an impact of very old age on postoperative mortality [5–8], some population-based studies on this topic showed unfavourable postoperative outcomes in octogenarians compared to younger patients [4,9–12]. However, less is known about octogenarians compared to other elderly age groups.

In the Netherlands, between 2000 and 2009 an increased resection rate has been observed in patients with pancreatic head carcinoma [13]. And although postoperative mortality after pancreatic surgery decreased between 2004 and 2009, elderly patients showed a twice as high mortality rate compared to patients younger than 70 years of age [14]. It is unknown, however, to what extent elderly patients benefitted from increasing resection rates and improving outcomes.

Therefore, the objective of this nationwide study is to examine resection rates, and short- and long-term outcomes among elderly patients who underwent pancreatic resection for primary pancreatic or periampullary carcinoma, with special attention to octogenarians.

Methods

Data collection

The nationwide Netherlands Cancer Registry (NCR) records data on all patients with newly diagnosed cancer in the Netherlands, a country with nearly 17 million inhabitants. Since 1989, the NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA), supplemented with data from the National Registry of Hospital Discharge Diagnoses. Completeness is estimated to be at least 95%. Information on patient characteristics (e.g. gender and date of birth), as well as tumour characteristics (e.g. date of diagnosis, site and subsite [International Classification of Diseases for Oncology (ICD-O-3)] [15], histology, stage (TNM classification) [16] and grade), and primary treatment are collected routinely from the medical records in all Dutch hospitals. Actual vital status (dead or alive) was

routinely obtained from the Municipal Personal Records Database, which contains information on the vital status of all Dutch inhabitants.

Patients

For this study all patients diagnosed with primary pancreatic, ampulla of Vater, extrahepatic bile duct and duodenum cancer (ICD-O C25, C24.1, C24.0, C17.0) in the period 2005–2013 were selected from the NCR. Patients with diagnosis at autopsy, age under 18 years, residing abroad, histologically confirmed neuroendocrine and non-epithelial malignancies were excluded. Before 2010 no distinction was available between diagnosis of distal and proximal extrahepatic bile duct carcinoma (both C24.0). Therefore, for analysis of resection rates patients diagnosed with extrahepatic bile duct carcinoma (C24.0) were excluded. To analyse outcomes, we selected all patients who underwent resection for histologically proven pancreatic (C25), ampulla of Vater (C24.1) and duodenum (C17.0) carcinoma as well as patients who underwent pancreatic surgery for extrahepatic bile duct carcinoma (C24.0). We excluded patients who underwent endoscopic tumour resection only (n = 51) and patients who underwent tumour resection abroad (n = 63).

To evaluate outcomes of elderly patients in more detail, the age of patients at diagnosis was divided into four groups: <70 years, 70–74 years, 75–79 years and ≥80 years. Patients aged 70 years and older were considered 'elderly' patients. Socioeconomic status (SES) was based on reference data from The Netherlands Institute for Social Research. Scores on social deprivation were derived from income, education and occupation per four-digit postal code, and were broken into three SES-categories (high: 1st–3rd, intermediate: 4th–7th, low: 8th–10th deciles). Due to the nature of the NCR, data on prior cancer diagnoses were available in all patients. In addition, comorbidity data was available in 13% of surgically treated patients in our study. Comorbidity was recorded according to a slightly modified version of the Charlson classification in all patients diagnosed in a NCR region (different time periods in three of nine NCR regions of the Netherlands). Serious comorbid conditions included previous malignancies, chronic obstructive pulmonary diseases, cardiovascular diseases, cerebrovascular diseases, digestive tract diseases, diabetes mellitus and other serious diseases. The number of comorbidities were categorised in three groups (0, 1, ≥2). Tumour stage (TNM) was categorised as 'loco-regional' (T1–2–3 or N+, M0), 'extended' (T4M0), 'metastatic' (M1) or 'unknown' (X), based on pathological TNM and irrespective of tumour location. To account for late fatal outcomes of postoperative complications [3], both 30- and 90-day mortality of any cause after date of tumour resection were evaluated. Survival time was defined as the time from the date of tumour resection to the date of death. Patients who were alive at 1 January 2015 were censored.

Statistical analysis

To compare resection rates in the four age groups and to compare categorical patient (gender, SES), tumour (location, stage, grade) and treatment characteristics of patients who underwent tumour resection, two-sided Pearson's Chi-square tests were used. Until 2012, analyses of two-year periods smoothed the resection rates. To control for potential incompleteness of non-resected patients in the most recent available year of diagnosis, sensitivity analyses were performed excluding 2013. A p-value < 0.05 was considered significant. Univariable and multivariable

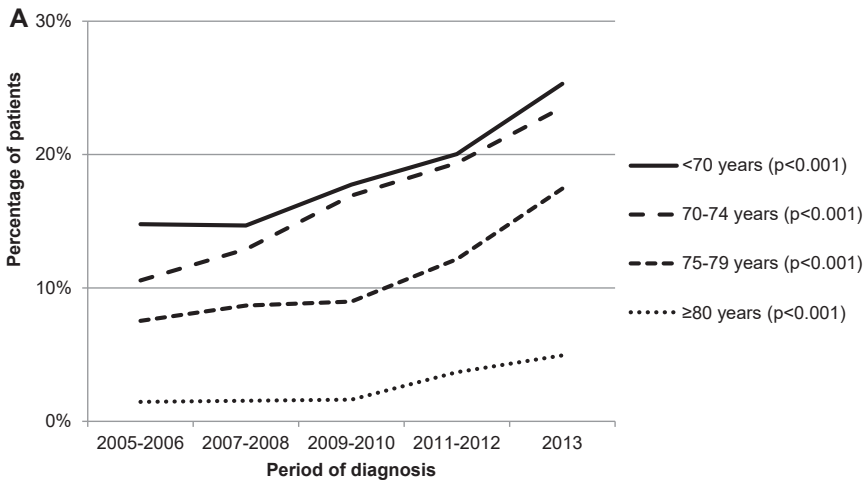
logistic regression analyses were performed to investigate the association of age with 30- and 90-day postoperative mortality. Kaplan-Meier and Cox proportional hazard regression analyses were used to evaluate the relation between age and overall survival. Characteristics with a $p < 0.10$ in the univariable analysis were entered into the multivariable models. In sensitivity analyses, the influence of the number and type of comorbid conditions was investigated. All analyses were performed using STATA/SE (version 13.0; STATA Corp., College Station, TX, USA).

Results

Resection rates

The median age of the 20,005 patients diagnosed with pancreatic (n = 17,742), ampulla of Vater (n = 1,427) and duodenum carcinoma (n = 836) in the period 2005–2013 was 71, 71 and 70 years, respectively (range 19–101 years). Of all these patients, 46% was younger than 70 years of age and 21% was aged 80 years or older. Over time, the proportion of patients undergoing tumour resection increased from 14% in 2005–2006 to 24% in 2013 ($p < 0.001$). This increase was more prominent in patients diagnosed with pancreatic (from 10% to 20%, $p < 0.001$) or ampulla of Vater carcinoma (from 52% to 69%, $p = 0.006$) than in patients with duodenum carcinoma (from 37% to 36%, $p = 0.26$).

Overall, resection rates have increased in all age groups (<70 years: from 20% to 30%; 70–74 years: 16–29%; 75–79 years: 10–22%; ≥80 years: 2.1–7.5% (all $p < 0.001$)). As shown in **Figure 1**, resection rates of patients diagnosed with pancreatic carcinoma and aged 70–74 years (11–24%, $p < 0.001$) approached resection rates of patients under 70 years of age (15–25%, $p < 0.001$). In octogenarians with pancreatic carcinoma, resection rates were lowest and an increase especially took place in most recent years (1–2–2–4–5% in consecutive periods, $p < 0.001$). For ampulla of Vater and duodenum carcinoma together, an increase was only found in patients of ≥80 years (7–23%, $p = 0.02$). Significance levels remained similar after excluding patients diagnosed in 2013.



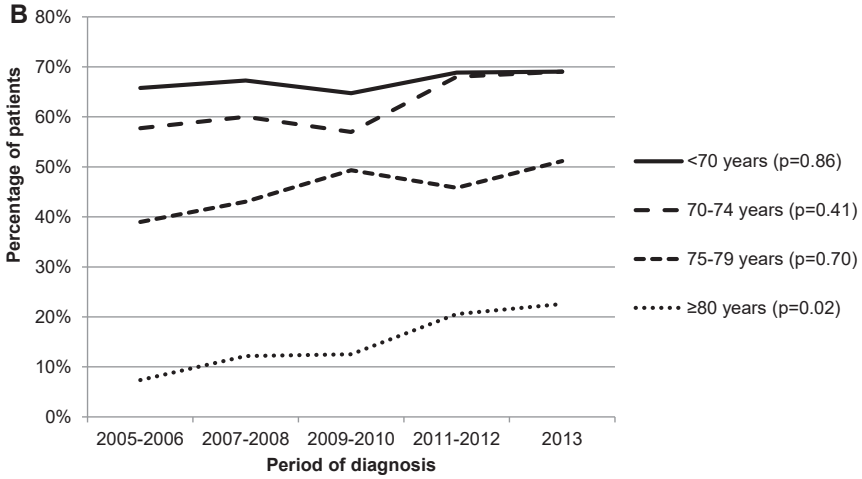


Figure 1. Resection rates by age group of patients diagnosed with primary pancreatic (A) and periampullary (B: ampulla of Vater, duodenum) carcinoma in the period 2005–2013 in the Netherlands.

Patients who underwent tumour resection

The median age of the 3,845 patients who underwent resection for pancreatic (n = 2,260 (59%)) or periampullary (n = 1585 (41%); ampulla of Vater, duodenum and distal bile duct) carcinoma was 67 years (range 19–90 years). Over time, the proportion of patients younger than 70 years of age decreased from 66% in 2005–2006 to 59% in 2013 and the proportion of octogenarians nearly doubled from 3.5% to 5.5% (p = 0.03). Patient and tumour characteristics per age group of resected patients are shown in **Table 1**. Compared to younger age groups, octogenarians more often had resection for periampullary carcinoma (p = 0.01). The prevalence of a prior cancer diagnosis and the number of comorbid conditions increased with older age (both p < 0.001), particularly an increase of cardiac and vascular diseases (both p < 0.001). With rising age, a decreasing proportion of patients with pancreatic carcinoma received adjuvant chemotherapy (48–36–15–3%, p < 0.001).

Table 1. Characteristics of patients who underwent tumour resection for primary pancreatic or periampullary (ampulla of Vater, duodenum and distal bile duct) carcinoma in the period 2005-2013 in the Netherlands, by age group.

	All patients	<70 years	70-74 years	75-79 years	≥80 years	Chi2
	N=3,845	N=2,373	N=781	N=510	N=181	p-value
	%	%	%	%	%	
Sex						0.14
Male	2,149(56)	56	57	56	48	
Female	1,696(44)	44	43	44	52	
Socioeconomic status (SES)						0.58
High	1,154(30)	31	28	29	29	
Intermediate	1,538(40)	39	41	44	34	
Low	1,153(30)	30	31	27	37	

Table 1 continues on next page

Continuation of table 1

	All patients	<70 years	70-74 years	75-79 years	≥80 years	Chi2
	N=3,845	N=2,373	N=781	N=510	N=181	p-value
	%	%	%	%	%	
History of cancer						<0.001
No	3,212(84)	87	81	78	72	
Yes	633(16)	13	19	24	29	
Comorbid conditions [a]	(n=426)	(n=261)	(n=91)	(n=66)	(n=8)	<0.001
0	122(29)	35	20	17	13	
1	125(29)	29	30	30	38	
2+	159(37)	29	48	53	50	
Unknown	20(5)	7	2	0	0	
Location of primary tumour						0.01
Pancreas	2,260(59)	60	60	56	49	
Periampullary	1,585(41)	40	40	44	51	
Tumour stage						0.19
T1-2-3 / N1 M0	3,336(87)	86	88	88	92	
T4 M0	384(10)	11	9	10	7	
M1	98(3)	3	2	2	<1	
X	27(1)	1	1	1	<1	
Tumour grade						0.57
Moderate/well diff.	2,044(53)	53	52	54	54	
Poorly diff.	1,158(30)	31	31	27	27	
Unknown	643(17)	16	17	19	19	

[a] Available in 3 out of 9 cancer regions (n=426, 11% of all patients).

Postoperative mortality

Overall, 4.6% of patients died within 30 days of surgery (from 5.7% in 2005–2006 to 3.2% in 2013, p = 0.06) and at time of 90-days postoperatively 7.8% of patients had deceased (9.2–7.5%, p = 0.21). Over time, 30-day mortality of elderly patients (≥70 years) halved from 9.2% in 2005–2006 to 4.5% in 2013 (p = 0.06) and 90-day mortality slightly decreased from 14.0% to 11.9% (p = 0.27). Less improvement of postoperative outcomes was observed in patients under 70 years of age (30-day mortality: 3.8–2.2%, p = 0.52 and 90-day mortality: 6.3–4.5%, p = 0.39).

With rising age, 30-day mortality worsened (p < 0.001, **Figure 2**). The highest 90-day mortality was found in the age group of 75–79 years of age (p < 0.001). However, postoperative outcomes of the three elderly age groups did not differ significantly from each other (≥70 years: 30-day p = 0.33; 90-day p = 0.37). In multivariable logistic regression models, after adjustment for confounding factors, all elderly patient groups showed significantly worse 30- and 90-day mortality compared to patients under 70 years of age (**Table 2**). No significant associations were found between number or types of comorbid conditions and postoperative mortality.

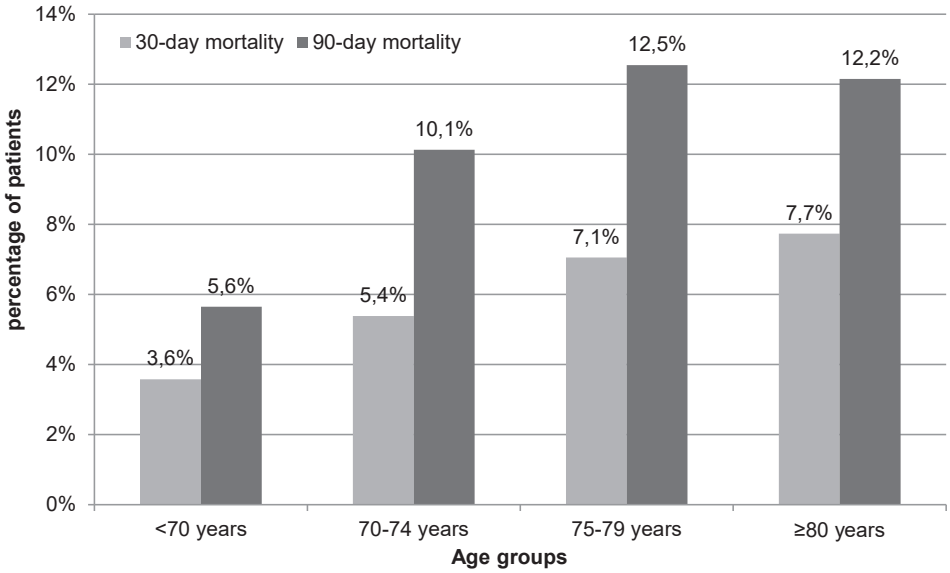


Figure 2. Unadjusted 30- and 90-day of patients who underwent resection for diagnosis of primary pancreas or periampullary carcinoma in 2005–2013 in the Netherlands, by age groups.

Table 2. Univariate and multivariate logistic regression analyses predicting postoperative outcomes (30-day and 90-day mortality) of patients who underwent resection for primary pancreatic or periampullary carcinoma in the period 2005-2013 in the Netherlands.

	30-day mortality			90-day mortality		
	Univariable		Multivariable	Univariable		Multivariable
Characteristics	OR (95% CI)	p-value	OR (95% CI)	OR (95% CI)	p-value	OR (95% CI)
Age		<0.001			<0.001	
<70 years	1.00		1.00	1.00		1.00
70-74 years	1.53 (1.05-2.24)		1.57 (1.07-2.29)	1.88 (1.41-2.52)		1.91 (1.42-2.55)
75-79 years	2.04 (1.37-3.06)		2.07 (1.38-3.10)	2.40 (1.75-3.28)		2.45 (1.78-3.36)
≥80 years	2.26 (1.25-4.06)		2.44 (1.35-4.41)	2.31 (1.43-3.73)		2.48 (1.53-4.02)
Period of diagnosis		0.06			0.21	
2005-2006	1.00		1.00	1.00		
2007-2008	0.84 (0.51-1.37)		0.82 (0.50-1.34)	0.84 (0.57-1.25)		
2009-2010	1.02 (0.65-1.60)		1.01 (0.65-1.59)	1.00 (0.69-1.43)		
2011-2012	0.65 (0.41-1.04)		0.62 (0.39-0.99)	0.69 (0.48-1.00)		
2013	0.54 (0.31-0.97)		0.52 (0.30-0.93)	0.82 (0.54-1.24)		
Sex		0.03			0.008	
Male	1.00		1.00	1.00		1.00
Female	0.71 (0.52-0.97)		0.71 (0.51-0.97)	0.72 (0.56-0.92)		0.71 (0.57-0.91)

Table 2 continues on next page

Continuation of table 2

	30-day mortality			90-day mortality		
	Univariable		Multivariable	Univariable		Multivariable
Characteristics	OR (95% CI)	p-value	OR (95% CI)	OR (95% CI)	p-value	OR (95% CI)
SES		0.89			0.25	
High	1.00			1.00		
Medium	1.04 (0.72-1.50)			1.10 (0.82-1.47)		
Low	1.10 (0.75-1.63)			1.29 (0.95-1.75)		
History of cancer		0.86			0.97	
No	1.00			1.00		
Yes	1.04 (0.69-1.55)			0.99 (0.72-1.37)		
Comorbid conditions [a]		0.83			0.86	
0	1.00			1.00		
1	0.97 (0.31-3.11)			1.24 (0.47-3.25)		
2+	1.30 (0.46-3.67)			1.27 (0.51-3.17)		
Unknown	-					
Primary tumour		0.09			0.29	
Pancreas	1.00		1.00	1.00		
Periampullary	1.30 (0.96-1.76)		1.22 (0.90-1.65)	1.14 (0.90-1.44)		
Tumour stage		0.51			0.05	
T1-2-3 / N+ M0	1.00			1.00		1.00
T4 M0	1.38 (0.88-2.17)			1.26 (0.87-1.82)		1.29 (0.88-1.87)
M1	1.17 (0.47-2.91)			2.09 (1.17-3.74)		2.40 (1.33-4.32)
X	1.74 (0.41-7.39)			2.18 (0.75-6.36)		1.90 (0.64-5.67)
Tumour grade		0.80			0.05	
Moderate/ well diff.	1.00			1.00		1.00
Poorly diff.	1.12 (0.80-1.58)			1.20 (0.92-1.58)		1.22 (0.92-1.60)
Unknown	1.06 (0.70-1.62)			1.46 (1.07-2.00)		1.42 (1.04-1.95)

N number of patients, OR odds ratio, CI Confidence Interval
[a] Available in 3 out of 9 cancer regions (n=426, 11% of all patients).

Survival

Patients with resected pancreatic carcinoma exhibited a worse one-, three- and five-year overall survival (OS; 63%, 24% and 16%, respectively) compared to patients with resected periampullary carcinoma (74%, 47% and 36%). Elderly patients had lower survival rates than patients younger than 70 years of age. Octogenarians had similar one-, three- and five-year OS (pancreas 53%, 21% and 13%; periampullary 73%, 40% and 28%) compared to both other elderly patient groups, especially in patients with pancreatic carcinoma (**Table 3**).

Patient characteristics like SES, a prior cancer diagnosis and the number of comorbid conditions of surgically treated patients were not associated with OS (univariable p = 0.53, p = 0.49 and p = 0.87, respectively). After adjustment for differences in tumour location, stage and grade,

adjuvant chemotherapy and period of diagnosis, OS of octogenarians who underwent pancreatic resection was similar to survival of other elderly patient groups (**Table 4**). In sensitivity analyses on type of comorbid conditions, only the presence of pulmonary diseases seemed independently associated with a poor OS (adjusted HR = 1.75, 95% CI 1.20–2.57). Octogenarians who survived 90 days postoperative exhibited OS close to that of patients younger than 70 years of age (HR (≥80 vs <70years) = 1.21, 95% CI 0.99–1.47, p = 0.07).

Table 3. Crude 1-, 3-, 5-year (yr) survival of patients who underwent tumour resection for primary pancreatic and periampullary carcinoma in the period 2005-2013 in the Netherlands, by age group.

	All patients				Pancreas				Periampullary			
	N=	1-yr (%)	3-yr (%)	5-yr (%)	N=	1-yr (%)	3-yr (%)	5-yr (%)	N=	1-yr (%)	3-yr (%)	5-yr (%)
All ages	3,845	68	33	24	2,260	63	24	16	1,585	74	47	36
<70 years	2,373	71	35	27	1,421	67	25	18	952	77	50	40
70-74 years	781	65	33	22	466	59	24	13	315	72	46	36
75-79 years	510	60	28	17	285	53	21	10	225	68	37	27
≥80 years	181	64	31	21	88	53	21	13	93	73	40	28
p-value		<0.001	<0.001	<0.001		<0.001	0.001	<0.001		0.02	0.004	0.002

Table 4. Univariate and multivariate Cox proportional hazards analyses predicting survival of patients who underwent resection for primary pancreatic or periampullary carcinoma in the period 2005-2013 in the Netherlands.

	Univariable		Multivariable	
Characteristics	HR (95%CI)	p-value	HR (95% CI)	p-value
Age		<0.001		
<70 years	Ref		Ref	
70-74 years	1.14 (1.04-1.26)		1.15 (1.05-1.27)	0.004
75-79 years	1.32 (1.18-1.48)		1.31 (1.17-1.47)	<0.001
≥80 years	1.19 (1.00-1.43)		1.25 (1.04-1.50)	0.02
Period of diagnosis		0.03		
2005-2006	Ref		Ref	
2007-2008	0.85 (0.75-0.96)		0.86 (0.76-0.98)	0.02
2009-2010	0.87 (0.77-0.97)		0.91 (0.81-1.03)	0.13
2011-2012	0.85 (0.76-0.96)		0.90 (0.79-1.01)	0.08
2013	0.95 (0.82-1.11)		0.97 (0.83-1.13)	0.71
Sex		0.10		
Male	Ref			
Female	0.94 (0.87-1.01)			
SES		0.53		
High	Ref			
Medium	1.05 (0.96-1.15)			
Low	1.01 (0.91-1.11)			

Table 4 continues on next page

	Univarable		Multivariable	
Characteristics	HR (95%CI)	p-value	HR (95%CI)	p-value
History of cancer		0.49		
No	Ref			
Yes	1.04 (0.94-1.15)			
Comorbid conditions [a]		0.87		
0	Ref			
1	1.12 (0.83-1.51)			
2+	1.04 (0.78-1.37)			
Unknown	0.97 (0.56-1.68)			
Primary tumour		<0.001		
Pancreas	Ref		Ref	
Periampullary	0.56 (0.52-0.61)		0.49 (0.44-0.53)	<0.001
Tumour stage		<0.001		
T1-2-3 / N+ M0	Ref		Ref	
T4 M0	1.09 (0.96-1.24)		1.34 (1.89-1.53)	<0.001
M1	2.34 (1.90-2.88)		2.49 (2.02-3.07)	<0.001
X	0.75 (0.46-1.22)		0.82 (0.50-1.34)	0.43
Tumour grade		<0.001		
Moderate/well diff.	Ref		Ref	
Poorly diff.	1.49 (1.37-1.62)		1.47 (1.35-1.61)	<0.001
Unknown	0.93 (0.83-1.03)		0.90 (0.80-1.01)	0.07
Chemotherapy		0.08		
No	Ref		Ref	
Yes	0.93 (0.85-1.00)		0.73 (0.66-0.80)	<0.001

HR hazard ratio, CI Confidence Interval
[a] Available in 3 out of 9 cancer regions (n=426, 11% of all patients).

Discussion

This nationwide population-based study showed a 3–4 times increase of resection rates among octogenarians with pancreatic or periampullary carcinoma between 2005 and 2013 in the Netherlands. Among patients who underwent tumour resection, the proportion of octogenarians showed a 50% increase, while no increase of postoperative mortality was found. All elderly patient groups (70 years) exhibited a higher short-term mortality risk compared to patients under 70 years of age, but no significant differences were found between the three elderly patient groups. Adjustment for other contributing factors did not change these results. Interestingly, (conditional) OS of surgically treated octogenarians approached survival of patients younger than 70 years of age.

In line with a recent population-based study in the USA [4], we found increasing resection rates in all age groups and especially in octogenarians. Although patients were less likely to be resected

with older age, the resection rate of patients aged 70–74 years now has reached a level similar to that of younger patients. Our study confirmed an earlier report from the Netherlands attributing an increased resection rate in patients with pancreatic head carcinoma to more patients with advanced tumours (T3 and/or N1) undergoing resection (data not shown) [13]. At that time however, no significant change in the age of resected patients was found. In our study including additional years, particularly in the most recent years increasing resection rates were observed in elderly patients. As a result, age of resected patients has increased (median age from 65 to 67 years). Our findings are in accordance with the recent Dutch guideline on pancreatic cancer [17], stating that high age alone should not be a contraindication for pancreatic surgery. The proportion of octogenarians in our study (4.7%), however, was in the lower range compared to reports from specialised centres (4.5–17%) [5–8] and compared to population-based studies on this subject reporting 5.7–12.4% octogenarians [3,4,10].

Despite increasing resection rates in the course of our study, 30-day postoperative mortality slightly decreased in elderly patients who underwent resection for pancreatic or periampulary carcinoma. Thirty-day postoperative mortality in octogenarians (7.7%) in our study was in line with previous population-based and multi-institutional studies showing a (30-day and/or in-hospital) postoperative mortality between 4.7% and 15.5% [3,4,10]. In concordance with a large observational study of patients undergoing pancreatoduodenectomy for cancer [12], short-term mortality risk of octogenarians in our study did not differ from that of other elderly age groups. In addition, our study showed that also long-term survival of octogenarians was similar to that of other elderly patient groups. Despite a high short-term mortality risk, long-term survival of octogenarians even approached survival of the youngest age group under 70 years of age. Although with increasing age the prevalence of prior cancer and comorbidities increased, these factors were not associated with short- and long-term mortality after surgery. Our results therefore indicate that octogenarians who underwent pancreatic surgery in the Netherlands were carefully selected. It was not known, however, whether all fit elderly patients with resectable pancreatic or periampullary cancers were indeed offered pancreatic surgery or were referred to specialised centres to be evaluated for pancreatic surgery. Centralisation of pancreatic surgery, which has been observed in the Netherlands in the past decade [14], may have unwanted side effects. Hospitals may increasingly differ in (patient and tumour) criteria to select or refer patients for surgery [18]. Therefore, possibly more elderly patients in the Netherlands could benefit from pancreatic surgery [2,10].

Several studies on surgical risks of patients with gastrointestinal cancers showed that postoperative mortality prolonged beyond the 30-day postoperative period [3,19–21]. In a recent study, a doubling of the 30-day mortality rate after pancreatic surgery was found by 90 days postoperative [3]. Our study population showed a 70% increase within the same time span, with 90-day mortality rates of elderly patients exceeding 10%. Major pancreatic surgery and postoperative complications itself may aggravate existing comorbid conditions or a fragile functioning, especially in elderly patients [22]. Preoperative use of geriatric assessment tools may provide additional insight in nutritional, physical, psychological and social risks of elderly patients [23]. Furthermore, the improved ability to support patients with severe postoperative

complications may have resulted in delayed mortality beyond the 30-day period. However, extending the time window of postoperative mortality risks until 90 days postoperatively may include patients who die from progressive disease [21]. In our study, both elderly patients and resected patients with metastatic disease showed an elevated 90-day mortality risk. Therefore, an extended postoperative time window in pancreatic surgery for cancer will reflect quality of the perioperative surgical process as well as adequate preoperative diagnosis and selection of resectable patients.

A major limitation of our study on elderly patients is the lack of national data on comorbidity. However, available comorbidity data were collected region-wide and nearly complete. In sensitivity analyses the number and type of comorbid conditions were not significantly associated with short- and long-term mortality after pancreatic resection for cancer, possibly except for pulmonary diseases. Although these analyses may suffer from a lack of power due to small numbers in elderly age groups, available data in the total study population on prior cancer diagnoses showed similar associations with outcomes. In addition, the influence of comorbidity on survival seems of less importance in cancers with poor prognosis, such as pancreatic cancer [24]. Furthermore, no information was available on postoperative complications and cause of death. Overall, mixed results were found on the association of high age and morbidity after pancreatic surgery for cancer [2,5,8,12]. However, in studies that differentiated between surgical and non-surgical complications, age differences were particularly found in non-surgical complications [12,25].

Conclusions

In the past decade, increased resection rates were observed in all age groups and especially in octogenarians with pancreatic or periampullary carcinoma on a nationwide level. Despite a high short-term mortality risk similar to other elderly patients surgically treated octogenarians showed long-term survival similar to younger patients. Careful patient screening and ongoing centralisation may further increase resection rates while improving postoperative mortality and survival. Selection for resection solely based on age seems not justified.

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Chapter 7

Elderly patients strongly benefit from centralization of pancreatic cancer surgery: a population-based study

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Ann Surg Oncol. 2016 Jun;23(6):2002-9.

Abstract

Background
Series from expert centers suggest that pancreas cancer surgery is safe for elderly patients but nationwide data, taking hospital volume into account, are lacking.

Methods
From the Netherlands Cancer Registry, all 3,420 patients who underwent pancreatoduodenectomy (PD) for primary pancreatic or periampullary carcinoma in 2005–2013 were selected. Associations between age (<75, ≥75 years), hospital volume (tertiles), and postoperative mortality (30, 90 day) were evaluated by Chi-square tests and logistic regression analyses. Overall survival was investigated by means of Kaplan–Meier and Cox proportional hazard regression analyses.

Results
The proportion of elderly patients (C75 years) undergoing PD increased from15% in 2005–2007 to 20% in 2011–2013 (p = 0.009). In low (\15 per year), medium (15–28 per year), and high (>28 per year) hospital volume tertiles, the proportion of elderly patients was 16, 20, and 17%, respectively (p = 0.10).With increasing hospital volume, 30-day postoperative mortality was 6.0–4.5–2.9% (p = 0.002) and 90-day mortality 9.3–8.0–5.3% (p = 0.001), respectively. Within each volume tertile, adjusted 30- and 90-day mortality of elderly patients was 1.6–2.5 times higher compared to outcomes of younger patients. Adjusted 30-day mortality in elderly patients was higher in low-volume hospitals (odds ratio = 2.87, 95% confidence interval 1.15–7.17) compared to high-volume hospitals. Similarly, elderly patients had a worse overall survival in low-volume hospitals (hazard ratio = 1.28, 95% confidence interval 1.01–1.63). Postoperative mortality of elderly patients in high-volume hospitals was similar to mortality of younger patients in low and medium-volume hospitals.

Conclusions
Elderly patients benefit from centralization by undergoing PD in high-volume hospitals, both with respect to postoperative mortality and survival. It would seem reasonable to place elderly patients into a high-risk category; they should only undergo surgery in the highest tertile-volume hospitals.

Introduction

At diagnosis, over half of patients with primary pancreatic or periampullary cancer is aged 70 years or older [1]. Although pancreatic resection is the only treatment option with curative intent, only 15–20% of pancreatic cancer patients are eligible for surgery [2,3]. Pancreatic surgery is regarded as low-volume, high-risk surgery. Many studies have shown a strong and consistent relation between high procedural volumes and favorable postoperative outcomes after pancreatic surgery [4–6]. Hospital volume represents various interdepending structure and process characteristics of hospitals influencing morbidity rates, management of complications, and postoperative mortality [7]. In the past decade, after centralization of pancreatic surgery, a decreased postoperative mortality after pancreatic surgery was observed in the Netherlands [8–10].

Together with improving postoperative mortality, an increased resection rate was observed in elderly pancreatic cancer patients in the United States [11]. Generally, elderly patients experienced worse postoperative outcomes compared to younger patients [11–13]. Because of higher rates of comorbid diseases and a decreased physiologic reserve, elderly patients may experience difficulties to counter complications after major surgery. Several studies showed a more than two times higher postoperative mortality in elderly patients who underwent pancreatic surgery, which is also found in the era of centralization [10,14]. However, little is known about the magnitude of the influence of hospital volumes on surgical outcomes of elderly patients. In addition, it is not known whether the centralization process of pancreatic surgery differs between younger and elderly patients.

Therefore, the purpose of this study was to investigate centralization, hospital volume, and postoperative mortality in elderly patients who underwent pancreatoduodenectomy (PD) for primary pancreatic or periampullary adenocarcinoma in the Netherlands.

Methods

Data source

The nationwide Netherlands Cancer Registry (NCR) covers nearly 17 million inhabitants and comprises population- based data on newly diagnosed malignancies. The primary source of notification of the NCR is the automated nationwide pathologic archive (PALGA), supplemented with data from the National Registry of Hospital Discharge Diagnoses. Since 1989, trained registration administrators collected data on patient, tumor, and treatment characteristics from the medical records in all Dutch hospitals. Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O) [15]. Tumor stage was based on the tumor, node, metastasis classification system(TNM) that was applicable (6th edition in 2003–2009 and 7th edition thereafter) [16]. Follow-up of vital status was obtained by annual linkage with the Municipal Personal Records Database, which contains the information of all Dutch inhabitants (dead or alive, or emigrated).

Patients and outcome measures

All patients who underwent PD (pylorus-preserving and Whipple procedures) for primary pancreatic (ICD-O code C25.0–9) or periampullary [located in ampulla of Vater (C24.1), distal extrahepatic bile duct (C24.0) or duodenum (C17.0)] adenocarcinoma in the period 2005–2013 were selected and included in this study.

Patients were divided into two age groups: younger (<75 years at time of diagnosis) and elderly (≥75 years) patients. Because of the nature of the NCR, data on prior cancer diagnoses were available. Because information on other comorbid diseases was lacking in the majority of patients, data on socioeconomic status (SES) were used [17, 18]. SES was based on reference data from the Netherlands Institute for Social Research. Scores on social deprivation were derived from income, education, and occupation per 4-digit postal code, and were broken into three SES categories (high, first to third deciles; intermediate, fourth to seventh deciles; low, eighth to 10th deciles). Pathologic tumor stage (TNM) was categorized as stage I, II, III, and IV according to tumor location.

Hospital volumes were defined as the number of PDs that were performed per hospital per year and were broken evenly into volume categories by tertile: low hospital volumes (LHV, <15 resections per year), medium hospital volumes (MHV, 15–28 per year), and high hospital volumes (HHV, ≥28 per year), to obtain a similar number of patients in each volume category. In sensitivity analysis, hospital volume tertiles were calculated within 3-year periods of surgery (2005–2007, 2008–2010, 2011–2013, **Figure 1**) to reduce the influence of many LHVs in the first time period.

To account for late fatal outcomes of postoperative complications, both 30- and 90-day mortality of any cause after date of resection were calculated [14]. Survival time was defined as the time between date of surgery and date of death. Patients alive as of January 1, 2015, were censored.

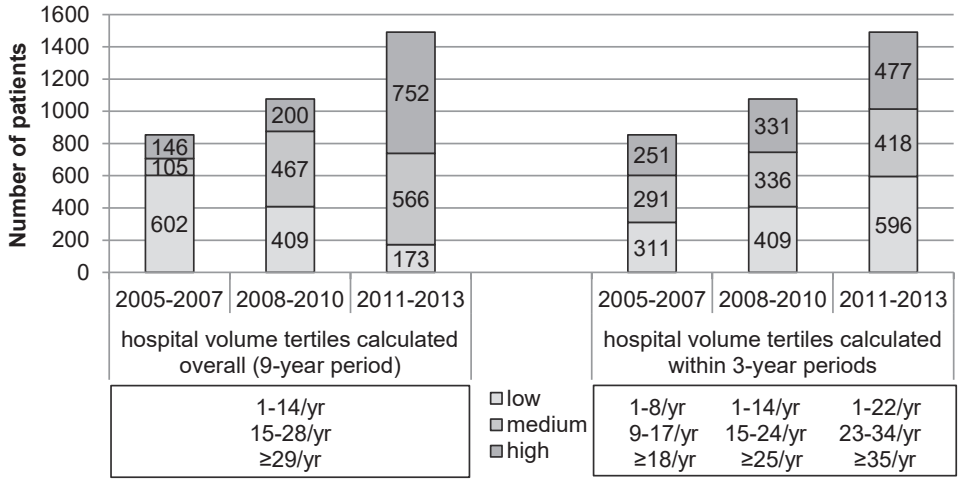

Figure 1. Hospital volume tertiles of 3420 patients who underwent pancreatoduodenectomy for primary pancreatic or periampullary adenocarcinoma in 2005–2013 in the Netherlands, calculated in two different ways.

Statistical analysis

To compare categorical characteristics of patients who underwent PD by age and by hospital volume, Pearson's Chi-square tests were used. A p value of <0.05 was considered significant. Chi-square tests were also used to compare postoperative outcomes (30 and 90 days) of younger and elderly patients within each hospital volume category. Univariable and multivariable logistic regression analyses were performed to investigate the association of age and hospital volume with postoperative mortality (30 and 90 days) after PD for pancreatic and periampullary carcinoma. Kaplan–Meier and Cox proportional hazard regression analyses were used to evaluate survival. All multivariable models were adjusted for the (possible) influence of year of surgery, sex, prior cancer, SES, and tumor location, stage, and grade. Multivariable Cox models were additionally adjusted for the use of adjuvant chemotherapy. All analyses were repeated with higher cutoff levels for age. Because of low numbers of octogenarians (n = 163) reducing the statistical power, an intermediate cutoff point at the 90th age percentile was also used (≥78 years, n = 303). All analyses were performed by STATA/SE 13.0 (StataCorp, College Station, TX).

Results

Patients

Of all 3,420 patients who underwent PD for primary pancreatic or periampullary carcinoma, the proportion of elderly patients (≥75 years, 18%) increased over time from 15% in 2005–2007 to 20% in 2011–2013 (p = 0.009). Elderly patients more often had a periampullary carcinoma (46 vs. 42%, p = 0.05) and a prior cancer (25 vs. 14%, p < 0.001) compared to younger patients. In **Table 1**, patient and tumor characteristics are compared between tertiles of hospital resection volumes. Between hospital volume tertiles, borderline significant age differences were found (≥75 years: 16, 20, and 17%, p = 0.10). However, over time, the strongest increase in the proportion of elderly patients was found at LHV (from 15% in 2005–2007 to 24% in 2011–2013, p = 0.02; MHV, 17–20%, p = 0.72; HHV, 14–18%, p = 0.25). A similar pattern was found for higher age cut-offs (≥80 years: LHV, 3–8%, p = 0.02; MHV, 5–6%, p = 0.37; HHV, 2–6%, p = 0.12) and for hospital volume tertiles calculated within 3-year periods (≥75 years: LHV, from 14% in 2005–2007 to 21% in 2011–2013, p = 0.009; MHV, 16–19%, p = 0.57; HHV, 15–19%, p = 0.43). Furthermore, the use of adjuvant chemotherapy in patients with pancreatic carcinoma increased with increasing hospital volumes for both younger (<75 years: 39–47–57% in LHV–MHV–HHV, p < 0.001) and elderly patients (≥75 years: 9–10–19%, p = 0.07; volume tertiles within 3-year periods).

Table 1. Patient, tumor and treatment characteristics of patients who underwent pancreatoduodenectomy (PD) for primary pancreatic or periampullary adenocarcinoma (ampulla of Vater, duodenum and distal bile duct) in 2005-2013 in the Netherlands, by hospital volume tertiles (Low, Medium, High hospital volume (HV)).

	All patients	Low volume	Medium volume	High volume	
	N=3,420	N=1,184	N=1,138	N=1,098	Chi-square
	N(%)	%	%	%	p-value
Sex					0.08
Male	1,928(56)	59	55	56	
Female	1,491(44)	41	45	44	

Table 1 continues on next page

Continuation of table 1

Age					0.10
< 75 years	2,811(82)	84	80	83	
≥ 75 years	609(18)	16	20	17	
History of cancer					0.14
No	2,873(84)	86	83	84	
Yes	547(16)	14	17	16	
Socioeconomic status (SES)					0.006
High	1,026(30)	29	28	34	
Intermediate	1,371(40)	41	39	40	
Low	1.023(30)	30	33	27	
Location of primary tumor					0.13
Pancreas	1,960(57)	58	59	55	
Periampullary	1,460(43)	42	41	45	
Tumor stage (TNM)					0.001
I	656(19)	23	18	16	
II	2,313(68)	63	68	72	
III	367(11)	11	11	9.8	
IV	61(1.8)	1.7	1.7	2.0	
X	23(0.7)	0.8	0.5	0.6	
Tumor grade					<0.001
Moderate/well diff.	1,835(54)	58	51	51	
Poorly differentiated	1,041(30)	26	31	34	
Unknown	544(16)	15	18	14	
Adjuvant chemotherapy (pancreas only, % yes)	810 (41)	22	48	56	<0.001

Low hospital volume <15 resections per year; medium 15–28 resections per year; and high >28 per year.
TNM tumor-node-metastasis classification system.

Postoperative outcomes

Over time, 30-day mortality in elderly patients showed a tendency to decrease, from 10.2% (13/127) in 2005–2007 to 5.1% (15/296) in 2011–2013 (p = 0.15); in younger patients, a decrease was found, from 4.3% (31/726) to 3.3% (40/1195) (p = 0.31). At 90 days after surgery, a similar pattern was found in younger (6.9–5.7%, p = 0.26) and elderly patients (15.0–10.8%, p = 0.47). Overall, HHV showed the most favorable 30-day (p = 0.002) and 90-day postoperative mortality rates (p = 0.001). As shown in Table 2, within all hospital volume tertiles, mortality was less favorable for elderly patients compared to younger patients. After adjustment for confounding factors, in LHV 30-day postoperative mortality of elderly patients was more than double that of younger patients, while differences in MHV and HHV were less pronounced (p = 0.10 and p = 0.31, respectively). Adjusted 90-day mortality in elderly patients was significantly increased within each hospital volume tertile (**Table 2**). Furthermore, in all hospital volume tertiles, elderly patients had a worse overall survival compared to younger patients (**Table 3**). After supplemental adjustment for adjuvant chemotherapy, the strongest reduction of the hazard ratio (HR) of mortality was found in HHV.

Table 2. Univariable and multivariable logistic regression analyses predicting 30-day and 90-day postoperative mortality of patients who underwent PD for primary adenocarcinoma, by age of patients within each hospital volume tertile.

				Univariable		Multivariable	
30-day mortality	N	P	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Low HV	1,184	6.0					
Age <75 years	989	5.2	0.006	1	0.007	1	0.007
Age ≥75 years	195	10.3		2.10 (1.22-3.61)		2.13 (1.23-3.70)	
Medium HV	1,138	4.5					
Age <75 years	913	3.9	0.08	1	0.08	1	0.10
Age ≥75 years	225	6.7		1.74 (0.94-3.24)		1.72 (0.91-3.25)	
High HV	1,098	2.9					
Age <75 years	909	2.8	0.48	1	0.48	1	0.31
Age ≥75 years	189	3.7		1.36 (0.58-3.19)		1.59 (0.65-3.88)	
90-day mortality	N	P	p-value	OR (95% CI)	P-value	OR (95% CI)	p-value
Low HV	1,184	9.3					
Age <75 years	989	8.4	0.02	1	0.02	1	0.01
Age ≥75 years	195	13.9		1.75 (1.10-2.79)		1.81 (1.13-2.91)	
Medium HV	1,138	8.0					
Age <75 years	913	6.6	<0.001	1	<0.001	1	0.001
Age ≥75 years	225	13.8		2.27 (1.43-3.60)		2.28 (1.42-3.65)	
High HV	1,097	5.3					
Age <75 years	908	4.5	0.01	1	0.008	1	0.004
Age ≥75 years	189	9.0		2.05 (1.20-3.50)		2.46 (1.32-4.59)	

HV hospital volume, <15 resections per year; medium, 15–28 resections per year; and high, >28 per year; p value by Chi-square test, N number of patients, P proportion of patients deceased, OR odds ratio, CI confidence interval.

Table 3. Univariable and multivariable Cox proportional hazard analyses predicting overall survival of patients who underwent PD for primary adenocarcinoma, by age of patients within each hospital volume tertile.

	Univariable analysis		Multivariable analysis		Multivariable analysis + adjuvant chemotherapy	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Low HV						
≥75 vs <75 years	1.29 (1.09-1.52)	0.004	1.27 (1.07-1.51)	0.006	1.21 (1.02-1.44)	0.03
Medium HV						
≥75 vs <75 years	1.24 (1.04-1.47)	0.02	1.45 (1.21-1.73)	<0.001	1.31 (1.09-1.57)	0.004
High HV						
≥75 vs <75 years	1.24 (1.01-1.51)	0.04	1.32 (1.08-1.61)	0.007	1.16 (0.94-1.43)	0.17

HV hospital volume, <15 resections per year; medium, 15–28 resections per year; and high, >28 per year
HR hazard ratio, CI confidence interval.

Age and hospital volume combined

Age groups and volume tertiles were combined in each model, taking as the reference group the category elderly patients who underwent PD in HHV (**Figure 2**). The adjusted 30-day mortality of elderly patients was worse in LHV compared to HHV (odds ratio [OR] = 2.87, 95% confidence interval [CI] 1.15–7.17). Ninety days after surgery, younger patients in HHV had a lower adjusted mortality (OR = 0.46, 95% CI 0.26–0.84) compared to elderly patients at HHV, but no significant difference was found between elderly patients in LHV and HHV (p = 0.16). Although elderly patients treated in HHV showed a better overall survival compared to elderly patients in LHV (HR = 1.28, 95% CI 1.01–1.63), they had a worse survival compared to younger patients in HHV (HR = 0.77, 95% CI 0.63–0.94) (**Figure 2**). In a second regression model including adjuvant chemotherapy, the worse survival of elderly patients in LHV persisted (HR = 1.29, 95% CI 1.02–1.64). Postoperative mortality and overall survival of elderly patients at HHV did not differ statistically from outcomes of younger patients at LHV and MHV (p ≥ 0.16). In sensitivity analyses, with hospital volume tertiles calculated within 3-year periods, a similar pattern was found (**Supplementary Table 1** and **Supplementary Figure 1**). Also, an age cut-off point at the 90th percentile (9% of patients) showed a worse postoperative mortality and overall survival for elderly patients at LHV compared to elderly patients at HHV [30 days: OR (≥78 years in LHV vs. ≥78 years in HHV) = 2.29, 95% CI 1.53–34.59; 90 days: OR = 2.93, 95% CI 1.11–7.75; overall survival: HR = 1.43, 95% CI 1.00–2.03]. Comparisons of other age–volume combinations with elderly patients in HHV did not reach statistical significance. Analyses of octogenarians compared to younger patients showed similar results.

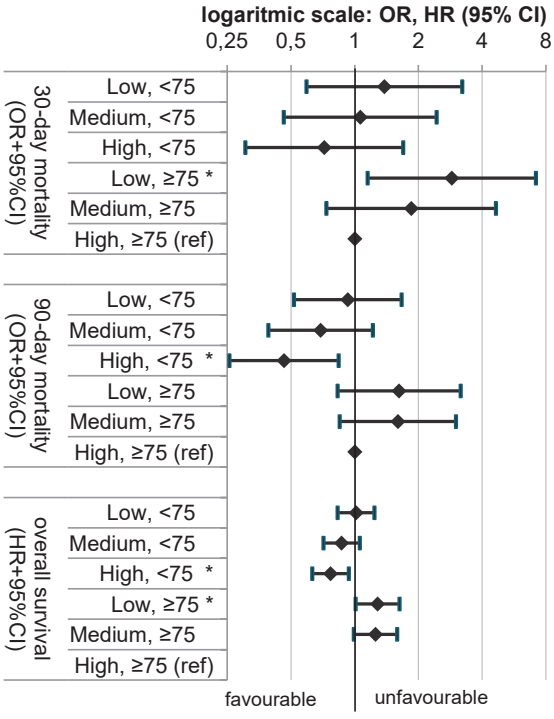

Figure 2. Multivariable analyses predicting postoperative 30- and 90- day mortality and overall survival of 3420 patients who underwent pancreatoduodenectomy for primary adenocarcinoma by age of patients (<75 years, ≥75 years) and hospital volume tertiles (low, medium, high) combined.
*p<0.05. OR odds ratio, HR hazard ratio, CI confidence interval, Ref reference category.

Discussion

This nationwide study of 3,420 patients who underwent PD for primary pancreatic or periampullary carcinoma in the Netherlands found lower 30- and 90-day mortality in elderly patients treated at HHV compared to lower hospital volumes. Within each hospital volume tertile, postoperative mortality of elderly patients was 1.6–2.5 times higher compared to younger patients. Mortality rates of elderly patients in high-volume hospitals equalled mortality rates of younger patients in low- and medium-volume hospitals, while mortality rates of elderly patients in low-volume hospitals were worse.

In earlier reports from the Netherlands based on data until 2009, centralization of pancreatic surgery was observed, but no change was found in the age distribution of patients undergoing resection [10,19]. With ongoing centralization (the number of hospitals performing PDs decreased from 42 in 2005 to 21 of 91 hospitals in 2013), our study showed that the age of patients undergoing PD increased, especially from 2011 onward. The 2011 Dutch evidence-based guideline on pancreatic and periampullary carcinoma state that advanced age by itself should not be a contraindication for pancreatic surgery [20]. Also in 2011, the Dutch Healthcare Inspectorate (IGZ) and Dutch Society for Surgery (NVvH) set a minimum hospital volume standard for pancreatic surgery (benign and malignant) at 20 PD procedures per year [21]. In our study, over time, a steeper increase of the age of patients who underwent PD for cancer was found in low-volume hospitals. This finding suggests that treatment guidelines and volume standards have stimulated pancreatic surgery in the elderly, especially in low-volume hospitals. One may speculate that low-volume hospitals may have had more trouble attaining the national volume standard for pancreatic surgery, while high-volume hospitals may have room to select fit elderly patients. On the other hand, patients who seek care at low-volume hospitals may be older compared to patients seeking care at high-volume (university) hospitals. In recent years, an increasing proportion of this reservoir of eligible elderly patients in low-volume hospitals may have been offered pancreatic surgery.

We also found that patients who underwent pancreatic resection in high-volume hospitals more often had a high SES. In studies on treatment decision making, especially elderly and low-educated patients seem less likely to take active roles in the treatment decision-making process [22]. Elderly or low-SES patients may hesitate to leave "their" nearby hospital with doctors who know their comorbid diseases well, or they may prefer the nearest hospital because of the short travel distance [23]. Also, referral patterns may already differ by age or SES at the level of general practitioners before the first hospital visit. With ongoing centralization of pancreatic surgery, a better understanding is needed of factors influencing referral and treatment decision making in elderly patients [22]. The centralization process should not stimulate referral of only younger patients to hospitals with higher volumes.

Despite the rising age of patients who underwent PD, a slight decrease of postoperative mortality was found during our study period. Older age and the presence of comorbid diseases are important risk factors for early postoperative mortality [12,24]. In several studies a (more

than) doubled postoperative mortality was found in elderly patients who underwent pancreatic surgery [10,14]. Mortality differences between hospital volume tertiles in our study may be the result of differences in the incidence of complications and the ability to manage them (failure to rescue) [7]. Generally, morbidity rates were high after pancreatic surgery [25,26]. In studies that differentiated between surgical and nonsurgical complications, age differences were particularly found with respect to nonsurgical complications [13,25,27]. In our study, age differences in nonsurgical complications and failure-to-rescue rate may have contributed to the strong additive relation of age and hospital volume concerning postoperative mortality. Furthermore, the mortality difference between elderly and younger patients seemed to increase slightly between 30 and 90 days after surgery, especially in medium- and high-volume hospitals. These results suggest that in medium and high-volume hospitals, a better ability to manage postoperative complications may have delayed some mortality beyond the 30-day period. Despite a possible delayed mortality, 90-day postoperative mortality of elderly patients in high-volume hospitals in our study remained similar to that of younger patients in low- and medium-volume hospitals. Therefore, elderly patients may benefit from undergoing pancreatic surgery in high-volume hospitals.

Overall, chemotherapy use after resection for pancreatic carcinoma was low in the Netherlands (41%). Adjuvant chemotherapy after resection of pancreatic carcinoma is now considered the standard of care [20,28,29]. Elderly patients and patients in low-volume hospitals in our study were less likely to receive adjuvant chemotherapy. Adjustment for variation of chemotherapy only slightly explained the decreased survival of elderly patients in low-volume hospitals. In these hospitals, other factors like postoperative complications may have contributed to both postoperative mortality and the omission of adjuvant chemotherapy [24]. The Netherlands is characterized by good access to health care facilities as a result of its well-organized health insurance. After diagnosis of pancreatic cancer, physicians should inform elderly patients about volume–outcome patterns in pancreatic surgery. Furthermore, when discussing minimum volumes of pancreatic surgery, special attention should be paid to the elderly and potentially other high-risk groups, such as patients with premalignant or extensive disease. These patients may be regarded as comprising specific high-risk categories; they should be operated on only in the highest tertile volume hospitals. In this way, high-risk patients are provided with similar operative risks as low-risk patients such as younger patients.

Our study has some major limitations, especially the lack of detailed data on the health status of patients. Adjustment for number and type of comorbid diseases may limit the magnitude of mortality differences between younger and elderly patients after PD surgery [12]. However, available data on SES and a prior diagnosis of cancer that were included in the multivariable models hardly influenced the association of age with postoperative outcomes after PD. SES may have little (additional) impact because patients who were offered high-risk pancreatic surgery will be relatively fit. Furthermore, comorbidity information had only limited impact on survival in cancers with poor prognosis like pancreatic cancer [30]. Second, in the NCR, no data were available on surgical and nonsurgical postoperative complications after PD. In 2013, the Dutch

Pancreatic Cancer Audit (DPCA) was launched, and in the future, this will provide more extensive case mix correction and investigation of postoperative complications [31].

Conclusions

Over time, the age of patients undergoing PD for primary pancreatic or periampullary adenocarcinoma increased. In low-volume hospitals, this increase was slightly more pronounced compared to medium- and high-volume hospitals. A better understanding is needed of the dynamics of centralization and factors influencing referral and treatment decision making in elderly patients. Furthermore, both older age and lower hospital volume were independently and strongly related to increased postoperative mortality after PD for primary adenocarcinoma (additive effect). To improve postoperative mortality and overall survival, elderly patients should undergo pancreatic surgery in hospitals with low baseline risks, i.e., the highest volume tertile facility. In this way, these patients are offered an operative risk comparable to that of younger patients.

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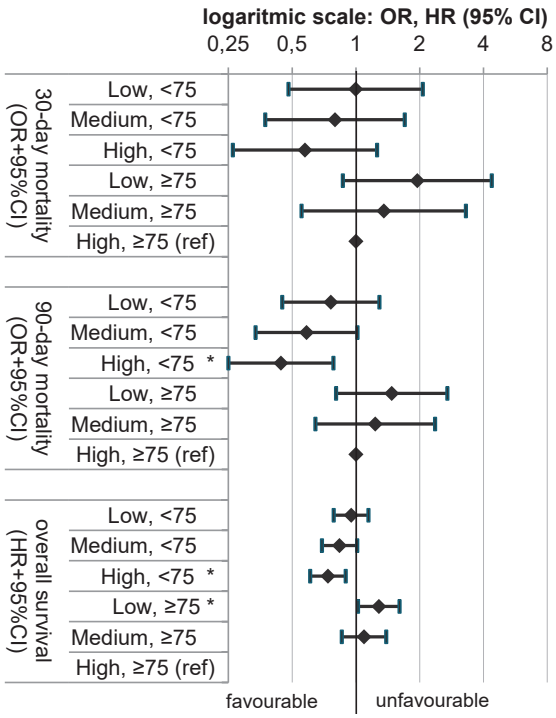
Supplementary table 1. Univariate and multivariable analyses predicting 30-day and 90-day postoperative mortality and overall survival of patients who underwent PD for primary adenocarcinoma, by age of patients within each hospital volume tertile calculated within 3-year periods.

				Univariable		Multivariable	
30-day mortality	N	P	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Low HV	1,316	5.6					
Age <75 years	1,081	4.9	0.02	1	0.02	1	0.01
Age ≥75 years	235	8.9		1.90 (1.12-3.22)		1.99 (1.16-3.39)	
Medium HV	1,045	4.4					
Age <75 years	860	4.0	0.13	1	0.13	1	0.15
Age ≥75 years	185	6.5		1.69 (0.86-3.32)		1.68 (0.84-3.36)	
High HV	1,059	3.2					
Age <75 years	870	2.9	0.18	1	0.19	1	0.18
Age ≥75 years	189	4.8		1.69 (0.78-3.68)		1.73 (0.78-3.87)	
90-day mortality	N	P	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Low HV	1,316	9.1					
Age <75 years	1,081	8.1	0.004	1	0.006	1	0.003
Age ≥75 years	235	14.0		1.87 (1.22-2.86)		1.95 (1.26-3.01)	
Medium HV	1,045	7.5					
Age <75 years	860	6.4	0.005	1	0.005	1	0.01
Age ≥75 years	185	12.4		2.08 (1.24-3.48)		1.97 (1.16-3.35)	
High HV	1,058	5.8					
Age <75 years	869	4.8	0.005	1	0.009	1	0.003
Age ≥75 years	189	10.1		2.20 (1.25-3.88)		2.45 (1.36-4.42)	
Overall survival	N			HR (95% CI)	p-value	HR (95% CI)	p-value
Low HV	1,316						
Age <75 years	1,081			Ref	0.001	Ref	0.001
Age ≥75 years	235			1.31 (1.12-1.54)		1.33 (1.13-1.57)	
Medium HV	1,045						
Age <75 years	860			Ref	0.03	Ref	0.004
Age ≥75 years	185			1.23 (1.02-1.48)		1. 32 (1.09-1.59)	
High HV	1,059						
Age <75 years	870			Ref	0.08	Ref	0.001
Age ≥75 years	189			1.19 (0.98-1.44)		1.38 (1.13-1.68)	

N number of patients, P proportion of patients deceased, p-value of Chi^2 test, OR odds ratio (logistic regression analysis), HR hazard ratio (Cox proportional hazard regression analysis), CI confidence interval.



Supplementary figure 1. Multivariable analyses predicting postoperative 30- and 90-day mortality and overall survival of 3,420 patients who underwent PD for primary adenocarcinoma, by age of patients (<75 years, ≥75 years) and hospital volume tertiles (Low, Medium, High HV, calculated within 3-year periods) combined (See Figure 1).

Chapter 8

Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer

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Br J Surg. 2017 Oct;104(11):1568-1577.

Abstract

Background
Despite improvements in diagnostic imaging and staging, unresectable pancreatic cancer is still encountered during surgical exploration with curative intent. This nationwide study investigated outcomes in patients with unresectable pancreatic cancer found during surgical exploration.

Methods
All patients diagnosed with primary pancreatic (adeno)carcinoma (2009–2013) in the Netherlands Cancer Registry were included. Predictors of unresectability, 30-day mortality and poor survival were evaluated using logistic and Cox proportional hazards regression analysis.

Results
There were 10,595 patients with pancreatic cancer during the study interval. The proportion of patients undergoing surgical exploration increased from 19.9 to 27.0% ($p < 0.001$). Among 2,356 patients who underwent surgical exploration, the proportion of patients with tumour resection increased from 61.6% in 2009 to 71.3% in 2013 ($p < 0.001$), whereas the contribution of M1 disease (18.5% overall) remained stable. Patients who had exploration only had an increased 30-day mortality rate compared with those who underwent tumour resection (7.8% versus 3.8%; $p < 0.001$). In the non-resected group, among those with M0 (383 patients) and M1 (435) disease at surgical exploration, the 30-day mortality rate was 4.7% and 10.6% ($p = 0.002$), median survival was 7.2 and 4.4 months ($p < 0.001$), and 1-year survival rates were 28.0% and 12.9%, respectively. Among other factors, low hospital volume (0–20 resections per year) was an independent predictor for not undergoing tumour resection, but also for 30-day mortality and poor survival among patients without tumour resection.

Conclusion
Exploration and resection rates increased, but one-third of patients who had surgical exploration for pancreatic cancer did not undergo resection. Non-resectional surgery doubled the 30-day mortality rate compared with that in patients undergoing tumour resection.

Introduction

Pancreatic cancer is one of the most dismal types of cancer, with incidence and mortality rates of 8.6 and 8.3 per 100 000 inhabitants respectively in developed countries [1], and a 5-year survival rate of 5–7% [2,3]. The incidence rises with increasing age, and more than half of patients diagnosed with pancreatic cancer are more than 70 years old [2,4].

Only 15–20% of patients have resectable disease at the time of diagnosis, and so accurate preoperative staging is crucial to prevent unnecessary explorations. CT is the cornerstone for staging suspected pancreatic tumours. However, positive and negative predictive values for resectability are in the range 54–91% and 73–100% respectively [5]. Although other imaging modalities such as endoscopic ultrasonography and MRI are employed occasionally, their additional value in determining resectability is limited [6,7]. Overall, preoperative imaging has limited ability accurately to estimate local tumour ingrowth or to detect small distant metastases. Consequently, a substantial proportion of patients who undergo surgical exploration with curative intent (in short, surgical exploration) still turn out to have unresectable disease (21–43%) [5,8–11]. Most studies on surgical exploration for pancreatic cancer are based on high-volume, single-centre experiences; nationwide data on this topic are scarce [12].

The volume–outcome relationship for pancreatoduodenectomy is well established, with better outcomes in hospitals with higher procedural volumes [13–15]. Along with centralization of pancreatic surgery in the Netherlands, resection rates in patients diagnosed with pancreatic cancer have increased [16,17], especially for tumours extending beyond the pancreas and in elderly patients. It is unclear how hospital volume influences the surgical outcomes of patients in whom locally advanced or metastasized disease is detected during exploration.

The aim of this nationwide study was to assess resection rates in patients who underwent surgical exploration with curative intent for pancreatic cancer, and to investigate predictors of postoperative 30-day mortality and survival among those with unresectable disease found during surgical exploration, with special attention to hospital volume and elderly patients.

Methods

The Netherlands Cancer Registry (NCR) records data on all patients with newly diagnosed cancer in the Netherlands, a country with 17 million inhabitants. Since 1989, newly diagnosed malignancies have been notified to the NCR by the automated pathological archive, supplemented with data from the National Registry of Hospital Discharge Diagnoses. Completeness is estimated to be at least 95%. Trained registrars routinely collect data on patient characteristics, tumour type and primary cancer treatment (tumour resection, radiotherapy, chemotherapy) extracted from medical records in all Dutch hospitals. Tumour location and histology are registered according to the ICD for Oncology (ICD-O-3) [18].

In patients with a histologically proven malignancy, the TNM staging classification is used [19, 20], whereas in those without a histological diagnosis (patients with imaging only) a summary stage is recorded (extent of disease). Data on actual vital status (dead or alive) is obtained routinely from the Municipal Personal Records Database, which keeps records of the vital status of all Dutch inhabitants.

Patients
For this study, all patients diagnosed with pancreatic ductal adenocarcinoma (ICD-O C25) between 1 January 2009 and 31 December 2013 were selected from the NCR. Patients diagnosed with pancreatic cancer at autopsy, and those younger than 18 years, residing abroad, or with confirmed neuroendocrine or non-epithelial malignancies, were excluded. Since 2009, nationwide data on 'surgical exploration with curative intent' and sites of distant metastases (with a maximum of 3 metastatic sites) have been available in the NCR. Because neoadjuvant treatment was provided sporadically in the present study period (1.7% of patients who had surgical exploration), only postoperative systemic treatment is reported. No information was available on imaging or palliation, for example whether patients had bypass surgery.

Definitions
The age of patients at diagnosis was divided into four groups: less than 70, 70–74, 75–79 and at least 80 years. Owing to the nature of the NCR, information on previous primary malignancies was available for all patients.

Data on socioeconomic status (SES) were used, based on reference data from the Netherlands Institute for Social Research [21]. Scores for social deprivation were derived from income, education and occupation by four-digit postal code, and were divided into three SES categories (high: 1st to 3rd deciles; intermediate: 4th to 7th deciles; low: 8th to 10th deciles).

Tumour stage was based on pathological TNM stage supplemented with clinical TNM, which also included intraoperative findings at the time of surgical exploration (2005–2010 TNM 6th edition [19]; 2010–2013 TNM 7th edition [20]).

Hospital volume was based on the total number of pancreatic resections for pancreatic or periampullary carcinoma per hospital per year, and applied to patients with pancreatic carcinoma who underwent surgical exploration with curative intent. Hospital volumes were divided evenly into three volume categories (tertiles): low (0–20 resections per year), medium (21–32 per year) and high (33 or more per year). For individual hospitals, the volume category may differ in consecutive years.

Postoperative mortality was defined as death from any cause within 30 days after surgical exploration. If the date of surgical exploration was missing (in 11 patients; primarily those who did not undergo resection), the date of histological confirmation was used. Survival was calculated from the date of surgical exploration to the date of death. Patients who were alive on 1 February 2016 were censored.

Statistical analysis

Chi-square tests were used to compare proportions of patients in subgroups of patient characteristics (age, sex, previous cancer, SES) and tumour characteristics (location, stage and grade). Univariable and multivariable logistic regression analyses investigated predictors of undergoing surgical exploration in the overall cohort, unresectability among individuals who had surgical exploration, and postoperative 30-day mortality among patients who did not undergo tumour resection. Kaplan–Meier analysis with log rank tests and Cox proportional hazard regression analyses were used to evaluate overall survival. Separate analyses were repeated for subgroups of patients who did not undergo resection because of non-metastasized and metastasized disease. In multivariable regression models, a backward stepwise selection was used with a $p > 0.10$ in likelihood ratio tests for removal of variables. Results are reported as either odds ratios or hazard ratios (HRs) with 95% confidence intervals (95% CI). Two-sided $p < 0.05$ was considered statistically significant. All analyses were performed using STATA®/SE version 14.0 (StataCorp, College Station, Texas, USA).

Results

In the study interval, there were 10 595 patients newly diagnosed with pancreatic adenocarcinoma (**Figure 1**), of whom 5,825 (55.0%) had distant metastases at the time of diagnosis. Most common sites of metastasis were the liver (41.9% of 10,595 patients), peritoneum (11.4%), lungs (9.3%) and distant lymph nodes (6.9%). Surgical exploration with curative intent was performed in 2,420 patients (22.8%); the rate increased from 19.9% in 2009 to 27.0% in 2013 ($p < 0.001$). Besides patients diagnosed in earlier years of the study, in the multivariable logistic regression model, elderly patients (aged at least 75 years), those with low SES, and patients with cancer in the pancreatic body/tail were less likely to undergo surgical exploration (**Table 1**).

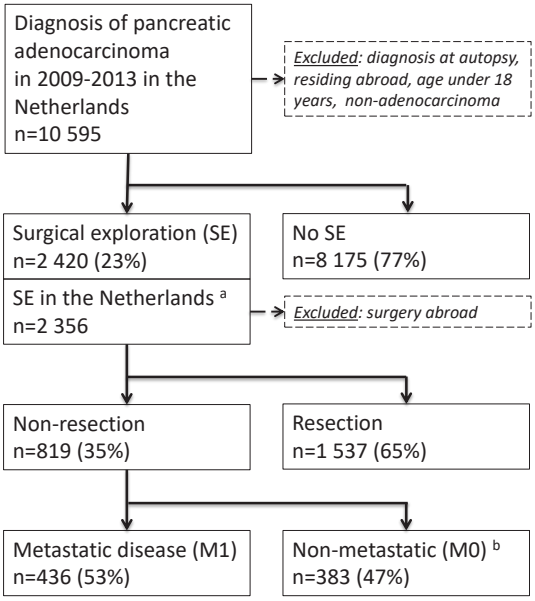

Figure 1. Flow chart for study of patients with pancreatic adenocarcinoma undergoing surgical exploration.

[a] Sixty-four patients who underwent surgical exploration abroad were included in the overall analysis of surgical exploration rates, but further analyses were restricted to those treated in the Netherlands.

[b] Includes tumour stage X (no signs of positive lymph nodes or distant metastasis, and extent of primary tumour unknown).

Table 1. Characteristics of patients diagnosed with pancreatic cancer and predictors for undergoing a surgical exploration.

			Univariable		Multivariable	
	No. of patients (*n* = 10 595)	Patients who underwent surgical exploration (*n* = 2420) [b]	OR (95%CI)	p-value	OR (95%CI)	p-value
Year of diagnosis			1.09 (1.06, 1.13)	< 0.001	1.10 (1.07, 1.14)	< 0.001
Sex				0.074		
Male	5343 (50.4)	1259 (23.6)	1.00			
Female	5252 (49.6)	1161 (22.1)	0.92 (0.84, 1.01)			
Age (years)				< 0.001		
< 70	4956 (46.8)	1468 (29.6)	1.00		1.00	
70–74	1812 (17.1)	514 (28.4)	0.94 (0.84, 1.06)		0.92 (0.81, 1.04)	0.175
75–79	1638 (15.5)	320 (19.5)	0.58 (0.50, 0.66)		0.55 (0.47, 0.63)	< 0.001
≥ 80	2189 (20.7)	118 (5.4)	0.14 (0.11, 0.16)		0.11 (0.09, 0.14)	< 0.001
History of cancer				0.178		
No	8828 (83.3)	2038 (23.1)	1.00			
Yes	1767 (16.7)	382 (21.6)	0.92 (0.81, 1.04)			
Socioeconomic status				0.035		
High	3180 (30.0)	767 (24.1)	1.00		1.00	
Medium	4238 (40.0)	973 (23.0)	0.94 (0.84, 1.04)		0.92 (0.82, 1.03)	0.145
Low	3177 (30.0)	680 (21.4)	0.86 0.76, 0.96)		0.87 (0.77, 0.98)	0.029
Primary tumour location				< 0.001		
Pancreatic head	6382 (60.2)	1920 (30.1)	1.00		1.00	
Non-head/NOS	4213 (39.8)	500 (11.9)	0.31 (0.28, 0.35)		0.27 (0.24, 0.30)	< 0.001
Summary tumour stage [a]			NR		NR	
Within pancreas	980 (9.2)	220 (22.5)				
Beyond pancreas	3454 (32.6)	1689 (48.9)				
Distant metastasis	5825 (55.0)	487 (8.4)				
Unknown	336 (3.2)	24 (7.1)				

OR odds ratio, CI confidence interval, NOS not otherwise specified, NR not relevant.
[a] Summary tumour stage (TNM and EoD).
[b] Row per cent.

Patients who underwent surgical exploration with curative intent

From 2009 to 2013, the number of hospitals performing surgical explorations for pancreatic carcinoma decreased from 38 to 31 of 91 hospitals. The median number of procedures per hospital was 9 (IQR 2–80) in the study period; three hospitals performed more than 150 surgical explorations. Of all 2,356 patients undergoing surgical exploration in the Netherlands, 819 (34.8%) did not undergo resection (**Figure 1**), 436 (18.5%) because of metastatic disease (liver 10.8%, peritoneum 7.2%, distant lymph node metastases 2.9%). Some 383 patients (16.3%) had

non-metastatic disease; poor physical condition was mentioned explicitly in four patients. The proportion of patients who did not undergo resection decreased significantly from 38.4% in 2009 to 28.7% in 2013 ($p < 0.001$) (**Figure 2**), mainly owing to a decline in non-metastatic disease (16.8% to 11.2%; $p = 0.001$). The non-resection rate was higher in hospitals with lower volumes (40.5%, 33.1% and 29.1% in low-, medium- and high-volume hospitals respectively; $p < 0.001$) (**Table 2**). In a multivariable regression model, the probability of non-resection was increased particularly among elderly patients (aged 80 years or more) and in low-volume hospitals.

Among 2,352 patients who underwent surgical exploration, 122 (5.2%) died within 30 days afterwards, 64 (7.8%) of 818 patients who did not undergo resection and 58 (3.8%) of 1,534 patients who had tumour resection ($p < 0.001$). Although the 30-day mortality rate of patients with non-resected M0 disease was comparable to that among patients who underwent resection (4.7% versus 3.8%; $p = 0.41$), by 90 days their risk of death was significantly higher (90-day mortality 18.5% versus 7.4% respectively; $p < 0.001$).

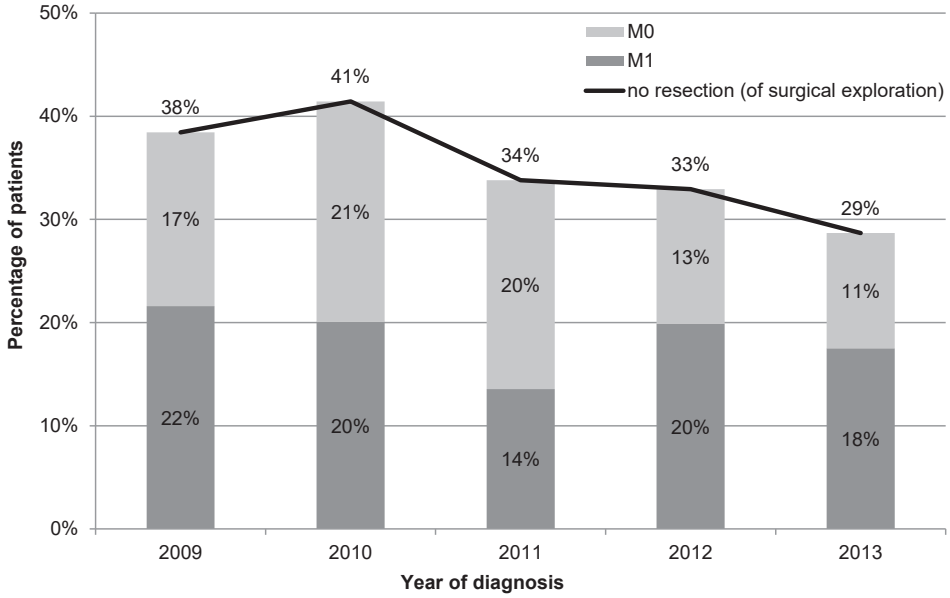

Figure 2. Trends over time for patients not undergoing resection at surgical exploration for pancreatic cancer in the Netherlands, 2009–2013.

Table 2. Characteristics of patients who underwent surgical exploration and predictors for not undergoing a tumour resection.

			Univariable		Multivariable	
	Patients who underwent surgical exploration (*n* = 2356)	Patients who did not undergo resection (*n* = 819) [b]	OR (95%CI)	p-value	OR (95%CI)	p-value
Hospital volume				< 0.001		
Low	889 (37.7)	360 (40.5)	1.66 (1.34, 2.06)		1.50 (1.20, 1.88)	< 0.001
Medium	803 (34.1)	266 (33.1)	1.21 (0.97, 1.51)		1.14 (0.91, 1.43)	0.257
High	664 (28.2)	193 (29.1)	1.00		1.00	
Year of diagnosis			0.88 (0.83, 0.93)	< 0.001	0.91 (0.85, 0.97)	0.004
Sex				0.098		
Male	1228 (52.1)	446 (36.3)	1.00		1.00	
Female	1128 (47.9)	373 (33.1)	0.87 (0.73, 1.03)		0.85 (0.71, 1.01)	0.061
Age (years)				0.232		
< 65	1421 (60.3)	477 (33.6)	1.00		1.00	
65–74	498 (21.1)	164 (32.9)	0.97 (0.78, 1.21)		0.97 (0.78, 1.21)	0.822
75–79	319 (13.5)	125 (39.2)	1.28 (0.99, 1.64)		1.29 (1.00, 1.65)	0.056
≥ 80	118 (5.0)	53 (44.9)	1.61 (1.10, 2.36)		1.70 (1.16, 2.49)	0.007
History of cancer				0.840		
No	1980 (84.0)	690 (34.9)	1.00			
Yes	376 (16.0)	129 (34.3)	0.98 (0.74, 1.23)			
Socioeconomic status				0.233		
High	749 (31.8)	251 (33.5)	1.00			
Intermediate	953 (40.4)	323 (33.9)	1.02 (0.83, 1.25)			
Low	654 (27.8)	245 (37.5)	1.19 (0.95, 1.48)			
Primary tumour location				0.616		
Pancreatic head	1869 (79.3)	645 (34.5)	1.00			
Non-head/NOS	487 (20.7)	174 (35.7)	1.05 (0.86, 1.30)			
Tumour stage (TNM) [a]			NR		NR	
I–II (T1–3 M0)	1545 (65.6)	121 (7.8)				
III (T4 M0)	264 (11.2)	196 (74.2)				
IV (M1)	475 (20.2)	436 (91.8)				
X	72 (3.1)	66 (91.7)				

OR odds ratio, CI confidence interval, NOS not otherwise specified, NR not relevant.
[a] Includes findings at surgical exploration.
[b] Row per cent.

Patients who did not undergo resection

Of 819 patients who did not undergo tumour resection, 436 (53.2%) had metastatic disease established at the time of surgical exploration: 321 of 645 patients (49.8%) with pancreatic head cancer and 115 of the remaining 174 patients (66.1%) (p < 0.001). No significant differences were

found according to age (p = 0.188) and hospital volume (p = 0.918). Postoperative chemo(radio) therapy was offered slightly more often to patients with metastatic disease (128 of 436 (29.4%) and 90 of 383 (23.5%) with M1 and M0 disease respectively; p = 0.058), as well as to patients in the highest volume tertile (94 of 360 (26.1%), 54 of 266 (20.3%) and 70 of 193 (36.3%) in low-, medium and high-volume hospitals respectively; p = 0.001).

Among 818 patients in the mortality analysis, 64 (7.8%) died within 30 days of operation: 46 of 435 with M1 disease (10.6%) compared with 18 of 383 (4.7%) with M0 disease (p = 0.002). In a multivariable logistic regression model, distant metastasis and treatment in low-volume hospitals were independent predictors of death within 30 days after surgery (**Table 3**).

Two patients died on the day of surgery and were excluded from the survival analysis. One- and 2-year overall survival rates among 817 patients who did not undergo resection were 20.0% and 4.0% respectively (12.9% and 2.5% in 435 patients with M1 disease; 28.0% and 5.7% in 382 patients with M0 disease). Median overall survival was 5.6 months overall, 4.4 months for those with M1 and 7.2 months in those with M0 disease (p < 0.001) (**Figure 3**). In the multivariable Cox regression model, overall survival was worst in elderly patients (75 years and older), those with a history of cancer, individuals with metastatic disease, patients with poorly differentiated tumours, those who underwent surgery in the later years of the study, and patients treated in low-volume hospitals (**Table 4**). Significant associations between low hospital volume and worse survival persisted after further adjustment for the influence of metastatic sites (HR (low versus high volume) = 1.43, 95% CI 1.18-1.72) and differences in the use of chemo(radio)therapy (HR (low versus high volume) = 1.29, 95% CI 1.06-1.55). In subgroup analysis, hospital volume was independently associated with overall survival among patients with M1 disease who did not undergo resection (HR (low versus high volume) = 1.57, 95% CI 1.22-2.01), but not in those with M0 disease (HR (low versus high volume) = 1.27, 95% CI 0.94-1.71).

Table 3. Predictors of 30-day postoperative mortality in patients with pancreatic cancer who did not undergo tumour resection following surgical exploration.

			Univariable		Multivariable	
	Patients who did not undergo resection (*n* = 818) [a]	Patients who died within 30 days (*n* = 64) [b]	OR (95%CI)	p-value	OR (95%CI)	p-value
Hospital volume				0.007		
Low	359	40 (11.1)	2.56 (1.22, 5.40)		2.55 (1.20, 5.45)	0.015
Medium	266	15 (5.6)	1.22 (0.62, 2.85)		1.20 (0.51, 2.82)	0.679
High	193	9 (4.7)	1.00		1.00	
Year of diagnosis			0.92 (0.76, 1.10)	0.355		
Sex				0.772		
Male	446	36 (8.1)	1.00			
Female	372	28 (7.5)	0.93 (0.55, 1.55)			

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Age (years)				0.100		
< 70	476	37 (7.8)	1.00		1.00	
70–74	164	7 (4.3)	0.53 (0.23, 1.21)		0.56 (0.24, 1.30)	0.180
75–79	125	13 (10.4)	1.38 (0.71, 2.68)		1.49 (0.75, 2.94)	0.251
≥ 80	53	7 (13)	1.81 (0.76, 4.28)		2.05 (0.84, 5.00)	0.112
History of cancer				0.181		
No	689	50 (7.3)	1.00			
Yes	129	14 (10.9)	1.56 (0.83, 2.91)			
Socioeconomic status				0.538		
High	251	16 (6.4)	1.00			
Medium	322	26 (8.1)	1.29 (0.68, 2.46)			
Low	245	22 (9.0)	1.45 (0.74, 2.83)			
Primary tumour location				0.052		
Pancreatic head	644	44 (6.8)	1.00			
Non-head/NOS	174	20 (11.5)	1.77 (1.01, 3.09)			
Tumour stage (TNM)				0.008		
I–II (T1–3 M0)	121	4 (3.3)	1.00		1.00	
III (T4 M0)	196	9 (4.6)	1.41 (0.42, 4.68)		1.35 (0.40, 4.51)	0.629
IV (M1)	435	46 (10.6)	3.46 (1.22, 9.81)		3.23 (1.13, 9.24)	0.028
X	66	5 (7.6)	2.40 (0.62, 9.26)		1.77 (0.45, 6.98)	0.415

Values in parentheses are percentages unless indicated otherwise.
OR odds ratio, CI confidence interval, NOS not otherwise specified.
[a] One patient lost to follow-up within 30 days.
[b] Row percent.

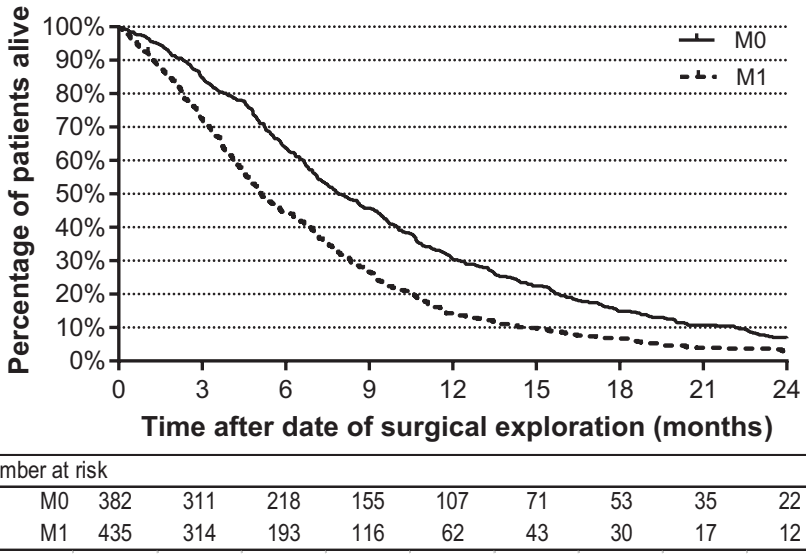

Figure 3. Comparison of overall survival for patients with distant metastases (M1) and those with non-metastasized (M0) pancreatic cancer among those who did not undergo resection at surgical exploration for primary pancreatic cancer in the Netherlands, 2009–2013. Log rank test p < 0.001.

Table 4. Predictors of overall survival in patients with pancreatic cancer not undergoing tumour resection.

	Univariable		Multivariable	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Hospital volume		0.031		
Low	1.26 (1.06, 1.51)		1.42 (1.17, 1.71)	< 0.001
Medium	1.20 (0.99, 1.44)		1.21 (1.00, 1.46)	0.052
High	1.00 (reference)		1.00 (reference)	
Year of diagnosis	1.06 (1.00, 1.11)	0.038	1.07 (1.01, 1.13)	0.018
Sex		0.416		
Male	1.00 (reference)			
Female	1.06 (0.92, 1.22)			
Age (years)		0.010		
< 70	1.00 (reference)		1.00 (reference)	
70–74	1.14 (0.95, 1.37)		1.16 (0.97, 1.39)	0.109
75–79	1.34 (1.10, 1.64)		1.39 (1.14, 1.71)	0.001
≥ 80	1.38 (1.04, 1.84)		1.42 (1.07, 1.90)	0.016
History of cancer		< 0.001		
No	1.00 (reference)		1.00 (reference)	
Yes	1.57 (1.30, 1.91)		1.48 (1.22, 1.79)	< 0.001
Socioeconomic status		0.089		
High	1.00 (reference)		1.00 (reference)	
Medium	0.99 (0.83, 1.17)		0.93 (0.79, 1.10)	0.411
Low	1.18 (0.98, 1.41)		1.15 (0.96, 1.38)	0.119
Primary tumour location		0.053		
Head	1.00 (reference)			
Non-head/NOS	1.19 (1.00, 1.41)			
Tumour stage (TNM)		< 0.001		
I–II (T1–3 M0)	1.00 (reference)		1.00 (reference)	
III (T4 M0)	0.93 (0.74, 1.17)		0.92 (0.73, 1.16)	0.494
IV (M1)	1.46 (1.19, 1.79)		1.47 (1.19, 1.81)	<0.001
X	0.83 (0.61, 1.13)		0.78 (0.57, 1.06)	0.114
Tumour grade		< 0.001		
Moderate/well differentiated	1.00 (reference)		1.00 (reference)	
Poorly differentiated	1.99 (1.42, 2.77)		1.87 (1.34, 2.62)	<0.001
Unknown	1.12 (0.87, 1.44)		1.15 (0.90, 1.49)	0.265

HR odds ratio, CI confidence interval, NOS, not otherwise specified.

Discussion

In this nationwide study, about one-third of patients who underwent surgical exploration for pancreatic cancer ultimately did not undergo resection, with a 30-day mortality rate of 7.8% and overall survival of 5.6 months. Independent predictors of 30-day mortality in this group were metastatic disease and treatment in low-volume hospitals; those for poor overall survival were older age and, among other factors, treatment in low-volume hospitals.

The Netherlands is characterized by good access to healthcare as health insurance is mandatory and distances to hospitals are generally short. Although observed disparities by SES are striking, they were already present before centralization of pancreatic surgery [22]. A possible association between low SES and a higher prevalence of co-morbid diseases has been reported [21].

Although resection rates have increased along with increasing centralization of pancreatic surgery in the Netherlands [16,17,23], a radical resection is deemed impossible in a considerable proportion of patients who undergo surgical exploration. The present nationwide results are largely in line with earlier institutional reports [5,8,10–12,24,25], showing that 12–22% of patients who undergo surgical exploration for pancreatic cancer do not have tumour resection because of metastatic disease, and 6–26% because of unresectable M0 (locally advanced) disease. The present study also shows that an increased surgical exploration rate over time paralleled an increased resection rate, mostly owing to a decrease in unresectable M0 disease detected at exploration. This finding may reflect both broadened resectability criteria and improved preoperative imaging [8]. Despite a decreasing trend in non-resection at surgical exploration, the magnitude is still worrying. Although a Swedish study [26] suggested that treatment delay was associated with a higher probability of finding unresectable disease, delay in the Netherlands seems relatively short (median 28 versus 42 days respectively) [27]. Furthermore, neoadjuvant treatment (such as FOLFIRINOX – folinic acid, fluorouracil, irinotecan, oxaliplatin), which could hamper correct preoperative staging [28], but also increases resection rates [29,30], was essentially not used in the present study period. Arterial resections and resection of isolated liver metastases could reduce rates of non-resection, but such extended resections were rarely performed in this interval, and their impact on overall survival has yet to be determined.

Outcomes among patients who did not undergo resection in the present series were worse than in previous studies from single high-volume centres [8–10, 31–33], with a postoperative mortality rate of 7.8% versus 1.7–6.5%, and median overall survival of 5.6 months versus 6.0–8.3 months, respectively. This difference is likely to be related to the nationwide design of this study, which included multiple centres with varying procedure volumes, as the postoperative mortality rate among patients who did not have tumour resection was in line with rates in recent multicentre and nationwide studies (6.5–8.2%) [12,34]. Patient outcome, however, does require further attention, as 30-day mortality in these patients was double that of patients who underwent resection, especially due to a high early mortality rate in patients with unanticipated metastatic disease.

In contrast to a previous study [6], older age was identified as an independent predictor of not undergoing resection. Surgical exploration may reveal an unexpected locally advanced tumour with a high risk of complications after resection. The risk of dying from complications (failure-to-rescue) increases with older age [35], and surgeons may have anticipated this. Such decisions may also explain the less clear association between older age and postoperative mortality.

In addition to pancreatic resections [13,15], a volume–outcome relation also seems present at time of perioperative decision-making and in outcomes after non-resection. The present study

confirmed the findings of a recent nationwide Italian study [12] that reported a rate of non-resection at surgical exploration for pancreatic cancer ranging from 24% in the highest-volume quintile to 63% in the lowest-volume quintile, with postoperative mortality rates from 4.9% to 10.6% respectively among patients who did not have tumour resection [12]. Furthermore, among patients who did not undergo resection in the present series, survival was worse in patients treated in low-volume hospitals than in those treated in high-volume institutions. In the Netherlands, commonly accepted criteria for preoperative imaging were incorporated into the national guideline for pancreatic cancer in 2011 [36]. Improvement in imaging techniques and assessment by experienced radiologists might further lower the risk of a negative surgical exploration and associated morbidity. Hence, these patients may be offered appropriate local or systemic treatment without further delay [37]. Considering the limited life expectancy of most patients who did not undergo resection, negative explorative surgery represents suboptimal quality of care [12,38].

In many patients not undergoing resection, bypass surgery is performed to treat or prevent biliary and gastric outlet obstruction. From a prognostic point of view, palliative chemotherapy may be preferred over routine prophylactic construction of bypasses24. However, in the present study, the use of chemotherapy in patients not undergoing resection in the Netherlands was relatively limited compared with that in previous institutional reports (49–76%) [10,24,31]. In light of the present finding that metastatic disease was detected at the time of exploration in one-fifth of patients, and taking into account the high morbidity after open bypass surgery [10,24,34], it may be worthwhile giving consideration to performing a staging laparoscopy immediately before laparotomy in the same session [24,39]. This strategy is of interest considering the excellent patency of the current generation of self-expandable metal stents, with the subsequently reduced need for palliative hepatojejunostomy [24,40]. A review [39] of diagnostic accuracy studies has confirmed that staging laparoscopy may significantly reduce the number of patients undergoing surgical exploration without resection.

The limitations of this study especially relate to the availability of specific data in the NCR. Apart from the lack of data on bypass surgery, surgical morbidity and the physical condition of patients, data on staging laparoscopy were available only in the later years of the study (2012–2013). Staging laparoscopy was not routine practice at that time and not recommended in the 2011 Dutch guideline for pancreatic cancer [36,41]. However, these data were included to avoid biased conclusions about diagnostic accuracy. After excluding data on staging laparoscopy (56 patients), a steeper decrease in non-resection rate was found (38.4, 41.4, 33.8, 30.8 and 24.2% in consecutive years of the study), albeit with similar postoperative outcomes. Finally, pancreatic cancer diagnoses without histological confirmation seem potentially incomplete in the NCR [42]. As virtually all patients who underwent surgical exploration had histological confirmation of cancer, their results are highly accurate.

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Chapter 9

Nationwide trends in chemotherapy use and survival of elderly patients with metastatic pancreatic cancer

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Cancer Med. 2017 Dec;6(12):2840-2849.

Abstract

Background
Despite an aging population and underrepresentation of elderly patients in clinical trials, studies on elderly patients with metastatic pancreatic cancer are scarce. This study investigated the use of chemotherapy and survival in elderly patients with metastatic pancreatic cancer.

Methods
From the Netherlands Cancer Registry, all 9,407 patients diagnosed with primary metastatic pancreatic adenocarcinoma in 2005–2013 were selected to investigate chemotherapy use and overall survival (OS), using Kaplan–Meier and Cox proportional hazard regression analyses.

Results
Over time, chemotherapy use increased in all age groups (<70 years: from 26 to 43%, 70–74 years: 14 to 25%, 75–79 years: 5 to 13%, all $p < 0.001$, and ≥80 years: 2 to 3% $p = 0.56$). Median age of 2,180 patients who received chemotherapy was 63 years (range 21–86 years, 1.6% was ≥80 years). In chemotherapy-treated patients, with rising age (<70, 70–74, 75–79, ≥80 years), microscopic tumor verification occurred less frequently (91-88-87-77%, respectively, $p = 0.009$) and OS diminished (median 25-26-19-16 weeks, $p = 0.003$). After adjustment for confounding factors, worse survival of treated patients ≥75 years persisted.

Conclusion
Despite limited chemotherapy use in elderly age, suggestive of strong selection, elderly patients (≥75 years) who received chemotherapy for metastatic pancreatic cancer exhibited a worse survival compared to younger patients receiving chemotherapy.

Introduction

Pancreatic cancer is one of the most dismal types of cancer, with a 5-year survival rate of only 5-7% [1,2]. These low survival rates reflect an advanced stage at diagnosis in the vast majority of patients: at least half of patients already have metastatic disease at time of diagnosis [3, 4]. Median survival of unselected patients with metastatic disease is only 2-3 months [3-5].

Pancreatic cancer is predominantly a disease of the elderly [2,6], at least half of all patients are over 70 years of age and more than one-fifth is older than 80 years [6,7]. Unfortunately, elderly patients are underrepresented in clinical trials. For example, the phase III study which showed that FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) significantly improved survival compared with gemcitabine monotherapy (median survival 11.1 vs 6.8 months, respectively) excluded patients over 75 years of age [8]. The phase III study on the combination of gemcitabine and nab-paclitaxel included patients until 88 years of age (median survival 8.5 months vs 6.7 months in patients with gemcitabine-alone), but the median age of 63 years suggests that few patients were older than 75 years [9].

Population-based studies have shown that in the past decades the administration of palliative chemotherapy steeply increased in patients with metastatic pancreatic cancer [3,10]. Whether the increased use of chemotherapy also applies to elderly patients, is unknown. Furthermore, some specialized institutions have reported acceptable safety and efficacy of chemotherapy in selected elderly patients with metastatic pancreatic cancer, with survival comparable with younger patients [11-13]. However, in these reports a direct comparison with younger patients (<75 years) was not performed [11,12] or a single age cut-off (<70, ≥70 years) was used [13] which may mask variation within the older age group. To the best of our knowledge, no population-based studies have been published which compare survival after chemotherapy according to age.

Therefore, the purpose of this nationwide study is to examine the use of chemotherapy and its impact on overall survival in elderly patients with metastatic pancreatic cancer, using multiple age groups.

Methods

Netherlands cancer registry

In the Netherlands, a country with approximately 16.8 million inhabitants, all newly diagnosed malignancies are recorded in the nationwide Netherlands Cancer Registry (NCR). Besides notification by the automated pathological archive (PALGA), the National Registry of Hospital Discharge Diagnoses is used. Subsequently, trained registrars collect information on patient, tumor and primary treatment from the medical records in all Dutch hospitals. The International Classification of Diseases for Oncology (ICD-O-3) is used for coding of morphology and tumor locations [14]. Histologically confirmed malignancies are staged according to the Tumor-Node-Metastasis (TNM) staging classification [15]. In patients without microscopically verified diagnosis

a summary stage is recorded (Extent of Disease, EoD). Data quality is high and completeness is estimated to be at least 95%. Follow-up for all patients is obtained by routinely linking the NCR to the Municipal Personal Records Database (BRP). The BRP contains information on the vital status of all Dutch inhabitants (dead or alive, date of death or emigration).
The NCR Review Board approved the current study.

Patients
For this study, from the NCR all patients were selected who were diagnosed with primary invasive pancreatic (ductal) adenocarcinoma in the period 2005–2013 (ICD-O-3 C25, morphology codes 8010, 8012, 8020, 8140, 8141, 8260, 8310, 8440, 8470, 8480, 8481, 8490, 8500, 8560, or a non-microscopic verified invasive neoplasm of the pancreas suspected for adenocarcinoma). Patients diagnosed at autopsy, younger than 18 years or residing abroad were excluded. TNM and EoD staging information were combined to select patients with metastatic disease at diagnosis (53% of patients).

To investigate a possible age gradient or age cut-off point, patients were divided into four age groups: <70 years, 70–74 years, 75–79 years and ≥80 years of age. Due to the nature of the NCR, information on prior primary malignancies was available in all patients. Additionally, a slightly modified version of the Charlson classification was recorded region-wide within 1–2 out of nine cancer regions (18% of all patients). Serious comorbid conditions included chronic obstructive pulmonary diseases, cardiovascular diseases, cerebrovascular diseases, digestive tract diseases, diabetes mellitus and other serious diseases. The number of comorbidities were categorized in three groups (0, 1, ≥2). Furthermore, data on socioeconomic status (SES) were used [16]. SES was based on reference data from The Netherlands Institute for Social Research. Scores on social deprivation were derived from income, education and occupation per 4-digit postal code, and were broken into three SES-categories (high: 1st–3rd, intermediate: 4th–7th, low: 8th–10th deciles). Registered treatment after diagnosis included the cancer treatment modalities as mentioned in the treatment plan and provided to the patient (i.e. resection, radiotherapy, chemotherapy). Time intervals between date of diagnosis and date of initiating chemotherapy were calculated to explore possible delay.

Survival time was calculated from the date of diagnosis to the date of death or 1 January 2015, whichever came first. To reduce the influence of survivor treatment selection bias in analysis of survival of patients with versus without chemotherapy [17], only patients were selected who survived at least 30–days after diagnosis (conditional survival). In addition to information about delay of starting chemotherapy, survival time from the starting date of chemotherapy was calculated.

Statistical analysis
In each age group of patients with metastatic pancreatic cancer, Chi square tests for trend were performed to assess the administration of chemotherapy in consecutive 3-year periods (2005–2007, 2008–2010, 2011–2013). A two-sided $p < 0.05$ was considered statistically significant. In patients receiving palliative chemotherapy, Chi-square tests were also used to compare patient,

tumor and treatment characteristics between age groups. To compare time intervals between groups of patients, nonparametric Kruskal–Wallis tests were used. Univariable and multivariable logistic regression analyses were performed to investigate the association of patient and tumor characteristics with the administration of chemotherapy. Kaplan–Meier analyses with log rank tests were used (1) to evaluate overall survival of all patients with metastatic disease and (2) to compare overall and conditional survival of chemotherapy-treated and untreated patients within the different age groups. In patients receiving chemotherapy, univariable and multivariable Cox proportional hazard regression analyses were performed to evaluate predictors for a worse survival, using survival time calculated from (1) date of diagnosis and from (2) starting chemotherapy. In multivariable models, a backward stepwise elimination procedure was used with a $p > 0.10$ in likelihood ratio tests for removal of variables. Missing values were included as separate categories or dummy variables. In sensitivity analyses using region-wide data only, the additional influence of the number and type of comorbid conditions was investigated (in addition to the predictors derived from the multivariable models in the total population). All analyses were performed using STATA/SE (version 13.0; STATA Corp., College Station, TX).

Results

Patients with metastatic pancreatic cancer

Of 9,407 patients diagnosed with metastatic pancreatic cancer in the period 2005–2013, 32% was 75 years or older. Twenty-three per cent of all patients received palliative chemotherapy. Over time, the administration of palliative chemotherapy more than doubled from 13% in 2005 to 30% in 2013 ($p < 0.001$). Although treatment with chemotherapy was far less common in elderly patients, an increased use of chemotherapy was found in all age groups (**Figure 1**). In consecutive 3-year periods, from 26% to 43% of patients under age 70 years received chemotherapy, from 14% to 25% of patients aged 70–74 years and from 5% to 13% of patients aged 75–79 years (all $p < 0.001$). Over age 80 years very few patients were treated with chemotherapy and the very small increase of 2–3% was not statistically significant ($p = 0.56$). Besides elderly patients (≥70 years) and patients diagnosed in earlier years, also patients living in low SES neighborhoods, without tumor verification, with tumors located in the pancreatic head and patients with multiple metastatic sites independently had a lower probability of receiving chemotherapy (**Table 1**), In addition, the accumulation of comorbid conditions showed a stronger association with not receiving chemotherapy than specific comorbid conditions.

Median overall survival (OS) of patients with metastatic pancreatic cancer was 9.5 weeks (with rising age of patients [<70, 70–74, 75–79, ≥80 years]: 13-10-8-5 weeks, respectively, $p < 0.001$), and OS was 7 weeks in untreated patients versus 25 weeks (5.7 months) in patients who received chemotherapy ($p < 0.001$). As many as 26% of all patients died within 30 days after diagnosis (with rising age: 19-26-32-43%, $p < 0.001$). In patients who survived 30 days, chemotherapy-treated patients under 75 years survived longer compared to untreated patients (conditional survival [CS] <70 years: median 26 vs 12 weeks, 70–74 years: 27 vs 11 weeks, both $p < 0.001$), but the survival difference was smaller in patients over 75 years of age (75–79 years: median 20 vs 11 weeks, $p < 0.001$, ≥80 years: 16 vs 10 weeks, $p = 0.02$, **Figure 2**).

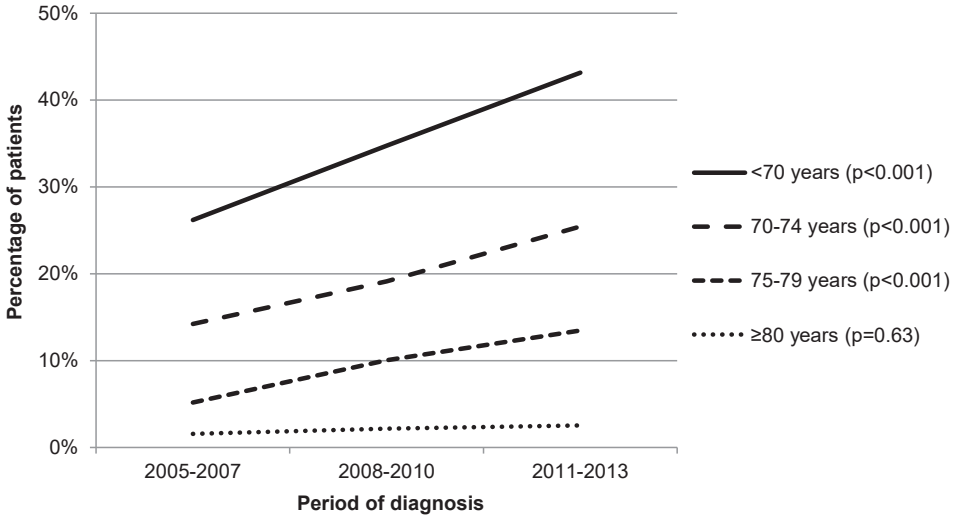


Figure 1. Administration of chemotherapy to patients diagnosed with metastatic pancreatic cancer in consecutive time periods in the Netherlands, by age group.

Table 1. Characteristics of patients with primary pancreatic adenocarcinoma and synchronous distant metastases in the period 2005-2013 in the Netherlands, by administration of chemotherapy (CT) and logistic regression analyses predicting administration of chemotherapy.

	Patients	CT	Univariable analysis		Multivariable analysis	
	N=9,407 (%)	%	OR (95% CI)	p-value	OR (95% CI)	p-value
Age				<0.001		<0.001
<70 years	4,729 (50)	35	1.00		1.00	
70-74 years	1,623 (17)	20	0.46 (0.41-0.53)		0.49 (0.43-0.57)	
75-79 years	1,437 (15)	9.9	0.20 (0.17-0.24)		0.23 (0.19-0.28)	
≥80 years	1,618 (17)	2.2	0.04 (0.03-0.06)		0.06 (0.04-0.09)	
Year of diagnosis	9,407 (100)	23	1.12 (1.10-1.15)	<0.001	1.12 (1.10-1.15)	<0.001
Sex				0.001		
Male	4,852 (52)	25	1.00			
Female	4,555 (48)	22	0.85 (0.77-0.93)			
History of cancer				<0.001		0.07
No	8,104 (86)	24	1.00		1.00	
Yes	1,303 (14)	18	0.70 (0.60-0.81)		0.86 (0.73-1.01)	
SES				<0.001		0.006
High	2,839 (30)	26	1.00		1.00	
Intermediate	3,736 (40)	23	0.89 (0.80-1.00)		0.95 (0.84-1.07)	
Low	2,832 (30)	21	0.76 (0.67-0.86)		0.81 (0.71-0.93)	
Tumour verification				<0.001		<0.001
Verified	6,486 (69)	30	1.00		1.00	
No verification	2,921 (31)	7	0.18 (0.15-0.21)		0.29 (0.25-0.34)	

Table 1 continues on next page

Continuation of table 1

	Patients	CT	Univariable analysis		Multivariable analysis	
	N=9,407 (%)	%	OR (95% CI)	p-value	OR (95% CI)	p-value
Primary tumour				<0.001		<0.001
Head of pancreas	4,567 (49)	21	1.00		1.00	
Body or tail	3,254 (35)	27	1.42 (1.28-1.57)		1.33 (1.19-1.49)	
Overlapping/NOS	1,586 (17)	20	0.95 (0.83-1.10)		0.98 (0.84-1.14)	
Metastatic site				<0.001		<0.001
1	6,283 (67)	24	1.00		1.00	
≥2	2,808 (30)	23	0.95 (0.86-1.06)		0.79 (0.70-0.89)	
Unknown	316 (3.4)	12	0.44 (0.31-0.62)		0.62 (0.43-0.90)	
Sensitivity analysis [a]						
Comorbid c.	(n=1,697)			<0.001	[b]	0.06
0	420 (25)	36	1		1.00	
1	466 (27)	26	0.63 (0.47-0.83)		0.78 (0.57-1.07)	
≥2	590 (35)	19	0.40 (0.30-0.54)		0.67 (0.48-0.94)	
Unknown	221 (13)	16	0.34 (0.23-0.52)		-	
Comorbid c.	(%yes)		(yes vs no)		[b]	
Diabetes	394 (27)	23	0.82 (0.63-1.08)	0.16		
Cardiac	353 (24)	15	0.43 (0.32-0.60)	<0.001		
Vascular	271 (18)	17	0.51 (0.36-0.72)	<0.001	0.69 (0.47-1.04)	0.07
Pulmonary	170 (12)	18	0.58 (0.38-0.87)	0.009		
Hypertension	450 (31)	23	0.79 (0.61-1.02)	0.07		
Digestive tract	151 (10)	28	1.11 (0.76-1.61)	0.60		

CT chemotherapy, Comorbid c. comorbid conditions, SES socioeconomic status, NOS not otherwise specified, OR odds ratio, CI confidence interval.

[a] Region-wide data only n=1,697 (18% of all patients). Multivariable model adjusted for variables included in model using nationwide data (age, year of diagnosis, history of cancer, SES, tumour verification, primary tumour and number of metastatic sites).

[b] excluding n=221 patients with unknown comorbid conditions because of collinearity.

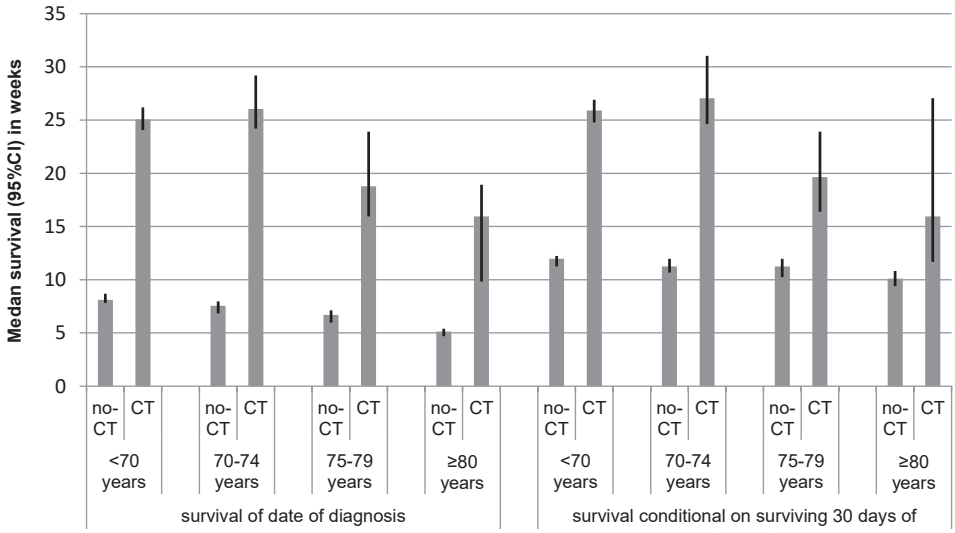


Figure 2. Median overall survival and conditional overall survival with 95% confidence interval of patients who received palliative chemotherapy (CT) for metastatic pancreatic cancer compared with untreated patients (no-CT), by age group.

Patients receiving systemic chemotherapy

Median age of 2,180 patients who received palliative chemotherapy for metastatic pancreatic cancer was 63 years (range, 21–86 years) and increased from 62 years in 2005–2007 to 64 years in 2011–2013. Eight per cent of treated patients were 75 years or older and only few patients were over 80 years of age (n = 35, 1.6%). With rising age (<70, 70–74, 75–79, ≥80 years), the prevalence of a prior cancer diagnosis and the number of comorbid conditions increased (both $p < 0.001$), particularly cardiac and vascular diseases ($p < 0.001$ and $p = 0.001$, respectively, **Table 2**). Furthermore, older patients less often had microscopic verification of the current cancer (91%, 88%, 87%, 77%, respectively, $p = 0.009$), although they all received chemotherapy.

The date of initiation of chemotherapy was available in 77% of patients and characteristics of these patients did not differ from the total group of patients (data not shown). Median time-to-chemotherapy was 25 days ([p25-p75] 15–43 days) and elderly patients started chemotherapy sooner after diagnosis (**Table 2**), as well as patients with non-head tumors (head: median 32 days, non-head: 21, $p < 0.001$) and patients with at least two metastatic sites (1: median 27 days, ≥2: 22 days, $p < 0.001$).

With rising age (<70, 70–74, 75–79, ≥80 years), median OS of treated patients decreased: 25, 26, 19, and 16 weeks, respectively, ($p = 0.003$). In univariable survival analysis of patients who received chemotherapy, a higher probability of worse OS was found in patients over 75 years of age, patients treated in earlier years of our study period, without microscopic tumor verification, with non-head cancer, and in patients with multiple metastatic sites (**Table 3**). In the multivariable Cox proportional hazard model, all these characteristics were independently associated with a poor OS. Compared with chemotherapy-treated patients younger than 70

years of age, patients over 75 years of age who received chemotherapy showed a worse OS (Hazard Ratio [HR] (75–79 vs <70) = 1.21, 95% CI 1.02–1.44; HR (≥80 vs <70) = 1.48, 95% CI 1.06–2.07), but the intermediate age group did not (HR (70–74 vs <70) = 0.92, 95% CI 0.81–1.03, p = 0.16). In sensitivity analysis, the number and type of comorbid conditions of treated patients seemed not significantly associated with a poor OS (borderline: pulmonary diseases: adjusted HR = 1.38, 95% CI 0.94–2.01, p = 0.10).

Using survival time calculated from the starting date of chemotherapy, median OS of treated patients was 20 weeks. With rising age (<70, 70–74, 75–79, ≥80 years), median survival was 20, 22, 16 and 13 weeks, respectively, (p = 0.006, **Figure 3**). No survival difference was found according to tumor location (univariable HR (body/tail vs head) = 1.07, 95% CI 0.96–1.19, p = 0.43), but other above-mentioned prognostic characteristics were independently associated with a worse OS (age: HR (70–74 vs <70) = 0.93, 95% CI 0.81–1.07, HR (75–79 vs <70) = 1.24, 95% CI 1.02–1.51, HR (≥80 vs <70) = 1.68, 95% CI 1.13–2.50).

Table 2. Characteristics of patients who received palliative chemotherapy (CT) for metastatic pancreatic cancer in the period 2005-2013 in the Netherlands, by age group.

	All patients	<70 years	70-74 years	75-79 years	≥80 years	Chi² p-value
	N=2,180	N=1,674	N=329	N=142	N=35	
	%	%	%	%	%	
Sex						0.49
Male	1,194(55)	56	51	54	57	
Female	986(45)	44	49	46	43	
SES						0.56
High	724(33)	33	34	29	40	
Intermediate	874(40)	40	38	42	46	
Low	582(27)	27	28	29	14	
History of cancer						<0.001
No	1,944(89)	91	85	77	77	
Yes	236(11)	8.7	15	23	23	
Comorbid c. [a]	(n=420)	(n=325)	(n=64)	(n=27)	(n=4)	<0.001
0	152(36)	42	17	22	0	
1	122(29)	30	25	26	50	
2+	110(26)	20	52	37	25	
Unknown	36(8.6)	8.3	6.3	15	25	
Comorbid c. (%yes) [a, b]	(n=384)	(n=298)	(n=60)	(n=23)	(n=3)	
Diabetes	92(24)	21	35	30	0	0.09
Cardiac disease	54(14)	9.7	28	26	67	<0.001
Vascular disease	45(12)	8.4	25	17	33	0.001
Pulmonary disease	30(7.8)	7.1	13	4.4	0	0.33
Hypertension	103(27)	24	40	26	33	0.09
Digestive tract disease	42(11)	9.7	10	26	33	0.06

Table 2 continues on next page

Tumour verification						0.009
Verified	1,968(90)	91	88	87	77	
No verification	212(9.7)	8.8	12	13	23	
Primary tumour						0.27
Head of pancreas	964(44)	44	48	44	34	
Body or tail	894(41)	42	36	39	57	
Other or overlapping	322(15)	15	16	17	8.6	
Number of metastatic sites						0.51
1	1,497(69)	69	69	63	69	
≥2	645(30)	29	28	37	31	
Unknown	38(1.7)	1.8	2.1	0.7	0	
Time interval to CT [c]						
Median [p25-p75] in days	25[15-42]	26[15-43]	26[16-48]	21[13-33]	18[13-34]	0.007
≥6 weeks	443(26)	27	29	17	12	0.03
Mortality of starting CT c						
30-day mortality	141(8.4)	8.0	8.5	10.0	20.0	0.17
90-day mortality	541(32)	31	31	44	48	0.02

Comorbid c. comorbid conditions, SES socioeconomic status, NOS not otherwise specified, N number of patients,
[a] Region-wide data only n=420 (18% of all patients).
[b] excluding patients with unknown comorbid conditions.
[c] If date of initiating chemotherapy is available n=1,676 (77% of all patients).

Table 3. Crude median overall survival and univariable and multivariable Cox proportional hazards regression analyses predicting survival of patients who received palliative chemotherapy for metastatic pancreatic cancer in the period 2005-2013 in the Netherlands. Survival calculated from date of diagnosis (100% of patients).

	MS	Univariable		Multivariable	
Characteristics	months	HR (95%CI)	p-value	HR (95% CI)	p-value
Age			0.003		0.008
<70 years	5.8	Ref		Ref	
70-74 years	6.0	0.93 (0.83-1.05)		0.92 (0.81-1.03)	
75-79 years	4.3	1.25 (1.05-1.48)		1.21 (1.02-1.44)	
≥80 years	3.7	1.58 (1.13-2.21)		1.48 (1.06-2.07)	
Year of diagnosis	5.7	0.98 (0.96-1.00)	0.05	0.98 (0.96-1.00)	0.03
Sex			0.30		
Male	5.5	Ref			
Female	6.2	0.96 (0.88-1.04)			
History of cancer			0.85		
No	5.7	Ref			
Yes	6.0	0.99 (0.86-1.13)			
SES			0.27		
High	5.8	Ref			
Medium	5.5	1.05 (0.95-1.16)			
Low	6.0	1.09 (0.98-1.22)			

Table 3 continues on next page

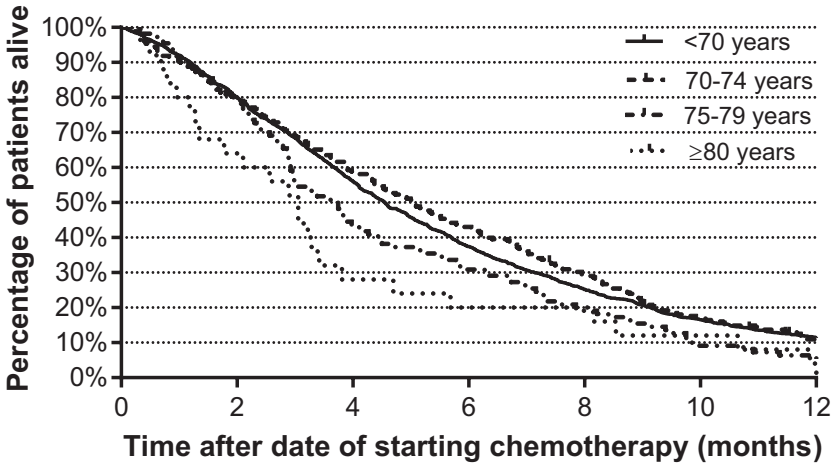
Continuation of table 3

	MS	Univariable		Multivariable	
Characteristics	months	HR (95%CI)	p-value	HR (95%CI)	p-value
Tumour verification			0.02		0.007
Verification	5.8	Ref		Ref	
No verification	4.9	1.19 (1.03-1.37)		1.22 (1.05-1.41)	
Primary tumour			<0.001		0.002
Head	6.2	Ref		Ref	
Body or tail	5.4	1.21 (1.11-1.33)		1.17 (1.07-1.29)	
Overlapping/NOS	5.7	1.17 (1.03-1.33)		1.17 (1.03-1.33)	
Metastatic sites			<0.001		<0.001
1	6.2	Ref		Ref	
≥2	5.0	1.38 (1.25-1.51)		1.36 (1.23-1.49)	
Unknown	5.6	1.13 (0.82-1.56)		1.07 (0.76-1.49)	
Sensitivity analysis [a]					
Comorbid c.			0.06	[b]	
0	5.8	Ref			
1	6.0	0.97 (0.76-1.23)			
≥2	5.4	1.18 (0.96-1.51)			
Unknown	6.3	0.71 (0.49-1.03)			
Comorbid c.	(if yes)	(yes vs no)		[b]	
Diabetes	5.8	1.10 (0.87-1.40)	0.42		
Cardiac	5.2	0.97 (0.72-1.30)	0.84		
Vascular	4.8	1.02 (0.74-1.40)	0.90		
Pulmonary	5.4	1.40 (0.96-2.03)	0.10	1.38 (0.94-2.01)	0.10
Hypertension	5.8	1.16 (0.92-1.46)	0.22		
Digestive tract	7.1	0.84 (0.61-1.16)	0.29		

MS median survival, Comorbid c. comorbid conditions, SES socioeconomic status, NOS not otherwise specified, HR hazard ratio, CI confidence interval.

[a] Region-wide data only n=420 (18% of all patients). Multivariable model adjusted for variables included in model using nationwide data (age, year of diagnosis, tumour verification, primary tumour and number of metastatic sites).

[b] excluding n=36 patients with unknown comorbid conditions because of collinearity.



number at risk							
<70 years	1289	1033	724	483	325	212	144
70-74 years	258	205	152	111	75	43	28
75-79 years	110	88	48	34	21	10	7
?80 years	25	16	7	5	5	3	1

Figure 3. Crude overall survival of patients who received palliative chemotherapy for metastatic pancreatic cancer, by age group. Survival calculated from date of starting chemotherapy (77% of patients). Log rank test p = 0.006.

Discussion

To our knowledge, this is the first nationwide study of patients with metastatic pancreatic cancer that investigated chemotherapy use and survival in multiple elderly age groups. The administration of palliative systemic therapy doubled between 2005 and 2013 in all age groups. Compared with younger patients receiving chemotherapy, treated patients over 75 years of age less often underwent microscopic tumor verification of cancer and showed a worse overall survival.

In accordance with previous population-based reports, overall survival of patients with primary metastatic pancreatic cancer in our study was only 2–3 months [4,5,18]. Our nationwide study also confirmed a recent regional report from the Netherlands that the administration of palliative chemotherapy has increased rapidly in the past decade [3]. Chemotherapy prescription in the Netherlands, however, (overall 23%, patients surviving 30 days 31%), seemed relatively low compared with population-based studies from the USA and France (42–54%) [10,19–21]. Although no information on the type of chemotherapy was available in our study, it is plausible that gemcitabine-based therapies were prescribed to the vast majority of patients in the selected time period [20–22]. Treatment preference for gemcitabine was mainly based on its favorable clinical benefit response (pain, performance status, weight) and toxicity profile compared to 5-fluorouracil (5-FU) [23,24]. Only recently, the studies by Conroy et al. on FOLFIRINOX

(oxaliplatin, irinotecan, fluorouracil, and leucovorin) [8] and Von Hoff et al. on the combination of gemcitabine and nab-paclitaxel (MPACT-trial) [9] opened new treatment perspectives [25–27]. However, despite a good performance status of included patients, prolonged survival in these studies went along with an increased risk of side effects. Possibly, modified FOLFIRINOX or gemcitabine with nab-paclitaxel treatment may be beneficial to older patients or patients with a less favourable performance status [28].

Similar to other reports [3,20,21], chemotherapy use in the current study was far less likely in elderly patients with metastatic pancreatic cancer. Although the number of octogenarians receiving chemotherapy hardly increased, in the course of our study the age of patients who received palliative chemotherapy rose. In patients aged 70–74 years who received chemotherapy, tumor verification rate, timing of chemotherapy, early mortality and overall survival in our study were very similar to that of treated patients younger than 70 years. However, although very few and therefore highly selected elderly patients over 75 years of age were treated with palliative chemotherapy, a poor survival after chemotherapy was particularly found in this elderly age groups. Survival of treated elderly patients in our nationwide study (≥75 years: median 4.0 months) was strikingly worse than the median of 7–8 months in previous mono-institutional cohorts of patients over 75 years of age [11,12]. Our observations are likely related to the nationwide character of our study with a less selective cohort of elderly patients. Furthermore, additional analyses of the MPACT-study data showed that older age (defined as ≥65 years) was an independent predictor for both worse overall and progression-free survival [29]. Unlike older age, in our study comorbid conditions seemed not strongly associated with a worse overall survival of treated patients. Possibly, a loss of 'functional reserve' due to the process of aging may add to a worse survival of elderly patients, resulting in increased toxicity or reduced dose adherence and consequently reduced treatment efficacy and survival. Therefore, geriatric characteristics and co-morbid features predictive of treatment intolerance should be better defined.

Overall, survival of the total group of patients who received palliative chemotherapy in our study was similar to other observational studies (median 5.7 vs 5–6.4 months) [13,20,22]. Although as many as 32% of patients in our study died within 90 days of starting chemotherapy, this may reflect the treatment goal directed at symptom management and the progressive character of pancreatic cancer. Generally, chemotherapy use in the last weeks of life is considered undesirable end-of-life care [30]. Particularly in pancreatic cancer patients with their already poor prognosis, palliative chemotherapy may jeopardize quality of end-of-life care and yield a limited cost-effectiveness [31]. Therefore, a better selection of patients with pancreatic cancer who may benefit from available palliative chemotherapies is clearly needed.

Most previous observational studies only included patients with microscopically confirmed pancreatic cancer [5,11,13,21,22,32]. Although pathologic confirmation of pancreatic cancer prior to chemotherapy is strongly recommended [27, 33], one in ten of treated patients in our study started chemotherapy without prior microscopic tumor verification. Especially in elderly patients, microscopic verification was often omitted. Although in selected patients, a

suspected mass on computer tomography (CT), elevated serum marker CA19-9 and cancer-specific symptoms may result in a high specificity for pancreatic cancer [34], misdiagnosis cannot be ruled out [35, 36].

Our population-based study also revealed that especially patients with pancreatic head tumors started palliative chemotherapy several weeks after diagnosis (median, 4–5 weeks). Many patients with pancreatic head tumors undergo stent placement to solve bile duct obstruction [37]. Other patients must recover from explorative surgical procedures [38–40]. Stent dysfunction and surgical morbidity may have delayed or precluded chemotherapy in a number of patients with metastatic disease. Indeed, patients with pancreatic head cancer in our study less likely received palliative chemotherapy (21%, vs 27% in patients with body or tail disease).

Important limitations in this population-based study concern the availability of data. Firstly, completeness of pancreatic cancer diagnoses in the NCR was questioned recently [41]. Although chemotherapy use in elderly patients and survival of untreated patients might slightly be overestimated, analyses of treated patients are expected to be highly accurate. Secondly, the NCR does not contain nationwide data on comorbid conditions and performance status of patients. However, patients who received palliative chemotherapy for pancreatic cancer may already have a relatively favorable performance status and available (region-wide) comorbidity data did not show significant associations with a poor survival. Furthermore, this nationwide population-wide study reflects real-world treatment and survival patterns and also included patients without microscopic confirmation of cancer and patients who underwent pancreatic resection (0.7%). Excluding these patient groups did not alter our results. Thirdly, although conditional survival analysis has reduced survivor treatment bias (immortal time bias), treatment choice was not at random (treatment selection bias) [17]. Therefore, the observed differences between treated and untreated patients are likely an overestimation of true survival differences. Finally, starting dates of chemotherapy were available in only three quarters of patients. However, patients were representative for the total patient population and the available data revealed important information about the treatment process. The recently initiated Dutch nationwide PAncreatic CAncer Project (PACAP), which combines data from the NCR with the Dutch Pancreatic Cancer Audit and Dutch Pancreatic Biobank, is expected to provide more detailed information on systemic treatment in patients with pancreatic cancer, such as type and amount of chemotherapy [42].

Conclusions

Despite a limited chemotherapy use in elderly patients, suggestive of strong selection, especially patients over 75 years of age who received chemotherapy showed a poor survival. Improved definition of the geriatric characteristics and co-morbid features predictive of treatment intolerance is necessary to optimize selection of elderly patients for palliative chemotherapy. In addition, appropriate chemotherapy regimens are required that are better tolerated by elderly patients.

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Chapter 10

Trends in treatment and survival of patients with nonresected, nonmetastatic pancreatic cancer: a population-based study

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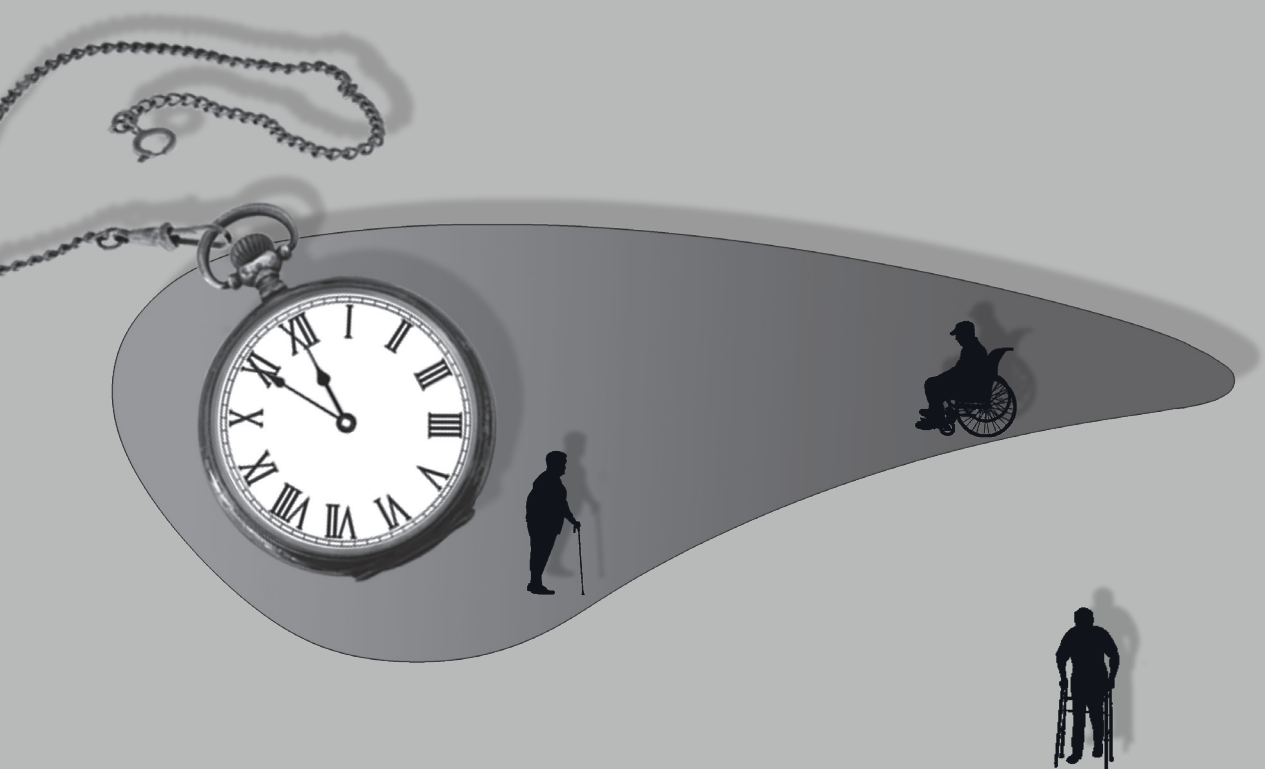
Cancer Med. 2018 Oct;7(10):4943-4951.



Abstract

Background
Nonresected, nonmetastatic (NR-M0) pancreatic cancer involves both locally advanced pancreatic cancer and patients who did not undergo resection due to poor health status or patient preference. This study investigates nationwide trends of characteristics, treatment, and survival of patients with NR-M0 pancreatic cancer.

Methods
From the Netherlands Cancer Registry, all patients diagnosed with pancreatic cancer between 2006 and 2014 were selected. Chemotherapy and overall survival (OS) of NR-M0 patients were evaluated for 3-year time periods and 2 age groups using chi-square tests for trend and Cox proportional hazard regression analysis.

Results
Of 18,234 patients, 33% had NR-M0 pancreatic cancer, which decreased over time (in consecutive 3-year periods: 38%-33%-28%, p<0.001). Of 5,964 NRM0 patients, 52% was over 75 years of age, 16% received chemotherapy, and median OS was 5.1 months. Chemotherapy use increased over time in younger patients (<75 years: from 23 to 36%, p-trend<0.001, ≥75 years: 3% to 4%, p-trend=0.053). In multivariable survival analysis, elderly age, low SES, nonconfirmed cancer, stage II-III disease, and earlier years of diagnosis were independently associated with a worse OS. Age of patients who received chemotherapy increased over time (median 62- 66 years) and median OS was 10.4 months without significant differences between time periods (p=0.177) or age groups (p=0.207).

Conclusions
Overall survival of NR-M0 pancreatic cancer remains poor which is partly related to advanced age of many patients. Despite an increase, chemotherapy is infrequently used. Future research should investigate to what extent the more widespread use of chemotherapy could improve survival in relation to age-related morbidity.

Introduction

Pancreatic cancer remains one of the most lethal cancers with a 5-year survival rate of 5- 7% [1, 2]. Since symptoms usually emerge late, about 50%- 60% of patients are diagnosed with metastatic disease [3, 4]. Only 10%- 20% of patients have resectable disease. The intermediate group of 30%- 40% generally is referred to as locally advanced pancreatic cancer (LAPC) [5, 6]. Nonresected patients in cancer registries have metastatic or unresectable disease diagnosed at imaging or at time of surgical exploration or are ineligible for surgery due to a poor health status or patient preference. As a result of increased resection rates for pancreatic cancer [7, 8], characteristics of the patient group with nonresected, nonmetastatic (NR-M0) disease may have changed.

For patients with pancreatic cancer not undergoing resection, chemotherapy is the main treatment modality. In patients with metastatic disease, population- based studies have shown that the administration of palliative chemotherapy steeply increased in the past decades [3, 9, 10]. Notably, this increased use of chemotherapy was found in the gemcitabine era, and thus, before the studies on FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) and nab-paclitaxel plus gemcitabine reported favorable results compared with gemcitabine alone [11, 12]. No randomized controlled trials have yet been published on these chemotherapy schemes in patients with LAPC. Despite a lack of randomized studies, an increased use of chemotherapy may also be found in patients with NR-M0 disease.

Population- based data on treatment and survival of patients with LAPC or NR-M0 disease are scarce [13]. In addition, little is known about survival of elderly patients with NR-M0 disease, with or without chemotherapy.

Therefore, the aim of this nationwide study was to investigate time trends in characteristics, treatment, and survival of patients with NR-M0 pancreatic cancer.

Methods

Data collection

The Netherlands Cancer Registry (NCR) records data on all patients with newly diagnosed cancer in the Netherlands, a country with 17 million inhabitants. Since 1989, newly diagnosed malignancies are notified to the NCR by the automated pathological archive (PALGA), supplemented with data from the National Registry of Hospital Discharge Diagnoses. Completeness is estimated to be at least 95%. Trained registrars in all Dutch hospitals routinely extract data on patient, tumor, and treatment characteristics. Tumor location and histology are registered according to the International Classification of Diseases for Oncology (ICD- O- 3) [14]. The tumour- node- metastasis (TNM) staging classification is used (6th edition in 2003- 2009 [15], 7th edition in 2010- 2016 [16]) for pathologically confirmed malignancies, while in other cases, a 1-digit extend of disease (EoD) is recorded. From 2012 onwards, TNM was recorded for all patients. Actual vital status (dead or alive, date of death or emigration) is obtained by

periodically linking the NCR to the Municipal Personal Records Database which keeps record on the vital status of all Dutch inhabitants.

Patients

From the NCR, all patients were selected who were diagnosed with pancreatic (ductal) adenocarcinoma between 2006 and 2014 (ICD-O-3 C25, morphology codes 8010, 8012, 8020, 8140,8141, 8260, 8310, 8440, 8480, 8481, 8490, 8500, 8560, or a nonconfirmed supposed adenocarcinoma). Patients diagnosed at autopsy, younger than 18 years or residing abroad, were excluded. The total population was divided into three groups: resected, nonresected, nonmetastatic (NR-M0), and metastatic pancreatic cancers. Since this division was based on findings of imaging and surgical exploration, a number of patients with nonresected disease underwent a laparotomy or laparoscopy (11% of NR-M0 patients in 2012-2014). The intermediate group of NR-M0 patients was the focus of the present study.

The study period was evenly divided into three 3-year periods: 2006- 2008, 2009- 2011, and 2012-2014. Patients were divided into two age groups: younger patients <75 years and elderly patients ≥75 years at diagnosis. Comorbidity was recorded regionwide in 2 out of 9 Dutch cancer regions (16% of all patients) according to a slightly modified version of the Charlson classification. Serious comorbid conditions included chronic obstructive pulmonary diseases, cardiovascular diseases, cerebrovascular diseases, digestive tract diseases, diabetes mellitus, and other serious diseases. The number of comorbidities was categorized into three groups (0, 1, and ≥2). In addition, due to the nature of the NCR, information on previous malignancies was available in all patients. Furthermore, socioeconomic status (SES) [17] was based on reference data from The Netherlands Institute for Social Research. Social deprivation scores were derived from data on income, education, and occupation per 4- digit postal code and were broken into three SES categories (high: 1st-3rd, intermediate: 4th-7th, and low: 8th-10th deciles). Both types of information on tumor stage (TNM and EoD) were combined into one summary stage: (a) "localized": tumor confined to the pancreas (TNM I); (b) "nonlocalized": "tumor extension into adjacent organs or tissues and/or into regional lymph nodes" (TNM II-III); (c) "metastatic": distant metastasis (TNM IV); and (d) unknown stage. In the period 2012-2014, a distinction between stage II (T3/N1M0) and stage III (T4M0) could be made. Registered treatments comprise tumor resection, chemotherapy, and/or local treatment such as radiotherapy applied for stage at diagnosis. No information was available about type of chemotherapy treatment. Survival time was calculated from the date of diagnosis to the date of death or emigration. Patients who were alive on 1 February 2017 were censored (1.6%). To investigate early mortality after diagnosis, 30- and 90-day mortality of any cause after date of diagnosis were calculated.

Statistical analysis

Chi-square tests for trend were used to analyze characteristics and treatment of the NR-M0 patients in consecutive 3-year periods. A two-sided p-value <0.05 was considered statistically significant. To evaluate overall survival of NR-M0 patients, Kaplan- Meier analyses and log- rank tests were used, as well as univariable and multivariable Cox proportional hazard analyses. In multivariable models, a backward stepwise selection was used with a p>0.10 for removal of

variables in likelihood ratio tests. Characteristics that were included (if applicable) were time periods, age, sex, history of cancer, SES, pathological confirmation of cancer, tumor location, summary tumor stage, chemotherapy, and local treatment. Sensitivity analyses were performed using regionwide data to investigate associations of the number and type of comorbid conditions (adjusted for predictors derived from the multivariable model in all patients). STATA/SE (version 14.0; STATA Corp., College Station, TX, USA) was used in all analyses.

Results

All patients

Median age of 18,234 patients diagnosed with pancreatic cancer in 2006-2014 was 71 years and 37% was 75 years or older. Pathology confirmation of pancreatic cancer occurred less frequently in patients with nonmetastatic disease (62% vs 69% in metastatic disease, p<0.001). Metastatic disease was present in 9,934 (54%) of patients, and 2,336 (13%) of patients underwent tumor resection. The remaining 5,964 (33%) patients had nonresected, nonmetastatic (NR-M0) pancreatic cancer. Compared with patients with resected and metastatic cancer, patients with NR-M0 pancreatic cancer were older (median 75 years vs 67 and 69 years, respectively) and had an intermediate overall survival (median 5.1 months [95% confidence interval: 4.9-5.2 months] vs 17.5 and 2.3 months, respectively).

Both tumor resection and diagnosis of metastatic disease increased over time. As a result, NR-M0 pancreatic cancer decreased from 2,052 (38%) patients in 2006-2008 to 2,026 (33%) in 2009-2011 and 1,886 (28%) in 2012-2014 (p-trend<0.001). This time trend was found within younger and elderly age groups alike, as was shown in **Figure 1**.

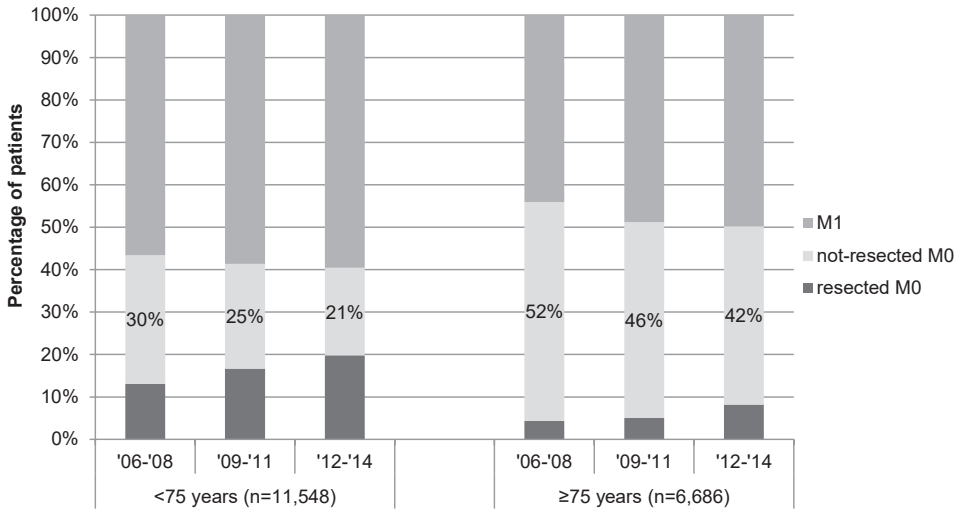


Figure 1. Distribution of resected, nonresected nonmetastatic (NR-M0), and metastatic (M1) pancreatic cancer, by periods within younger and elderly age categories (both p<0.001).

Patients with NR-M0 pancreatic cancer

Overall, 52% of 5,964 patients with NR-M0 pancreatic cancer was aged 75 years and older, with a significant increase over time (50%, 52%, and 54%, p-trend=0.008; **Table 1**). Pathological confirmation of cancer occurred in 47% of NRM0 patients and increased over time in younger patients only. Arterial involvement was found in 39% of NR-M0 patients (TNM stage III, 2012-2014).

Only 16% (967/5,964) of patients with NR-M0 disease received chemotherapy, with an increase in consecutive 3-year periods from 13%, 17%, to 19% (p-trend<0.001), particularly in younger patients (<75 years: from 23% to 36%, p-trend<0.001, **Table 1**). Of patients over 75 years, only 3.5% were treated with chemotherapy (2.8% to 4.3%, p-trend=0.053). In addition, 5.4% of patients received local therapy such as radiotherapy or (sporadic) ablative treatments (in consecutive periods: 5.5%-4.2%-6.7%, respectively, p-trend=0.121).

At time of 90-days after diagnosis, 33% (1,978/5,964) of patients had died, particularly elderly patients (<75 years: 24%, ≥75 years: 41%, p<0.001). No time trends were found in early mortality (**Table 1**). One- and 2-year overall survival (OS) of patients with NR-M0 pancreatic cancer were 18% and 5%, respectively (data not shown). In consecutive 3-year periods, median OS was 4.9, 5.1, and 5.1 months, respectively (p=0.088, **Table 1**). For patients aged <75 years and ≥75 years, median OS was 6.3 and 3.9 months, respectively (p<0.001). In the younger age group, a very small improvement of OS was found in the study period (from 5.9 to 6.4 months, p=0.052; ≥75 years: 3.8 to 4.0 months, p=0.322). Furthermore, median OS was 10.4 months in patients who received chemotherapy vs 4.2 months in untreated patients (p<0.001). In the multivariable Cox proportional hazard model, elderly age, low SES, nonconfirmed cancer, nonlocalized disease, and diagnosis in earlier years of the study period were independently associated with a worse OS (**Table 2**). In a second model including treatment, the increased use of chemotherapy could not completely remove differences between time periods. Among cases with available comorbidity data, only the presence of pulmonary disease was additionally associated with a worse OS (n = 864, HR = 1.29, 95% CI 1.06- 1.59).

Table 1. Characteristics of patients with nonresected, nonmetastatic (NR-M0) pancreatic carcinoma, by time periods within younger and elderly age groups.

	All patients					Patients younger than 75 years					Patients 75 years and older				
	All	2006-2008	2009-2011	2012-2014		All	2006-2008	2009-2011	2012-2014		All	2006-2008	2009-2011	2012-2014	
N=	5,964	2,052	2,026	1,886	Chi2	2,872	1,035	965	872	Chi2	3,092	1,017	1,061	1,014	Chi2
	(%)	%	%	%	p-trend	(%)	%	%	%	p-trend	(%)	%	%	%	p-trend
Pathological confirmation					0.022					<0.001					0.208
Confirmed	2,790(47)	45	46	49		1,874(65)	63	63	71		916(30)	28	30	30	
Not confirmed	3,174(53)	55	54	51		998(35)	37	37	29		2,176(70)	72	70	70	
Primary tumor					0.098					0.014					0.860
Pancreatic head	4,499(75)	77	76	74		2,057(72)	73	73	68		2,442(79)	80	79	79	
Body or tail	784(13)	12	12	16		464(16)	15	15	18		320(10)	9.1	8.9	13	
Overlapping/ NOS	681(11)	11	12	11		351(12)	11	12	14		330(11)	11	12	8.3	
Summary stage					0.595					0.260					0.631
Localized	1,467(25)	26	26	22		352(12)	15	12	9.5		1,115(36)	37	39	32	
Non-localized	3,789(64)	59	64	67		2,287(80)	75	80	84		1,502(49)	43	49	53	
Unknown	708(12)	15	10	11		233(8)	9.8	7.8	6.5		475(15)	20	12	15	
TNM stage I-II-X				61					43					77	
TNM stage III				39					57					23	
Chemotherapy (%yes)	967(16)	13	17	19	<0.001	858(30)	23	31.5	36	<0.001	109(3.5)	2.8	3.5	4.3	0.053
Local therapy (%yes)a	324 (5.4)	5.5	4.2	6.7	0.121	288(10)	10	7.8	13	0.074	36(1.2)	1.0	0.9	1.6	0.212
Deceased within 30 days of diagnosis (%yes)	739(12)	12	12	13	0.275	191(6.7)	6.5	6.3	7.2	0.529	548(18)	17	18	18	0.704

Deceased within 90 days of diagnosis (%yes)	1,978(33)	33.2	32.8	33.51	0.838	697(24)	25	24	24	0.938	1,281(41)	42	41	41	0.761
Median OS (95%CI) in months	5.1 (4.9-5.2)	4.9 (4.6-5.2)	5.1 (4.8-5.5)	5.1 (4.8-5.5)	0.088[b]	6.3 (6.0-6.6)	5.9 (5.5-6.4)	6.7 (6.0-7.1)	6.4 (6.1-6.7)	0.052[b]	3.9 (3.7-4.1)	3.8 (3.5-4.2)	3.9 (3.6-4.4)	4.0 (3.6-4.3)	0.322[b]

OS overall survival, CI Confidence Interval, NOS not otherwise specified

[a] For example. conventional radiotherapy, SBRT, RFA, IRE. b Log rank test.

Table 2. Univariable and multivariable Cox proportional hazards analyses predicting overall survival of patients with nonresected, nonmetastatic (NR-M0) pancreatic cancer.

	N=	MS	Univariable analysis		Multivariable analysis		Multivariable analysis including treatment	
		months	HR(95%CI)	p-value	HR(95%CI)	p-value	HR(95%CI)	p-value
Overall	5,964	5.1						
Period of diagnosis				0.090				
2005-2008	2,052	4.9	Ref		Ref		Ref	
2009-2011	2,026	5.1	0.93 (088-0.99)		0.93 (0.87-0.99)	0.020	0.94 (0.88-1.00)	0.043
2012-2014	1,886	5.1	0.97 (0.89-1.02)		0.94 (0.88-1.00)	0.067	0.99 (0.93-1.05)	0.664
Age				<0.001				
<75 years	2,87	6.3	Ref		Ref		Ref	
≥75 years	3,092	3.9	1.36 (1.29-1.43		1.39 (1.31-1.47)	<0.001	1.21 (1.14-1.28)	<0.001
Sex				0.249				
Male	2,745	5.1	Ref					
Female	3,219	5.1	1.03 (0.98-1.08)					
History of cancer				0.008				
No	4,956	5.1	Ref					
Yes	1,008	4.5	1.10 (1.03-1.18)					
Socioeconomic status				0.001				
High	1,718	5.4	Ref		Ref		Ref	
Intermediate	2,405	4.9	1.03 (0.96-1.09)		1.03 (0.96-1.09)	0.416	1.01 (0.95-1.08)	0.762
Low	1,841	4.7	1.12 (1.05-1.20)		1.12 (1.05-1.20)	0.001	1.11 (1.04-1.19)	0.002
Pathological confirmation				<0.001				
Confirmed	2,79	6.0	Ref		Ref		Ref	
Not confirmed	3,174	4.1	1.18 (1.12-1.24)		1.09 (1.03-1.16)	0.004	0.99 (0.94-1.05)	0.827
Primary tumor location				0.108				
Head of pancreas	4,499	5.1	Ref					
Body or tail	784	5.2	0.93 (0.86-1.00)					
Overlapping/NOS	681	4.7	1.02 (0.94-1.10)					

Summary stage				<0.001				
Localized	1,467	4.9	Ref		Ref		Ref	
Non-localized	3,789	5.5	1.04 (0.98-1.11)		1.27 (1.18-1.36)	<0.001	1.34 (1.25-1.44)	<0.001
Unknown	708	3.5	1.25 (1.14.1.37)		1.31 (1.19-1.43)	<0.001	1.27 (1.16-1.39)	<0.001
Chemotherapy				<0.001	X			
No	4997	4.2	Ref				Ref	
Yes	967	10.4	0.53 (0.49-0.56)				0.56 (0.52-0.61)	<0.001
Local therapy				<0.001	X			
No	5640	4.7	Ref				Ref	
Yes	324	11.3	0.55 (0.49-0.62)				0.77 (0.68-0.87)	<0.001

MS median survival, SES socioeconomic status

Patients with NR-M0 disease who received chemotherapy

Median age of 967 patients with NR-M0 pancreatic cancer who received chemotherapy was 64 years (range 34- 85 years) and increased in consecutive 3-year periods (median age 62, 63, 66 years, respectively, p=0.007). Of these treated patients, as many as 17% did not undergo pathological confirmation of cancer (**Table 3**), which decreased over time (19%, 20%, 12% of treated patients in consecutive time periods, p=0.015). Most patients receiving chemotherapy had locally advanced disease (stage II-III: 87%, 91%, and 94% in consecutive 3-year periods, p=0.013; stage III: 67% of 357 treated patients diagnosed in 2012-2014). One- and 2-year survival were 41% and 11%, respectively. Median OS of treated patients was 10.5, 9.6, and 10.8 months in consecutive time periods (p=0.177; **Table 3**) and did not differ significantly between age groups (<75 years: 10.6 and ≥75 years: 9.2 months, p=0.207; data not shown).

Table 3. Characteristics of patients with nonresected, nonmetastatic (NR-M0) pancreatic carcinoma receiving chemo(radio)therapy, by time periods.

	All patients	2006-2008	2009-2011	2012-2014	
	N=967	N=269	N=341	N=357	Chi2
	(%)	%	%	%	p-trend
Median age (range)	64 (34-85)	62 (34-83)	64 (36-84)	66 (38-85)	0.007
Pathological confirmation					0.015
Confirmed	807(83)	81	80	88	
Not confirmed	160(17)	19	20	12	
Primary tumor					0.102
Pancreatic head	645(67)	68	68	64	
Body or tail	206(21)	22	17	24	
Overlapping/NOS	116(12)	9.7	14	11	
Summary stage					0.013
Localized	62(6.4)	9.7	5.3	5.0	
Non-localized	878(91)	87	91	94	
Unknown	27(2.8)	3.7	3.8	1.1	
TNM stage I-II-X	117 (33)			33	
TNM stage III	240 (67)			67	
Local therapy (%yes) [a]	247(26)	36	19	24	<0.001
Deceased within 90 days of diagnosis (%yes)	101 (14)	11	16	13	0.342
Median OS	10.4	10.5	9.6	10.8	0.177 [b]
(95%CI) in months	(9.9-10.9)	(9.4-11.8)	(8.7-10.7)	(10.2-11.5)	

OS overall survival, CI Confidence Interval, NOS not otherwise specified

[a] For example, conventional radiotherapy, SBRT, RFA, IRE. [b] Log rank test.

Discussion

One-third of patients with pancreatic cancer in the Netherlands (2006-2014) had nonresected, nonmetastatic (NR-M0) disease. At least half of these nearly 6,000 NR-M0 patients were over 75 years of age and two- fifth of patients had stage III disease. The median overall survival of NR-M0

pancreatic cancer was 5.1 months. Only 16% of NR-M0 patients received chemotherapy with a median survival of 10.4 months. In the course of our study, a 50% increase in chemotherapy use was found within the younger age group (<75 years), though without significant improvement of survival.

In the past decade, the resection rate for pancreatic cancer in the Netherlands has increased [7, 8], whereas detection of metastatic disease also increased (stage migration) [3]. Consequently, the proportion of patients in the remaining group with NR-M0 pancreatic cancer decreased until less than one-third in 2012-2014, while age of patients with NR-M0 disease increased. In addition, only 40% of the NR-M0 patient group in 2012-2014 had stage III disease. Particularly in the remaining 60% of NR-M0 pancreatic cancer patient stage I-II, elderly patients were overrepresented (≥75 years: 68%). Several retrospective studies suggested underutilization of surgical treatment in elderly patients with localized pancreatic cancer [18-20]. However, many NR-M0 patients die soon after diagnosis; in our study, 41% of patients over 75 years died within 90 days. Though in a previous study comorbidity of (elderly) patients was not associated with the application of pancreatic surgery [18], a poor general health status at time of diagnosis may have precluded surgical treatment. Accurate identification of a poor health status of patients is of utmost importance for optimal treatment decision making [21].

Most patients not eligible for pancreatic surgery due to a poor performance status are also not candidates for chemotherapy. In the current study period in the Netherlands, the administration of chemotherapy to NR-M0 patients was very limited (16%), which can largely be attributed to the high number of elderly patients with early- stage disease (77% of stage I-II and 43% of stage III patients were aged ≥75 years). In addition, a restraint of medical oncologists to give chemotherapy to elderly patients and patient preferences could have added to limited chemotherapy use. Also in the subgroup of patients with stage III disease, chemotherapy use in our study (34% in 2012-2014) was limited compared with population-based studies in the United States (>50%) [13, 22]. Similar data on chemotherapy use were found in a previous study of our group in patients with metastatic pancreatic cancer [10].

Despite a major increase in chemotherapy use in NR-M0 patients under 75 years in the current study, overall survival hardly improved. However, the study period mainly covers the gemcitabine era, chemotherapy use and response rates may simply be too low to show a survival improvement in all NR-M0 pancreatic cancer patients. Possibly, increasing prescription of more effective chemotherapy schemes such as FOLFIRINOX and nab-paclitaxel with gemcitabine may affect overall survival in years following the current study period. In addition, the age of chemotherapy-treated patients in our study has substantially risen from median 62 to 66 years, though still few elderly patients received chemotherapy (≥75 years: 11%). A careful selection and better support of elderly patients for chemotherapy treatment is therefore relevant and can be facilitated by the use of geriatric assessment tools [23].

Strikingly, pathological confirmation of cancer in our study was lacking in one in six NR-M0 patients who received chemotherapy. Because a misdiagnosis cannot be ruled out [24],

pathological confirmation before chemotherapy is highly recommended [25]. The absence of pathological confirmation in treated patients is worrisome and requires further attention in multidisciplinary team discussions in the Netherlands.

In recent systematic reviews of nonrandomized studies with LAPC patients only, approximately one quarter of patients could undergo resection after neoadjuvant chemo(radio)therapy [26, 27] and overall survival of patients receiving FOLFIRINOX [28] with or without resection was 24 months [26], which was comparable with survival of patients with initially resectable pancreatic cancer. In the current nationwide study, chemotherapy was combined with radiotherapy in only a minority of chemotherapy-treated NR-M0 patients [25, 29]. Re-evaluation of NR-M0 patients after several months of chemo(radio)therapy may be worthwhile to identify patients for possible resection or eligibility for other treatments directed at local tumor control. An experienced multidisciplinary team or expert panel can provide in this need.

This study has several limitations that are related to the retrospective data that were used. Firstly, due to the available notification sources, the NCR is at risk of incompleteness of pancreatic cancer in elderly patients [30]. Therefore, chemotherapy use and survival of elderly NR-M0 patients may be slightly overestimated in our study, while early mortality may be underestimated. Survival may also be slightly overestimated because some patients of the large group without histological confirmation of pancreatic cancer were incorrectly diagnosed [24]. Despite these limitations, the available unselected data of an often neglected group of pancreatic cancer patients revealed important findings about trends in everyday clinical practice. Secondly, survival trends of NR-M0 patients in the course of the study period must be interpreted with caution as a result of changing characteristics of this subgroup and possible residual confounding of unmeasured characteristics. Thirdly, although the proportion of patients with stage III disease in our study (12% of all stage I-IV in 2012-2014) was comparable with other population-based studies (7%-13%) [13, 19, 31] staging may be suboptimal in patients who were staged based on imaging only. Locally advanced and metastatic disease was found in a substantial proportion of patients who preoperatively were thought to have resectable disease [32, 33]. Furthermore, TNM staging information cannot discriminate between the currently used categories of resectable, borderline resectable, and irresectable pancreatic cancer, based on the extent of arterial and venous involvement [34]. Finally, data on comorbid conditions were available in only a subgroup of patients, and no information was available about performance status and quality of life of patients. In the future, the Dutch nationwide PAncreatic Cancer Project (PACAP) will provide more detailed information [35].

In conclusion, our study showed that the group of NR-M0 pancreatic cancer patients is heterogeneous, consisting of patients with irresectable tumors due to arterial involvement (stage III) and many patients with advanced age and (supposed) stage I-II tumors. Despite an increase in the use of chemotherapy in younger patients, overall survival of all patients hardly improved over the described time period.

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Chapter 11

Summary
General discussion

Summary

Data from the NCR one year before and one year after publication of the multidisciplinary evidence-based guideline for pancreatic and periampullary carcinoma (2011) were used for evaluation of implementation and adherence of the guideline (**Chapter 2**). Three quality indicators were selected based on relevance and their potential for improvement: (1) adjuvant chemotherapy, (2) discussion within a multidisciplinary team (MDT) meeting, and (3) maximum waiting time starting treatment of three weeks.

Generally, guideline compliance was low. The use of adjuvant chemotherapy in patients with resected pancreatic carcinoma increased from 44% in 2010 to 54% in 2012, mainly due to an increase in patients under 75 years of age receiving chemotherapy. Variation between hospital volume categories decreased over time and no differences between types of hospitals were found (university, large teaching, regional hospital). Of patients with pancreatic or periampullary carcinoma in 2012, 64% was discussed in a MDT meeting; especially elderly patients and patients not receiving tumour-directed treatment were less likely to be discussed. In addition, patients diagnosed in a regional hospital less often were discussed within a MDT compared with patients in university or teaching hospitals. In 39% of patients, potentially curative treatment (neoadjuvant treatment or surgical exploration with curative intent) was initiated within three weeks of a final MDT meeting. Patient and tumour characteristics were not associated with waiting times, but university hospitals less often started treatment within three weeks compared with large teaching and regional hospitals.

Although the administration of adjuvant chemotherapy slightly increased between 2010 and 2012, a longer study period and specific focus were thought to provide more insight in the increased use of chemotherapy and variation between providers. In **Chapter 3**, patients who underwent a pancreatoduodenectomy for pancreatic adenocarcinoma in a pancreatic center in 2008-2013 were included (n=1195). To deal with immortal time bias and reduce the possible effect of surgical complications, patients who deceased within 90 days postoperatively were excluded. The administration of adjuvant chemotherapy increased from 33% in 2008 to 52-54% in 2009-2011 and 59-61% in 2012-2013. Elderly patients and those with TNM stage I (versus II/III) were less likely to receive adjuvant chemotherapy (multivariable regression analysis). Although no difference was found between type of surgical center (university, non-university), chemotherapy use still ranged between 35% and 68% in individual centers (case-mix adjusted). Furthermore, median time to adjuvant chemotherapy was 6.6 weeks and did not differ between type of surgical center (university, non-university) or hospital of chemotherapy (surgical center, non-center). The use of adjuvant chemotherapy was associated with improved survival, but no influence was found for time-to-chemotherapy at a cut-off point of 6 weeks.

Several years before a minimum volume standard was set, voluntary centralisation of pancreatic surgery was initiated in the Leiden region (1.7 million inhabitants). In **Chapter 4**, this centralisation process was evaluated by comparing three time periods in the NCR (n=249): start volume discussion (1996-2000), quality standards introduced (2001-2005) and all pancreatic

surgery centralised (2006-2008). Following centralisation (2006-2008), the mean annual hospital volume of oncologic pancreatic resections increased from 1.7-2.0 to 23 resections, no pancreatic resections were performed outside the two centers (total nine hospitals), resection rate non-significantly increased from 14% to 18% (p=0.08) and overall survival following resection (2-year: 39% to 55%, p=0.09) significantly improved after adjustment for confounding factors (HR(2006-2008 vs 1996-2000)=0.50, 95% confidence interval 0.34-0.73). No improvement was found between the two earlier periods.

In 2011, the Dutch Society of Surgeons (i.e. NVVH) set a national minimum volume standard of 20 pancreatoduodenectomies (PD) per hospital per year in the Netherlands, but an optimal volume cut-off level was still unknown. **Chapter 5** evaluates ongoing centralisation of more than 3400 PDs for pancreatic or periampullary carcinoma in the NCR to find out whether a higher volume cut-off could further improve outcomes. Between 2005 and 2013, the number of hospitals performing PDs halved from 42 to 21, annual number of PDs per hospital increased from median 4 to 23 and the proportion of patients undergoing a PD in a hospital that performed 40 PDs or more increased from 14% to 36%. Compared to centers performing 40 PDs or more, in each lower volume category a higher postoperative 90-days mortality, decreased use of adjuvant chemotherapy and lower number of examined lymph nodes was observed. In centers performing less than 20 procedures annually, a significantly worse overall survival and conditional survival (patients alive at 90 days postoperatively) were found. These results were adjusted for changes in hospital volumes over time and other confounders.

Pancreatic cancer is primarily a disease of aged patients and quality initiatives in 2011 (guideline and volume standard) may have affected surgical care for elderly patients in the Netherlands. According to the Dutch guideline, high age alone should not be a contraindication for pancreatic surgery. Therefore, **Chapter 6** examined trends in resection rates according to age, as well as 30- and 90-days postoperative mortality and long-term survival of resected patients.

Although resection rates were lower at older age (≥75 years), during the study period 2005-2013 resection rates of patients have increased in all age groups (pancreatic carcinoma <70 years: from 15 to 25%, 70–74 years: 11 to 24%, 75–79 years: 8 to 17%, ≥80 years: 1 to 5%, all p<0.001; duodenum and ampulla of Vater carcinoma no significant increase except ≥80 years 7 to 23%, p=0.02). Among octogenarians with pancreatic or periampullary cancer, the 3-4 times increase was especially found in the most recent years.

Postoperative mortality slightly decreased over time (30-day 5.7 to 3.2%, p=0.06; 90-day 9.2 to 7.5%, p=0.21), while the age of resected patients increased from median 65 to 67 years and the proportion of octogenarians nearly doubled (3.5% to 5.5%, p=0.03). Although postoperative mortality (30-days, 90-days) was higher in all elderly age groups (≥70 years) compared with younger patients, no significant differences were found between elderly patient groups. Interestingly, long-term survival of octogenarians who survived the postoperative period (90-days) approached survival of patients younger than 70 years of age.

In addition, **Chapter 7** investigated the influence of hospital volume and ongoing centralisation on surgical care for elderly patients (≥75 years) who underwent a pancreatoduodenectomy (PD) for primary pancreatic or periampullary carcinoma in 2005-2013 in the Netherlands. Although the proportion of elderly patients did not differ between hospital volume tertiles (16, 20 and 17%, p=0.10), an increase of elderly patients over time was slightly more obvious in low hospital volumes (HV). The administration of adjuvant chemotherapy was highest in high HV, in both younger and elderly patients (p<0.001 and p=0.07 respectively). In accordance with our previous study in **Chapter 5**, the most favourable 30-day and 90-day postoperative mortality was found in high HV. In low HV, adjusted 30-day postoperative mortality of elderly patients was more than double that of younger patients (p=0.007), while differences in medium and high HV were less pronounced (p=0.10 and p=0.31, respectively). At time of 90-day postoperatively, adjusted mortality in elderly patients was significantly higher (1.8-2.5 times) within each hospital volume tertile. Although in all hospital volume tertiles elderly patients had a worse survival compared with younger patients, after adjustment for the use of adjuvant chemotherapy these differences decreased most in high HV. Combined analyses of both age groups and hospital volume tertiles (6 categories) showed that mortality of elderly patients in high HV was comparable with that of younger patients in low and medium HV, while outcomes of elderly patients in low HV were worse.

Unresectable pancreatic cancer is sometimes encountered during surgical exploration with curative intent, but population-based studies investigating this subject are scarce. In the period 2009-2013 (**Chapter 8**), the proportion of patients undergoing surgical exploration with curative intent for pancreatic carcinoma increased from 20 to 27% (p<0.001). Among 2356 patients who underwent surgical exploration in the Netherlands, the proportion of patients with tumour resection increased from 62% in 2009 to 71% in 2013 (p<0.001), mainly due to a decline in unresectable non-metastatic disease. Independent predictors for non-resectional surgery were earlier years, elderly age (≥80 years) and low hospital volumes (0–20 resections per year, vs ≥33 resections, tertiles).

In the non-resected patient group, among those with non-metastatic (M0) and metastatic (M1) disease at surgical exploration, the 30-day mortality rate was 4.7 and 10.6% (p=0.002), median survival was 7.2 and 4.4 months (p<0.001), and 1-year survival rates were 28 and 13%, respectively. Independent predictors for 30-day postoperative mortality of non-resected patients were the presence of metastatic disease and surgical treatment in low-volume hospitals, and those for poor survival were older age (≥75 years) and, among other factors, surgery in low-volume hospitals.

More than half of the patients with pancreatic adenocarcinoma have metastatic disease at time of presentation. **Chapter 9** investigates the use of chemotherapy and survival in this large group of pancreatic cancer patients. Although chemotherapy use for metastatic pancreatic cancer decreased with rising age of patients, the administration of palliative chemotherapy almost doubled between 2005-2007 and 2011-2013 in all age groups (<70 years: from 26 to 43%, 70–74 years: 14 to 25%, 75–79 years: 5 to 13%, all p<0.001, and ≥80 years: 2 to 3%, p=0.56).

Median overall survival of 9407 patients with metastatic pancreatic cancer in 2005-2013 was 9.5 weeks. As many as 26% of patients already died within 30 days after diagnosis (with rising age: 19-26-32-43%, p<0.001).

Median age of 2180 patients who received palliative chemotherapy for metastatic pancreatic cancer increased over time from 62 to 64 years. With rising age of chemotherapy-treated patients (<70, 70–74, 75–79, ≥80 years), microscopic tumour confirmation was performed less frequently (91-88-87-77%, respectively, p=0.009) and overall survival diminished (median 25-26-19-16 weeks, p=0.003). After adjustment for confounding factors, worse survival of treated patients ≥75 years persisted.

The remaining group of patients with non-resected, non-metastatic (NR-M0) pancreatic cancer comprises both patients with locally advanced pancreatic cancer (LAPC) and inoperable patients due to a poor health status. In **Chapter 10**, time trends in characteristics, treatment and survival of NR-M0 patients were investigated. The proportion of patients with NR-M0 pancreatic cancer decreased sharply between 2006 and 2014 (in consecutive 3-year periods: 38%, 33%, 28% of all patients, p-trend<0.001).

Although the age of the NR-M0 patient group (n=5964) increased in consecutive 3-year periods (≥75 years: 50-52-54%, p-trend=0.008), the administration of chemotherapy also sharply increased from 13%, 17% to 19% (p-trend<0.001). A 50% increase of chemotherapy use was found in younger patients (<75 years: from 23% to 36%, p-trend<0.001), but only 3.5% of NR-M0 patients over age 75 years were treated with chemotherapy (2.8% to 4.3%, p-trend=0.053). Furthermore, 5.4% of patients (also) received local therapy (5.5-4.2-6.7%, respectively, p=0.121). Overall, 33% of NR-M0 pancreatic cancer patients died within 90 days after diagnosis (<75 years: 24%, ≥75 years: 41%, p<0.001).

Of 967 patients with NR-M0 pancreatic cancer who received chemotherapy, 17% had no histological confirmation of cancer and 67% of patients had Stage III disease (T4M0, diagnosis in 2012-2014). Despite an increased age of treated patients from median 62 to 66 years, overall survival of chemotherapy-treated patients did not differ significantly between age groups (<75 years: 10.6 and ≥75 years: 9.2 months, p=0.207) or time periods (10.5-9.6-10.8 months, p=0.177).

General discussion

The general objective of this thesis was to evaluate quality of care for patients diagnosed with pancreatic (or periampullary) carcinoma in the Netherlands, with focus on quality of care for elderly patients. In part I (**Chapters 2-5**) national quality assessment and quality improvement of pancreatic cancer care was studied, by means of evaluation of guideline adherence and centralisation of pancreatic cancer surgery. To evaluate quality of care for elderly patients more specifically (part II, **Chapters 6-10**), multiple elderly age groups were distinguished above 70 years of age. Nationwide trends in surgical and systemic treatment were studied, as well as short-term mortality and long-term survival . All studies were performed with population-based data from the NCR.

In this chapter, we discuss the main findings of the thesis and place them in the broader context of quality of care, quality improvement and future perspectives.

In the past decade in the Netherlands, the number of patients with newly diagnosed pancreatic cancer has increased by 35% from circa 1,700 in 2005 to 2,400 in 2017 [1]. At least half of this growing patient population is aged 70 years or older at time of diagnosis and about one-fifth of patients is over 80 years of age. Unfortunately, elderly patients are underrepresented in the available studies on which the evidence in guidelines is based [2]. Population-based studies provide valuable information on everyday clinical practice [3].

In the Netherlands, compared with younger patients…
…elderly patients were less likely to be discussed in a Multidisciplinary Team (MDT) meeting (**Chapter 2**).
…elderly patients did not exhibit a longer waiting time between final MDT and start of treatment (**Chapter 2**).
…elderly patients were less likely to undergo a resection for pancreatic or periampullary cancer (**Chapter 6**).
…elderly patients with pancreatic cancer were less likely to undergo a surgical exploration as well as resection at surgical exploration (**Chapter 8**).
…elderly patients with pancreatic cancer who did not undergo resection at surgical exploration had a worse overall survival (**Chapter 8**).
…elderly patients who underwent resection for pancreatic or periampullary cancer had an increased postoperative mortality and worse overall survival (**Chapter 6**). However, once octogenarians survived the postoperative period, they showed survival close to that of younger patients.
…elderly patients who underwent resection for pancreatic or periampullary cancer exhibited an increased postoperative mortality and worse overall survival in high, medium and low hospital volume categories, and the most unfavourable outcomes were found in elderly patients undergoing resection in low volume hospitals (**Chapter 7**).
…elderly patients who underwent resection for pancreatic cancer less likely received adjuvant chemotherapy (**Chapter 2 and 3**).

…elderly patients with pancreatic cancer less likely received palliative chemotherapy for metastatic and non-resected non-metastatic pancreatic cancer (**Chapter 9 and 10**).
…elderly patients who received palliative chemotherapy for metastatic pancreatic cancer had a worse overall survival (**Chapter 9**).

Pancreatic cancer care in elderly patients

No single age cut-off
With rising age of patients, the use of surgical and systemic treatments in accordance with the evidence-based guideline decreased. The process of aging is characterised by a loss of functional reserve of several organ systems, increased prevalence of chronic diseases and enhanced susceptibility to stress [4]. A different pace of this process in individuals results in a large heterogeneity within the elderly patient group. In many studies of pancreatic cancer treatment in elderly patients a single age cut-off point was used at age 70, 75 or 80 years. In this thesis, the use of multiple elderly age groups showed gradual patterns and important differences between consecutive elderly age groups.

Elderly patients and standard of care
The Dutch guideline on pancreatic and periampullary cancer (2011) [5] explicitly stated that high age even above 80 by itself should not be a contraindication for pancreatic surgery. A previous report already showed that resection rates in the Netherlands had increased until 2009, mainly because more patients with extensive pancreatic head tumours underwent resection (T3) [6], which was also confirmed at a regional level following centralisation (**Chapter 4**). This thesis showed that, especially from 2011 onwards, resection rates increased in octogenarians with pancreatic or periampullary cancer (**Chapter 6**). As a result, age of resected patients has increased (median age 65 to 67 years; octogenarians 3.5% to 5.5%). Still, the proportion of octogenarians among resected patients was relatively low compared to other population-based studies (5.7-12.4%) [7-9]. According to a recent population-based study using age-standardised (cancer registry) data from 7 countries, increased resection rates in the Netherlands (**Chapter 6**) have now reached a medium level compared with other European countries and the USA (16% versus 13-21%) [10].

In several observational studies in the USA, underutilisation of surgical treatment was suggested [11, 12]. This thesis found that many non-resected patients died very soon after their pancreatic cancer diagnosis, and thus were no surgical candidates (**Chapter 10**). Especially elderly patients were at increased risk of dying soon (NR-M0 ≥75 years: mortality 1- and 3-months of diagnosis: 18% and 41%). In addition, up to one-third of pancreatic cancer patients who were deemed resectable ultimately had unresectable disease at time of surgical exploration (**Chapter 8**), which was in line with a previous Italian study [13]. We also found that elderly patients were at increased risk of not undergoing resection during exploration. More information is needed about the health status and surgical risks of the remaining non-surgically treated patients with supposed resectable disease.

For patients with irresectable or metastatic pancreatic adenocarcinoma, the Dutch guideline (2011) recommended systemic treatment with gemcitabine [5]. A preference for gemcitabine was based on its larger clinical benefit and better toxicity profile compared with 5-fluorouracil (5-FU) [14, 15]. This thesis showed that the administration of palliative chemotherapy in the Netherlands was far less likely in elderly patients. In octogenarians, chemotherapy use was almost none and hardly increased over time.

Treatment and outcome patterns
While the increased resection rate of patients aged 70-74 years in the Netherlands nowadays equals that of patients younger than 70 years of age (**Chapter 6**), this pattern was not found for palliative chemotherapy (**Chapter 9 and 10**). However, a higher proportion of treated elderly patients balanced with worse treatment outcomes. Postoperative mortality and overall survival of resected patients aged 70-74 years were worse compared with those of younger resected patients. Although the use of palliative chemotherapy was less likely in patients aged 70-74 years compared with younger patients, survival of chemotherapy-treated patients aged 70-74 years did not differ from that of younger patients who received palliative chemotherapy.

Strikingly, despite a high short-term mortality, the increasing numbers of resected octogenarians in this thesis showed a long-term survival approaching that of patients under 70 years (**Chapter 6**). In the sporadic chemotherapy-treated octogenarians, however, therapeutic margins seem small and complications or early discontinuation may have added to a worse (median) survival compared with younger patients (**Chapter 9**). Similar to surgically treated patients, a differentiation between short-term and long-term outcomes after chemotherapy treatment may provide valuable insight. Furthermore, it is unknown in which patient groups and at what pace the use of FOLFIRINOX and gemcitabine with nab-paclitaxel took place in clinical practice in the Netherlands. A recent study in the province of Ontario, Canada found that the use of FOLFIRINOX increased from 41% of chemotherapy-treated patients with metastatic pancreatic cancer in 2012 to 56% in 2014 [16]. It seems plausible that in the Netherlands from 2011 onward an increasing number of younger patients with metastatic disease have received the new schemes, while elderly patients continue to receive gemcitabine monotherapy. Consequently, the survival gap between younger and elderly patients receiving chemotherapy for metastatic disease may have widened.

Assessing functional age
For cancer treatment planning in elderly patients, 'functional age' rather than 'chronological age' is important [17, 18]. Geriatric Assessment (GA) is a useful tool in the management and follow-up of elderly cancer patients. As recommended by the Society of Geriatric Oncology (SIOG) in 2014, the following domains should be evaluated: comorbidity and functional status, cognition and mental health status, fatigue, social status and support, nutrition, and presence of geriatric syndromes [19]. This assessment can be complemented with biological markers [20]. Recently, the American College of Surgeons and the American Geriatrics Society developed best practice guidelines for preoperative GA of the growing numbers of elderly surgical patients [21]. In addition, the American Society of Clinical Oncology (ASCO) Guidelines for Geriatric

Oncology were published for assessment and management of vulnerable older patients receiving chemotherapy [22].

Geriatric Assessment frequently reveals deficits in elderly patients that are not routinely captured in a standard examination, which can help to improve selection of elderly patients for cancer treatments[19, 21]. It was suggested that for example, octogenarians who are too frail to undergo pancreatic surgery can be offered SBRT to attain local tumour control ('plan B') [23]. During the study period in this thesis, the Dutch guidelines on pancreatic cancer contained no specific recommendations that were applicable to medium-healthy or frail elderly patients (no 'plan B'). As of 2012, the American National Comprehensive Cancer Network (NCCN) and the European Society for Medical and Digestive Oncology (ESMO-ESDO) Clinical Practice Guidelines for pancreatic adenocarcinoma distinguished between good and poor performance status of patients with regard of recommendations on the type of palliative chemotherapy [24, 25].

Quality of pancreatic cancer care

Guideline dynamics: early and late adaptors

Similar to evaluation of compliance with the NCCN guidelines [11], overall compliance with the Dutch guideline on pancreatic and periampullary cancer seemed relatively poor (**Chapter 2**). Between 2010 and 2012 (before and after publication of the Dutch guideline), only a small increase of the administration of adjuvant chemotherapy was found in the Netherlands. However, the largest increase was seen from 2008 to 2009 (33% to 52%, patients alive 90-days postoperatively) (**Chapter 3**). This increase coincided with a positive advice of the Commission BOM [26] in November 2008 on adjuvant treatment with gemcitabine. In the same study in **Chapter 3**, a second (smaller) increase indeed was observed after publication of the Dutch guideline in 2011 (52% in 2011 to 59% in 2012). Furthermore, the large variation of adjuvant chemotherapy treatment that was found between hospitals in **Chapter 3** (range 35-68%) may have decreased over time. Contrary to 2010, in 2012 no significant variation was found between health care providers (type and volume of hospitals, cancer regions) (**Chapter 2**) [27]. A decreasing variation between health care providers indicates that also 'late' adaptors are changing their clinical practice.

The publication of landmark studies, financial reimbursement and the summarising of available evidence in guideline recommendations seem important moments to reach or convince health care providers. In the past decade in the Netherlands, the proportion of patients with metastatic pancreatic cancer receiving chemotherapy more than doubled from 13% to 30% (**Chapter 9**). As shown by Bernards et al in a study in the Eindhoven region, the administration of palliative chemotherapy started to increase some ten years before publication of the studies on FOLFIRINOX (2011) and nab-Paclitaxel and gemcitabine (2013) [28]. In 2001, however, a first consensus-based Dutch national guideline for pancreatic cancer was published [29]; palliative gemcitabine 'could be considered' for irresectable pancreatic cancer patients, referring to the study by Burris et al. (1997) [14]. It seems plausible that this study and the first Dutch guideline thereafter have stimulated the application of palliative chemotherapy for pancreatic cancer in

the Netherlands [28]. Despite a major increase, chemotherapy use in unresected patients in the Netherlands in this thesis still seemed relatively low compared with that in population-based studies from the USA and France covering the same time period (histologically confirmed stage IV or III-IV: 30-34% versus 42-63% respectively) [30-33].

Careful and accurate staging discussed in a multidisciplinary team that incorporates expert knowledge is of utmost importance to advise on optimal cancer treatment for patients with pancreatic cancer. In 2012, more than one-third of all patients diagnosed with pancreatic or periampullary cancer in the Netherlands were not discussed in a multidisciplinary team at all, especially elderly patients not receiving cancer treatment (**Chapter 2**).

In a qualitative study in two German university hospitals, individual oncologists recommended rather different treatment strategies for the same patient with LAPC [34], mainly based on an either optimistic or pessimistic interpretation of the patients' medium age and health status. This variation in interpretation between clinicians can be reduced by the discussion and weighing of patient and tumour characteristics in a multidisciplinary team. For example, multidisciplinary team discussions altered about one-third of 252 pre-meeting individual treatment proposals for upper gastrointestinal cancer [35]. However, being discussed in a multidisciplinary team that lacks expert knowledge may still result in under- or overtreatment of patients. After re-evaluation in a specialised unit less than half of 116 patients referred for suspected unresectable disease were ultimately diagnosed with LAPC [36].

Volume dynamics: bottom-up and top-down
After a decade of pleading for centralisation of pancreatic surgery [37, 38], voluntary centralisation initiatives (bottom-up) became successful in a few regions in the Netherlands (**Chapter 4**) [39]. Although the achieved improvements were important for participants, these 'best practices' not necessarily stimulate bottom-up centralisation agreements elsewhere.

To accelerate the centralisation process from 2011 onwards, a minimum annual volume of 20 pancreatoduodenectomies (PDs) became mandatory [40]. This thesis showed that the number of hospitals performing PDs for pancreatic or periampullary cancer halved from 42 in 2005 until 21 in 2013 (**Chapter 5**). **Chapter 8**, however, showed that in 2013 31 hospitals have performed surgical explorations for pancreatic cancer, thus including distal resections and surgical explorations without resection. This discrepancy in the number of hospitals in 2013 is interesting and requires further investigation. Possibly the discrepancy can be explained by incidental findings at time of non-pancreatic or non-cancer surgery or by distal pancreatectomies performed in hospitals not being pancreatic centers. Strictly taken the volume standard for PD does not cover distal pancreatectomies, though in several cancer networks these sporadic procedures were included in mutual agreements about centralisation.

This thesis further showed that higher age and lower hospital volumes were both strong independent predictors for non-resection surgery and poor outcomes, with elderly patients in low hospital volumes having the lowest likelihood of undergoing tumour resection at time

of surgical exploration and exhibiting the worst outcomes after surgery (resection and non-resection) (**Chapter 7 and 8**). Many elderly patients must be regarded high-risk surgical patients who benefit most from pancreatic surgery in high-volume hospitals. Following the volume standard in 2011, however, the largest relative increase of surgically treated elderly patients was observed in low-volume hospitals (**Chapter 7**).

Further centralisation of high-risk patients in specialized high-volume centers or specific quality standards for providing surgical treatment to high-risk patient categories may be necessary to improve their operative risks [18]. Which preoperative patient and tumour characteristics of elderly patients particularly contribute to a high-risk profile for pancreatic surgery (e.g. comorbidities, performance status, nutritional status, tumour symptoms, tumour extent, vessel involvement) should yet be determined [21, 41].

Centralisation of pancreatic surgery may also have undesirable side effects. A previous study suggested that the probability of undergoing a resection was higher in pancreatic cancer patients diagnosed in pancreatic centers (19 hospitals in 2013) in the Netherlands, though overall survival did not clearly differ in the investigated study period (2005-2013) [42]. Possibly the study was performed 'too early', since studies on upper gastrointestinal cancer surgery found an association between hospital of diagnosis, curative intent treatment and survival particularly in the time period following introduction of a volume standard [43, 44].

Pancreatic cancer care in pancreatic centers is rapidly evolving due to a high level of study participation [45]. In non-centers, the knowledge of available studies and newest insights can easily lag behind on pancreatic centers. However, large variation of treatment and treatment outcomes may also exist between pancreatic centers, as was found in **Chapter 3** with regard to adjuvant chemotherapy.

Previous studies in the Netherlands found that the administration of palliative chemotherapy for metastatic pancreatic cancer differed between hospitals and regions [28, 46], though without significant survival disparities. However, high hospital volumes of systemic treatment seem associated with better overall survival [47]. These studies were performed in the 'gemcitabine era' until 2011. Thus far, it is unknown whether differences in the type of prescribed chemotherapy contribute to survival disparities between healthcare providers. For example, clinicians in hospitals with low volumes of pancreatic cancer diagnoses may rely on guideline recommendations ('late adaptors'), while those in pancreatic centers already may change their practice at time of publication of landmark studies ('early adaptors'). Possibly, the uptake of new chemotherapy combinations for metastatic pancreatic cancer follows this pattern (FOLFIRINOX, nab-paclitaxel/gemcitabine, [48, 49]).

Implications for clinical practice

Decision-making: multidisciplinary collaboration networks
Pancreatic centers participating in the DPCG possibly can play a larger role in a fast dissemination of evidence to all hospitals in the Netherlands. Regional multidisciplinary (expert) team meetings and expert panels have the potential of improving patient selection for pancreatic cancer treatment. Given current developments in resectability criteria, systemic treatment and neoadjuvant systemic approach for pancreatic cancer patients [18, 50], multidisciplinary expertise in pancreatic cancer care instead of surgical experience alone is of utmost importance. Regional collaboration between pancreatic centers and non-centers in multidisciplinary teams may be supplemented with a stepped or graduated system (service levels) to optimise the patient flow and workload between referring hospitals and pancreatic centers, as well as between pancreatic surgical centers and (few) expert pancreatic centers.

Decision-making: elderly patients' perspective
Optimal staging of the tumor and subsequent treatment advise must be combined with objective examination of the (elderly) patients' health status. Currently, the weighing of health constraints of medium-healthy patients and the related likelihood of complications of treatment are mainly based on clinician's experiences and values. Geriatric Assessment and prediction models (www.evidencio.com) may be important aids for risk profiling of patients in everyday clinical decision-making and can also facilitate proper shared decision-making.

Shared decision-making (SDM) is increasingly valued by patients and clinicians, based on patient autonomy and informed consent. Patients are stimulated to ask their doctor three simple questions [51] (in Dutch: http://3goedevragen.nl/): what are available treatment options, pros and cons of each option, and what does that mean for my situation. However, SDM may be problematic especially in elderly patients with pancreatic cancer. Firstly, there is a tremendous lack of evidence about outcomes of treatment options according to risk profiles of elderly patients. Secondly, in life-threatening situations such as a pancreatic cancer diagnosis, SDM is more difficult. Thirdly, elderly patients are less likely to take an active role in interactions with their doctor [52]. When a patient takes a passive role, however, treatment decisions may represent doctors' values rather than patients' values. Last but not least, elderly persons facing a cancer diagnosis weight cancer treatment options and treatment goals differently from younger patients. With rising age, quality of life and maintaining functional independence become much more important than overall survival [53, 54]. Preferences of elderly patients may vary widely, depending on their physical, psychological and social situation. Therefore, the potential benefits of cancer treatment in terms of prolongation of disease-free or progression-free survival and overall survival of elderly patients must be well balanced against time spent with symptoms and time spent on recovering from (complications of) treatment. However, even well-informed healthy elderly patients may actively choose to withhold from pancreatic cancer treatment.

Strengths and limitations: pancreatic cancer care and the NCR

In this thesis, the nationwide population-based database of the Netherlands Cancer Registry was used to investigate guideline-based treatments and outcomes. These observational data have its strengths and weaknesses.

Data quality: a 'soft denominator'
Compared with other cancer types, pancreatic cancer data is at increased risk of incompleteness and poor quality. Firstly, microscopic verification of pancreatic cancer is lacking in a relatively high proportion of patients (about one third of patients in the NCR, **Chapter 1**) [46, 55-57]. However, wide variation was found between Cancer Registries (EUROCARE: range <50% and >95% verified) [58]. Differences between registries in sources and procedures of notification hamper comparisons of treatment use and survival between countries [58-63]. Fest et al suggested that available notification sources of the NCR (**Chapter 1**) were suboptimal [64]. Unregistered patients were likely to be older, did not receive cancer treatment and died soon after diagnosis [59, 64]. Secondly, re-evaluation of imaging or revision of pathology material may reveal a non-malignant process or a non-adenocarcinoma malignancy [65, 66]. In addition, due to the proximity of other structures around the head of the pancreas, identifying the correct tumour site of origin can be notoriously difficult [67, 68]. Although treatment use and survival rates of elderly patients in the Netherlands may be slightly overestimated, comparison of data from the NCR and Statistics Netherlands (SN, Mortality : Incidence ratio decreased from 1.15 in 2005 to 1.05 in 2015 [62]) indicate that time trends in cancer treatment in this thesis must be considered reliable, as well as results about treated patient groups.

Methodological issues: stage migration, immortal time and treatment selection bias
Within patient groups specified in this thesis (resected, metastatic, NR-M0 pancreatic cancer), stage migration effects may have influenced the interpretation of survival trends over time (e.g. M1: 50% in 2005 to 57% in 2015). Therefore, time trends of survival within each patient group may be misleading. However, median overall survival of the total patient population of pancreatic cancer patients has slightly increased from 3.3 months in 2005 to 3.9 months in 2015 and 1-year overall survival increased from 15% to 21% (**Figure 1**). This improvement is likely a result of the increased use and quality of cancer treatments in the past decade, in particular surgical treatment. Since only one third of all patients received cancer treatment in this time period (from 21% in 2005 to 42% in 2015), for example an 80th or 90th percentile may provide additional insight in survival trends of pancreatic cancer patients [69].

Survivor treatment bias (immortal time bias) must be considered in survival comparisons between treated and untreated patients [70], especially in patient groups with a poor prognosis [71]. Treated patients must survive a certain period of time to be able to start treatment. In this thesis, conditional survival analysis was used to reduce immortal time bias in comparisons between chemotherapy-treated and untreated patients (**Chapter 3 and 9**). A landmark at 90 days after surgery was also used for unravelling long-term survival and short-term mortality (**Chapter 5 and 6**).

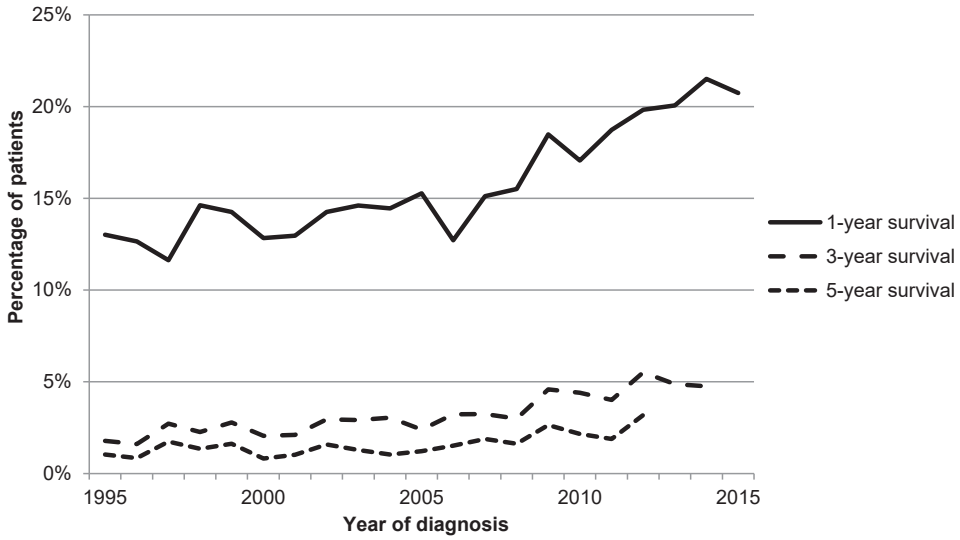

Figure 1. Overall 1-3-5-year survival of all patients diagnosed with pancreatic adenocarcinoma between 1995 and 2015.

Treatment selection bias is inevitable in observational non-randomised studies. Characteristics of treated patients frequently differ in a systematically and often unmeasurable way from those of untreated patients. These differences often influence outcomes such as overall survival. Conditional survival analyses only slightly reduce treatment selection bias. In many situations, rigorous multivariable adjustment, and even propensity score methods, still cannot remove overt and hidden biases [72], while using an instrumental variable is not always possible or appropriate. Therefore, in this thesis the results from comparisons between treated and untreated patients must be interpreted with some caution (**Chapter 3 and 9**).

Strength of the NCR: the population perspective

Despite the growing population of elderly cancer patients, older patients are underrepresented in clinical trials and the few elderly patients who participate in clinical trials are not representative for the total elderly patient population [2, 3, 73]. Population-based studies provide valuable information on everyday clinical practice [3], such as dissemination and effectiveness of (new) therapies. For example, a small increase in overall (or progression-free) survival observed in a large clinical trial may disappear when a new treatment is applied in routine practice to older or less healthy patients who possibly experience greater toxicity, more dose reductions or early discontinuation of treatment. In this thesis, compared with younger patients, elderly patients receiving systemic treatment experienced a worse overall survival (**Chapter 9**). Furthermore, improvement within a group of treated patients may be biased when a more selected patient population actually received the treatment. For example, for several gastrointestinal cancers in the Netherlands, reported improvement of postoperative mortality coincided with a decreased resection rate in the past decades in the NCR [74].

Using the NCR: a living database
In the course of time, the NCR contains an increasing number of registered details on multidisciplinary cancer treatment and outcomes, as well as on the patient journey through multiple hospitals. The data are collected uniformly in all hospitals by independent and trained registrars of the Netherlands Comprehensive Cancer Organisation (IKNL). The quality of data in the NCR is continuously improved by quality checks and feedback on used data.

Increasing collaboration between the Dutch Pancreatic Cancer Group (DPCG) and the Netherlands Comprehensive Cancer Organisation (IKNL) resulted in the launch of an 'Alvleesklierkankerregister' (2016). Several details on the diagnostic process, systemic treatment and oncological outcomes of patients with pancreatic cancer in the NCR become available for future use. The NCR is also part of the Dutch Pancreatic Cancer Project (PACAP) [75], together with the Dutch Pancreas Biobank ('Parelsnoer'), the Dutch Pancreatic Cancer Audit (DPCA) and Patient Reported Outcome Measurements (PROMs). In addition, new applications make use of the NCR, such as NKR-Online, Oncoguide and Oncolinq.

Concluding remarks

In this era of a growing aged population and increasing numbers of elderly patients with pancreatic cancer, receiving more cancer treatments, objective information is needed about their short- and long-term benefits and risks. Studies collected in this thesis showed that with rising age, patients were less likely to receive guideline-based cancer treatment and are at risk of worse outcome after treatment. However, patients within elderly age groups may differ considerably from each other with respect to their 'functional age' or 'risk profile' for optimal cancer treatment. Patients' demands and the likelihood of attaining functional independence (again) must be weighed careful against benefits and risks of cancer treatment.

Although healthy elderly patients can safely receive standard of care according to the Dutch guidelines, optimal cancer treatment for frail elderly patients and the 'medium' healthy group of patients is largely unknown. An update of the Dutch guideline on pancreatic and periampullary cancer (2011) is expected in 2018. Guidelines should comprise a 'plan B' (best treatment given certain circumstances). A 'plan B' is needed for less healthy elderly patients who want to be treated and who currently are not offered cancer treatment. Or who are at increased risk of fatal complications from optimal treatment.

Older age and low hospital volume were strong predictors of unfavourable treatment process and outcomes. Both age and hospital volume are proxy measures and thereby only simple representatives of an underlying complexity of (supposed) characteristics. In this thesis, we found that surgical risks of elderly patients were lower in high-volume hospitals. Development of non-surgical local treatments and less toxic chemotherapy schemes are necessary for tailor-made treatment of less healthy ('frail') elderly patients.

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Appendices

Nederlandse samenvatting

Inleiding

De alvleesklier (of pancreas) is een langwerpig orgaan van ongeveer 15 cm in het retroperitoneum achter de maag. De endocriene functie bestaat o.a. uit de aanmaak van insuline dat het bloedsuikergehalte in het bloed reguleert en de exocriene functie betreft de aanmaak en het transport naar de twaalfvingerige darm (of duodenum) van enzymen voor de vertering van voedsel.

In Nederland wordt jaarlijks zo'n 2400 keer de diagnose alvleesklierkanker geregistreerd. Daarmee is dit een minder vaak voorkomende maar zeker niet een zeldzame type kanker. Vaak wordt met de algemene term alvleesklierkanker (pancreascarcinoom) het (ductaal) adenocarcinoom bedoeld, de meest voorkomende (95%) en ook de agressiefste vorm. Vrijwel iedereen die de diagnose pancreascarcinoom krijgt, overlijdt uiteindelijk aan deze kanker. In vergelijking met andere kankers is de prognose extreem slecht, de helft overlijdt binnen enkele maanden en 5 jaar na diagnose is nog slechts zo'n 6% van alle patiënten in leven.

Pancreascarcinoom komt vooral voor op oudere leeftijd; minstens de helft van de patiënten is ouder dan 70 jaar. Roken is een belangrijke risicofactor voor het ontstaan van deze kanker. Kenmerkend voor pancreascarcinoom is dat deze vaak lange tijd geen of slechts vage klachten geeft. Met behulp van CT-scan of MRI wordt beoordeeld of een eenmaal ontdekt pancreascarcinoom 'resectabel' (verwijderbaar met operatie) is, d.w.z. er is geen of hooguit beperkte ingroei in de grote bloedvaten direct achter de pancreas en er zijn geen uitzaaiingen zichtbaar (bijv. in lever of buikvlies). Bij hooguit 1 op de 5 patiënten met pancreascarcinoom is dit het geval.

Alvleesklierkankerchirurgie is complexe chirurgie. Hoewel er in recenter jaren minder patiënten overlijden na of door een operatie, is het risico op complicaties nog steeds hoog. Afhankelijk van de tumorlocatie wordt gekozen voor - de meest voorkomende - pancreatoduodenectomie (Whipple of pylorus-sparende PD) waarbij pancreas, duodenum, papil van Vater, galblaas en al dan niet een deel van de maag worden verwijderd, of voor een pancreasstaartresectie (inclusief de milt). Soms blijkt tijdens de operatie pas dat de kanker niet of niet geheel verwijderd kan worden of dat er toch uitzaaiingen zijn.

Patiënten waarbij geen radicale resectie van het pancreascarcinoom kan plaatsvinden, komen - na weefselonderzoek en bevestiging van de diagnose – in aanmerking voor palliatieve chemotherapie. Jarenlang werd op dit vlak nauwelijks vooruitgang geboekt. Recent lieten echter een tweetal combinatieschema's, waarover is gepubliceerd in 2011 (FOLFIRINOX) en 2013 (nab-paclitaxel & gemcitabine), een substantieel overlevingsvoordeel zien ten opzichte van gemcitabine alleen. Wel bleken deze schema's vaker en ernstiger bijwerkingen te geven. Ook na resectie van het pancreascarcinoom bestaat volgens de richtlijn (2011) een indicatie voor aanvullende chemotherapie (adjuvant). Op dit moment wordt onderzocht of er meerwaarde is van chemotherapie of chemoradiotherapie voorafgaand aan een operatie (neoadjuvant).

Doel van dit proefschrift

Mensen worden ouder als gevolg van betere gezondheidszorg en leefomstandigheden. Bovendien bereikt de naoorlogse babyboom generatie inmiddels een oudere leeftijd. Deze dubbele vergrijzing van de Nederlandse bevolking, tezamen met het feit dat alvleesklierkanker voornamelijk een ziekte is op oudere leeftijd, zal in komende decennia een forse toename opleveren van aantallen oudere patiënten met alvleesklierkanker. Hoewel epidemiologische informatie over incidentie en overleving van de totale populatie publiek toegankelijk is op de website van de NKR (www.cijfersoverkanker.nl), is er weinig bekend over behandeling en behandeluitkomsten van specifieke groepen van alvleesklierkanker patiënten in Nederland. In 2011 is een evidence-based richtlijn pancreas- en periampullair carcinoom gepubliceerd en in datzelfde jaar werd ook een minimum volumenorm van 20 pancreatoduodenectomieën (PD) per ziekenhuis ingevoerd. Deze kwaliteitsinitiatieven kunnen bij oudere patiënten anders hebben uitgepakt dan bij jongere patiënten.

Doel
Dit proefschrift evalueert kwaliteit van zorg voor patiënten gediagnostiseerd met pancreas (of periampullair) carcinoom in Nederland, en met name of oudere patiënten een vergelijkbare kwaliteit van zorg ontvingen als jongere patiënten.

Alle studies in dit proefschrift zijn uitgevoerd met behulp van gegevens in de Nederlandse Kankerregistratie (NKR) over pancreas (en periampullair) carcinoom in het afgelopen decennium. De NKR bevat gegevens over nieuw gediagnosticeerde kankers in Nederland vanaf 1989. Signalering van nieuwe diagnoses op basis van onderzocht lichaamsmateriaal via PALGA wordt aangevuld met signalering van ziekenhuisontslagdiagnoses (LMR, vanaf 2014: LBZ) via DHD en – indien nodig - DBC's in individuele ziekenhuizen. Bij een derde van de geregistreerde alvleesklierkankerdiagnoses in de NKR heeft namelijk geen weefselonderzoek plaatsgevonden (bij darmkanker is dit minder dan 3%).

Belangrijkste bevindingen

In deel I lag de nadruk op landelijke kwaliteitsevaluatie en kwaliteitsverbetering, met name het volgen van aanbevelingen in de richtlijn (2011; **Hoofdstuk 2-3**) en het centralisatieproces van pancreaschirurgie (**Hoofdstuk 4-5**).

Ten behoeve van een evaluatie van het gebruik van de richtlijn voor pancreas- en periampullaire carcinomen (2011) zijn in **Hoofdstuk 2** gegevens uit de NKR over één jaar voor en één jaar na publicatie van de richtlijn geselecteerd. De evaluatiecommissie koos drie kwaliteitsindicatoren uit de richtlijn: (1) adjuvante chemotherapie, (2) bespreking in een multidisciplinair overleg (MDO), en (3) wachttijd van MDO tot start van behandeling met curatieve intentie van maximaal 3 weken.

Over het algemeen werd de richtlijn slechts beperkt gevolgd. Het gebruik van adjuvante chemotherapie na resectie van het pancreascarcinoom nam toe van 44% in 2010 tot 54% in 2012, met name bij patiënten jonger dan 75 jaar. Variatie tussen ziekenhuisvolumes nam af in de tijd en er werden geen significante verschillen gezien tussen type ziekenhuizen (UMC, STZ, algemeen). Van patiënten met een pancreas- of periampullair carcinoom in 2012, bleek 64% besproken in een MDO; met name oudere patiënten en patiënten zonder tumorgerichte behandeling waren minder vaak besproken. Bovendien waren patiënten in algemene ziekenhuizen minder vaak besproken dan patiënten gediagnosticeerd in UMCs of STZ-ziekenhuizen. Van de patiënten die een op curatie gerichte behandeling kregen (neoadjuvante behandeling of chirurgische exploratie), was 39% binnen 3 weken na het (laatste) MDO met deze behandeling gestart. Patiënt- en tumorkenmerken bleken niet gerelateerd aan de wachttijd, maar UMCs waren minder vaak binnen 3 weken gestart met behandelen dan STZ of algemene ziekenhuizen.

Hoewel het gebruik van adjuvante chemotherapie licht steeg tussen 2010 en 2012, kan een langere studieperiode extra inzicht verschaffen in het patroon van toename en in variatie tussen ziekenhuizen. In **Hoofdstuk 3** zijn alle 1195 patiënten geselecteerd die 90 dagen na een PD in een pancreascentrum vanwege een adenocarcinoom van de pancreas nog in leven waren. Het gebruik van adjuvante chemotherapie nam toe van 33% in 2008 naar 52-54% in 2009-2011 en dan tot 59-61% in 2012-2013. Hoewel geen verschil werd gevonden tussen UMCs en niet-UMCs, varieerde het chemotherapie gebruik tussen individuele centra met een factor twee (35-68%, gecorrigeerd voor patiënt- en tumorkenmerken). Verder verschilde de tijd tot adjuvante chemotherapie (mediaan 6,6 weken) niet tussen pancreascentra (UMC of niet-UMC) of tussen ziekenhuizen van chemotherapie (pancreascentrum of niet-centrum). Het gebruik van adjuvante chemotherapie was geassocieerd met een betere overleving.

Enige jaren voordat een landelijke volumenorm werd ingevoerd, was in de Leiden regio (1,7 miljoen inwoners) een vrijwillige centralisatie van pancreasoperaties afgesproken. In **Hoofdstuk 4** is dit centralisatieproces geëvalueerd door 3 tijdsperiodes te vergelijken in de NKR (n=249): start van de volume discussie (1996-2000), introductie van kwaliteitsafspraken (2001-2005) en centralisatie van alle alvleesklierkankeroperaties in 2 ziekenhuizen (2006-2008). Na centralisatie vertienvoudigde het gemiddelde resectievolume per operatieziekenhuis, waren er geen operaties buiten de 2 centra uitgevoerd, nam het resectiepercentage toe en verbeterde de 2-jaars overleving na resectie. Er was geen verbetering zichtbaar tussen de eerste 2 periodes.

In 2011 voerde de Nederlandse Vereniging voor Heelkunde een minimum volumenorm in van 20 pancreatoduodenectomieën (PD) per ziekenhuis per jaar in Nederland, maar een optimaal volume afkappunt is nog onbekend. **Hoofdstuk 5** evalueert de voortgaande centralisatie van meer dan 3400 PDs voor pancreas- of periampullair carcinoom in de NKR om te kijken of een hoger volume afkappunt (≥40 per jaar) de uitkomsten kon verbeteren. Tussen 2005 en 2013 halveerde het aantal ziekenhuizen dat PDs uitvoerde van 42 naar 21, nam het aantal PDs per ziekenhuis per jaar toe van (mediaan) 4 naar 23 en het percentage patiënten dat een PD onderging in een ziekenhuis met minstens 40 PDs per jaar ging van 14% naar 36%. In vergelijking met ziekenhuizen die 40 of meer PDs per jaar uitvoerden, werd in alle lagere volumecategorieën

een hogere 90-dagen mortaliteit, een lager gebruik van adjuvante chemotherapie en een lager aantal onderzochte lymfklieren gezien. In centra met jaarlijks minder dan 20 operaties werd tevens een significant slechtere overleving op de langere termijn gezien.

In deel II lag de focus sterker op kwaliteit van zorg voor oudere patiënten (**Hoofdstuk 6-10**); waar mogelijk zijn meerdere leeftijdsgroepen boven 70 jaar onderscheiden om een leeftijdsgradiënt te kunnen bestuderen (**Hoofdstuk 6, 8-9**).

Volgens de Nederlandse richtlijn (2011) mag een oudere leeftijd op zichzelf niet een contra-indicatie zijn voor pancreaschirurgie. Daarom onderzoekt **Hoofdstuk 6** trends in resectiepercentages binnen 4 leeftijdscategorieën (<70, 70-74, 75-79, ≥80 jaar) in de periode 2005-2013, evenals 30- en 90-dagen postoperatieve sterfte en lange-termijn overleving van gereseceerde patiënten.

Hoewel resectiepercentages bij 75-plussers met pancreascarcinoom lager waren, was in alle 4 leeftijdsgroepen sprake van een duidelijke toename gedurende de studieperiode. Bij patiënten met een duodenum- of papil van Vater carcinoom was alleen bij 80-plussers een duidelijke toename zichtbaar. Verder vond de toename bij 80-plussers vooral plaats in de meest recente jaren van de studieperiode (2011-2013).

De postoperatieve sterfte daalde lichtjes over de tijd, terwijl de leeftijd van gereseceerde patiënten toenam (mediaan 65 naar 67 jaar) en het percentage 80-plussers bijna verdubbelde naar 5,5%. Hoewel de postoperatieve sterfte in alle leeftijdsgroepen boven 70 jaar verhoogd was ten opzichte van jongere patiënten, waren er geen significante verschillen tussen de 3 leeftijdsgroepen boven 70 jaar. Opvallend was dat de lange termijn overleving van 80-plussers die de postoperatieve periode hadden overleefd dichtbij de overleving van patiënten jonger dan 70 jaar lag (zie ook **Casus**).

In aanvulling op bovenstaande onderzoekt **Hoofdstuk 7** de invloed van ziekenhuisvolume op chirurgische zorg voor oudere patiënten (≥75 jaar) die een pancreatoduodenectomie (PD) ondergingen voor pancreas- of periampullair carcinoom in 2005-2013 in Nederland. Hoewel het percentage oudere patiënten niet significant verschilde tussen volume tertielen (3 ongeveer even grote groepen), was een toename over de tijd iets meer uitgesproken in lage ziekenhuisvolumes. Het gebruik van adjuvante chemotherapie was het hoogst in hoge ziekenhuisvolumes bij zowel jongere als oudere patiënten. In lage volumes was de 30-dagen postoperatieve sterfte van oudere patiënten meer dan tweemaal zo hoog dan die van jongere patiënten, terwijl verschillen in medium en hoge ziekenhuisvolumes minder uitgesproken waren. Op het moment van 90-dagen postoperatief was de sterfte van oudere patiënten duidelijk hoger binnen alle volume tertielen. Gecombineerde analyses van beide leeftijdsgroepen en volume tertielen (totaal 6 groepen) lieten zien dat sterfte van oudere patiënten in hoge ziekenhuisvolumes vergelijkbaar was aan dat van jongere patiënten in lage en medium volumes, terwijl uitkomsten van ouderen in lage volumes slechter waren.

Casus: Operatie of niet?

Een vitale 84-jarige man met geelzucht, die zijn tijd verdeelde tussen mantelzorg voor zijn vrouw, een volkstuin en vrijwilligerswerk, was verwezen voor beoordeling van resectabiliteit van een verdachte massa in de alvleesklier. Een galwegstent verbeterde de eetlust en huidskleur weer snel. Dit en bezorgde geluiden van artsen over de risico's op zijn leeftijd maakten de man aanvankelijk huiverig voor een operatie. Nader onderzoek toonde een goede conditie en de chirurg sprak zijn vertrouwen uit in een goede afloop. Daardoor kon de man zijn blik verplaatsen naar de langere termijn. Ook al zou hij waarschijnlijk lange tijd een stapje terug moeten doen, de man wilde graag zijn vrouw blijven ondersteunen en koos daarom alsnog voor een operatie. De Whipple-operatie van een papilcarcinoom verliep goed, maar het postoperatief beloop bleek gecompliceerd en emotioneel zwaar. Na twee spoedoperaties binnen anderhalve week, i.v.m. een gallekkage via de drain en een bloeding in de lever, was de man namelijk zo ernstig verzwakt dat zelfstandig eten en lopen niet meer lukten. Terwijl de man heel langzaam weer opkrabbelde, overleed zijn vrouw. Een week na de begrafenis, na negen weken ziekenhuis en 15 kilo afgevallen, verhuisde de man naar een zorghotel om verder te revalideren. Na nog eens 9 weken was hij voldoende hersteld om weer naar zijn eigen huis te gaan. Het is hem niet gelukt om zijn 'oude' vitaliteit van voor de operatie te bereiken, maar met stok en rollator in plaats van de fiets lukt het hem nog steeds om zelfstandig te blijven wonen. Spijt van de operatie, die inmiddels 3,5 jaar achter hem ligt, heeft hij beslist niet.

Soms wordt pas tijdens chirurgische exploratie van de buik ontdekt dat een pancreascarcinoom niet verwijderd kan worden. Populatie studies over deze patiëntencategorie zijn schaars. In de periode 2009-2013 (**Hoofdstuk 8**) nam het percentage chirurgische exploraties met curatieve intentie vanwege pancreascarcinoom toe en binnen deze groep van 2356 patiënten nam het percentage tumorresecties eveneens toe, vooral door een afname van niet-resectabele ziekte zonder afstandsmetastasen (LAPC en enkele niet-fitte patiënten). Onafhankelijke voorspellers voor een niet-resectie tijdens operatie waren oudere studiejaren, oudere leeftijd (≥80 jaar) en lage ziekenhuisvolumes (tertielen). Voor 30-dagen postoperatieve sterfte na niet-resectie waren dat de aanwezigheid van afstandsmetastasen en lage ziekenhuisvolumes, en onafhankelijke voorspellers van een slechtere overleving waren, naast nog andere factoren, een oudere leeftijd (≥75 jaar) en een operatie in ziekenhuizen met lage volumes.

Meer dan de helft van alle patiënten met pancreascarcinoom heeft bij diagnose al uitgezaaide ziekte (afstandsmetastasen). **Hoofdstuk 9** onderzoekt chemotherapie gebruik en overleving in deze grootste patiëntgroep met pancreascarcinoom. Hoewel chemotherapiegebruik sterk afneemt met een stijgende leeftijd van patiënten, verdubbelde het chemotherapie gebruik tussen 2005-2007 en 2011-2013 in leeftijdsgroepen tot 80 jaar. De helft van de 9407 patiënten met afstandsmetastasen was binnen 9,5 weken overleden. Maar liefst een kwart van alle patiënten overleed al binnen 30 dagen na diagnose, variërend van een vijfde van degenen jonger dan 70 jaar tot meer dan twee-vijfde van de 80-plussers.

De leeftijd van 2180 met palliatieve chemotherapie behandelde patiënten nam in de studieperiode toe van (mediaan) 62 naar 64 jaar. Bij behandelde ouderen vond minder vaak weefselonderzoek plaats om de kanker te bevestigen en de overleving van behandelde patiënten (mediaan 5,7 maanden) was significant slechter bij patiënten van 75 jaar en ouder.

De resterende patiëntgroep van niet-gereseceerd niet-uitgezaaid (NR-M0) pancreascarcinoom bestaat enerzijds uit patiënten met lokaal gevorderd pancreascarcinoom (LAPC) en anderzijds

uit inoperabele patiënten als gevolg van een slechte gezondheid. In **Hoofdstuk 10** zijn trends in de tijd van kenmerken, behandeling en overleving van deze NR-M0 patiënten onderzocht.

Tussen 2006-2008 en 2012-2014 daalde het percentage patiënten met NR-M0 pancreascarcinoom scherp van 38% naar 28%. Ruim de helft van de 5964 NR-M0 patiënten was 75 jaar of ouder, twee-vijfde had een stadium III tumor (T4M0) en slechts 16% kreeg chemotherapie. In de patiëntgroep jonger dan 75 jaar nam het chemotherapiegebruik sterk toe (van 23% naar 36%), maar van een duidelijke verbetering van de overleving was (nog) geen sprake. Minder dan 5% van de oudere patiënten werd behandeld met chemotherapie.

De leeftijd van de groep van 967 NR-M0 chemotherapiegebruikers steeg van (mediaan) 62 naar 66 jaar, twee-derde had een stadium III tumor, bij maar liefst 1 op de 6 patiënten was de kanker niet PA-bevestigd en de overleving van behandelde patiënten was (mediaan) 10,4 maanden.

Conclusies

In dit tijdperk van een vergrijzende populatie en toenemende aantallen ouderen met een diagnose alvleesklierkanker die bovendien vaker een kankerbehandeling ontvangen, is objectieve informatie gewenst over hun korte en lange termijn opbrengsten en risico's. De studies die zijn verzameld in dit proefschrift lieten zien dat patiënten bij een oplopende leeftijd minder vaak kankerbehandelingen volgens de richtlijn ontvingen en een verhoogd risico hadden op een slechtere uitkomst na behandeling. Patiënten binnen oudere leeftijdsgroepen kunnen echter sterk van elkaar verschillen wat betreft hun 'functionele leeftijd' of 'risicoprofiel'. Voor individuele oudere patiënten dienen bovendien patiëntvoorkeuren en de kans om na behandeling (opnieuw) een functionele onafhankelijkheid te bereiken zorgvuldig te worden meegewogen in de beoordeling van opbrengsten en risico's van een kankerbehandeling.

Gezonde oudere patiënten kunnen veilig de standaardbehandelingen volgens de (Nederlandse) richtlijn ontvangen. Echter, optimale kankerbehandelingen voor kwetsbare oudere patiënten en voor de tussengroep van matig gezonde patiënten zijn grotendeels onbekend. Een update van de Nederlandse richtlijn voor pancreas- en periampullair carcinoom wordt verwacht in 2018. Richtlijnen zouden ook een 'plan B' (beste behandeling gegeven bepaalde omstandigheden) moeten bevatten. Een 'plan B' is nodig voor minder fitte oudere patiënten die behandeling zouden willen maar heden geen kankerbehandeling krijgen aangeboden. Of die een sterk verhoogd risico hebben op ongewenste uitkomsten van optimale kankerbehandeling.

Oudere leeftijd en kleinere ziekenhuisvolumes bleken sterke voorspellers voor ongewenste uitkomsten van behandelingen. Beiden zijn een simpele weerspiegeling van een onderliggende complexiteit van (veronderstelde) kenmerken. In dit proefschrift vonden we dat chirurgische risico's van oudere patiënten lager waren in hoog-volume ziekenhuizen. Daarnaast zijn ontwikkeling van niet-chirurgische lokale behandelingen en minder toxische chemotherapie schema's nodig voor behandeling-op-maat van kwetsbare oudere patiënten.

List of publications

List of publications

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PhD portfolio

PhD portfolio

Name PhD-student:	L.G.M. van der Geest (Lydia)
PhD period:	2014 - 2018
Promotors	Prof.dr. O.R.C. Busch, Prof.dr. V.E.P.P. Lemmens
Co-promotor	Prof.dr. M.G.H. Besselink

	Year	Workload (hours/ECTS)
Courses		
Scientific Writing in English at Leiden University	2014	24 (0.9)
Advanced statistical methods, by Saskia le Cessie and Suzanne Cannegieter (Dep of Biostatistics / Clinical Epidemiology, LUMC)	2014	16 (0.6)
Workshop Oral presentation at IKNL	2015	8 (0.3)
Multilevel analysis, by Jos Twisk (EpidM, VUMC), at IKNL	2015	16 (0.6)
The AMC World of Science	2016	20 (0.7)
Medical Literature: Embase/Medline via Ovid, Endnote, Searching for a Systematic Review, Citation Analysis and Impact Factors, Searching for Evidence) at AMC	2016-2017	12 (0.5)
Statistical Methods for population-based cancer survival analysis, by Paul Dickman (Karolinska Institute, Stockholm, Sweden), at IKNL	2016	24 (0.9)
Cancer Predictions, by Mark Rutherford and Paul Lambert (University of Leicester, UK), workshop at IKNL	2017	8 (0.3)
Presentations		
DPCG study evening, Utrecht (oral)	2014	16 (0.6)
IKNL symposium 'NKR in Beweging', Jaarbeurs, Utrecht (oral)	2015	32 (1.1)
IKNL symposium 'NKR in Beweging', Jaarbeurs, Utrecht (oral)	2016	32 (1.1)
European Pancreatic Club, Liverpool, UK (poster)	2016	32 (1.1)
European Cancer Congress (ECCO), Amsterdam, The Netherlands (oral, poster, poster pitch)	2017	32 (1.1)
NVGE voorjaarscongres, Veldhoven (oral)	2017	16 (0.6)
E-AHPBA, Mainz, Germany (oral)	2017	16 (0.6)
International conferences		
E-AHPBA, Manchester, UK	2015	32 (1.1)
EPC, Liverpool, UK	2016	32 (1.1)
ECCO, Amsterdam	2017	32 (1.1)
E-AHPBA, Mainz, Germany	2017	32 (1.1)
IACR, Utrecht	2017	8 (0.3)
IHPBA, Geneva, Switzerland	2018	32 (1.1)

Dutch seminars and conferences		
4-D Multidisciplinary Gastrointestinal Oncology Congress, Doorn	2014	16 (0.6)
IKNL-symposium 'NKR in beweging', Utrecht	2015	8 (0.3)
IKNL-symposium 'NKR in beweging', Utrecht	2016	8 (0.3)
2nd 5-D Congress, Ermelo	2016	16 (0.6)
Federadag 'Cancer and Numbers', Enschede	2016	8 (0.3)
Cancer Cancer Amsterdam, 1st retreat, Noordwijkerhout	2017	8 (0.3)
IKNL Symposium 'NKR naar buiten', Utrecht	2017	8 (0.3)
NVGE voorjaarscongres, Veldhoven	2017	16 (0.6)
3rd 5-D Congress, Ermelo	2018	16 (0.6)
Dutch Highlights I-HPBA, Zeist	2014, 2016	4 (0.1)
DPCG and DHCG study evenings (3-4 times a year)	2014-2018	40 (1.4)
IKNL reference meetings	2014-2018	24 (0.9)
IKNL weekly seminars (methodology, articles, work-in-progress)	2014-2018	100 (3.6)
National reports		
Report 'Evaluatie gebruik richtlijn pancreascarcinoom. Landelijke evidence-based richtlijn versie 2.0'	2014	40 (1.4)
Report 'Vroege ontdekking van slokdarm-, alvleesklier- en eierstokkanker. Kansen en knelpunten bij tumoren met een slechte prognose.' Signaleringscommissie Kanker van KWF Kankerbestrijding., contribution NCR-data pancreatic carcinoma.	2014	16 (0.6)
Report 'Kankerzorg in Beeld: Variatie': 3 chapters	2014	280 (10)
Report 'Kankerzorg in Beeld: Ouderen': 1 chapter	2016	80 (2.8)
Teaching		
Lectures Hepato-Pancreato-Biliary carcinoma for registry clerks NCR at IKNL	2014-2018	80 (2.8)
Other tasks		
Supervising registration quality of HPB-carcinoma in the NCR, answering questions of registry clerks, advising on data requests for HPB-carcinoma in the NCR and web-based tool NKR-Online	2012-2018	280 (10)
Extending the NCR for hepatocellulair carcinoma ('10-items', start 2014) and pancreatic carcinoma ('NKR+ project', start 2015) in collaboration with DHCG and DPCG, and periodical evaluation of data quality and registration time	2014-2018	>280 (10)
Regional reports about HPB-malignancies (orals)	2015-2018	240 (8.6)
Reviewing manuscripts for Cancer, European Journal of Cancer Prevention, Digestive Surgery, Journal of Geriatric Oncology	2014-2018	30 (1)
Scientific Committee DPCG (acting for Valery Lemmens)	2018	12 (0.5)
Awards and Prizes		
DPCG-IPSEN Science Travel Award	2017	-
Total		2082 (74)

Dankwoord

Dankwoord

De laatste loodjes, ruim 4 jaar na de officiële start van mijn promotietraject! Dat het nu eindelijk zover is, is beslist niet het werk van mijn persoon alleen. Dit is de ruimte om ieder te bedanken die direct of indirect een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift. Voor het geval ik nog iemand 'vergeet': allen bedankt (en mijn oprechte excuses).

Het begon met een "Nee." Stomverbaasd keken professor Olivier Busch en Marc Besselink me aan. Ze hadden me net een aanbod gedaan voor een PhD-traject bij het AMC-UvA over alvleesklierkanker in Nederland. Een prachtig aanbod inderdaad. Beste Olivier en Marc, het lag niet aan jullie. Voor mij was destijds de tijd niet rijp om een traject als buitenpromovendus in te stappen. Maar jullie hadden wel wat losgemaakt. Toen Valery Lemmens in 2014, op onze eerste werkdag na de tweede fusie van IKNL (met IKZ), instemde om mijn tweede promotor te worden, was mijn 'dreamteam' compleet!

Een 'dreamteam' bleken jullie inderdaad! Wat heb ik geboft met jullie begeleiding. Allereerst gaat mijn dank uit naar mijn copromotor dr. Besselink, inmiddels professor in de HPB-chirurgie. Beste Marc, ik heb genoten van onze bijzondere samenwerking. Jij bent iemand van de 'buitencategorie', met je tomeloze energie en enthousiasme, je continue stroom aan nieuwe ideeën voor onderzoek en je antennes die feilloos nieuwe mogelijkheden voor samenwerking oppikken. Daarmee kun je bergen verzetten, en dat doe je dan ook. Op mijn vraag wanneer je mijn paper kunt becommentariëren, mailt Marc op vrijdagavond doodleuk terug: "Heb nog een stuwmeertje van zo'n 18 papers, maar eind van het weekend lukt wel." En inderdaad! Sta jij ooit 'uit'?
Gelukkig heb je er begrip voor dat anderen wèl rust nodig hebben, bijvoorbeeld toen IKNL-ontwikkelingen steeds meer van mijn tijd opslokten. "Het maakt niet uit hoe langzaam je gaat, zolang je maar niet stopt." (Confucius 551-479 v.Chr) gold zeker voor de afgelopen jaren. Marc, dank je wel ook voor je vertrouwen dat het proefschrift er zou komen toen ik het tempo door privéomstandigheden nog verder moest vertragen.

Dan mijn promotor prof.dr. Busch, beste Olivier, leeftijdgenoot, dank je wel dat je me deze unieke kans hebt geboden om als niet-medicus doctor (dr.) in de Geneeskunde te worden, dat vinden mijn vrienden een goeie grap. Vanaf enige afstand voorzag je me 'vaderlijk' van wijze adviezen, hield de grote lijn in de gaten en hakte af en toe een knoop door, een echte chirurg. Olivier, ik bewonder je enorme kennis en kunde in de HPB-chirurgie die je enthousiast en met humor deelt met anderen, alsmede je vaardigheden om die mudvolle agenda van DPCG-vergaderingen in hoog tempo - maar met ruimte voor alle meningen - tot een goed einde te brengen. Je gaat er tegenwoordig vaker bij staan, is dat voor een nog beter overzicht?

Prof.dr. Lemmens, beste Valery, jouw rol bleef wat meer op de achtergrond, maar je was beslist niet minder belangrijk voor me. Aan jou kon ik letterlijk alles vragen of voorleggen, niets was gek of dom, en je kennis van epidemiologie, wetenschappelijke mores en het klinische veld is

meer dan indrukwekkend. Wat heb ik een bewondering voor je rustige beschouwende en altijd positieve kijk op de zaak.

Dank ook aan de leden van mijn promotiecommissie, Prof.dr. D.J. Gouma, Prof.dr. H.W.M. van Laarhoven, Prof.dr. J.E.A. Portielje, Prof.dr. J.M. Klaase, Dr. M.G.H. van Oijen en Dr. J.E. van Hooft, voor alle tijd en energie die jullie in het lezen van mijn proefschrift wilden steken. Ik kijk ernaar uit om hierover met jullie van gedachten te kunnen wisselen op 15 februari 2019. Speciaal Johanneke, wat gaaf dat jij deel wilt uitmaken van mijn commissie, we kennen elkaar al wat langer uit de Leiden regio en wat heb ik altijd genoten van je beeldende beschrijvingen van de dilemma's in je spreekkamer bij de behandeling van oudere patiënten.

Mijn dank gaat ook uit naar alle co-auteurs voor jullie waardevolle opmerkingen en aanvullingen. En natuurlijk ook voor de prettige samenwerking! Ik heb veel geleerd van jullie unieke klinische perspectieven, vanuit allerlei specialismen in universitaire en niet-universitaire ziekenhuizen.

Alle datamanagers NKR van IKNL, zonder jullie inspanningen was mijn proefschrift niet mogelijk geweest. Ik heb diep respect voor jullie vermogen om die veelkleurige klinische praktijk via de vele registratieregels te vertalen naar beschikbare items en categorieën in de NKR.
Beste IKNL collega's, onderzoekers en niet-onderzoekers, het was een genoegen om met jullie samen te werken en van jullie te kunnen leren. Allereerst Rob, Janina, Marjorie en Sandra, kernteam van het tumorteam Upper GI & HPB, het tempo ligt hoog en het enthousiasme is groot, wat gaaf om daarin mijn (HPB-)steentje te mogen bijdragen. Voorts alle collega's in de wekelijkse GI-overleggen, het brede tumorteam Upper GI & HPB, de brain-boost-lunches, onderzoekersoverleggen, etc, bedankt voor alle inhoudelijke discussies en de gezelligheid. Mijn voormalige Leidse collega's en huidige Utrechtse collega's, bedankt voor alle kopjes thee, gezamenlijke lunches, het uitwisselen van lekkere recepten en vooral gezelligheid met elkaar. Mijn speciale dank is voor mijn collega Marja en haar vader, die mij zo genereus hun verhaal doneerden voor Hoofdstuk 11. Helaas is je vader tijdens de afronding van dit proefschrift overleden, bijna 4 jaar na de Whipple operatie. Ik wens jou en je familie veel sterkte!

Janneke en Tara, wat fijn dat jullie mijn paranimfen willen zijn! Een IKNL-collega en een AMC-collega, dat doet helemaal recht aan het feit dat mijn proefschrift uit een combinatie van beide organisaties is voortgekomen. En wat voor collega's, verschillende achtergronden en persoonlijkheden maar beiden ruimdenkend en heerlijk no-nonsense, daar hou ik van!

DPCG PhD-ers, wat fijn dat ik er als (oudere) buitenpromovendus gewoon bij mocht horen! Ik heb genoten van jullie enthousiasme en gezelligheid tijdens congressen, uitjes voor DPCG-promovendi en DPCG-vergaderingen. Dank daarvoor! Bengt, jij was de eerste DPCG-PhD-er met wie ik mocht samenwerken, en je bent me net voor met het verdedigen van je eigen proefschrift! Van harte! Het samenwerken was aan beide kanten nog even wennen, vertrouwen moet groeien. Het werd een dusdanig positieve ervaring dat je collega's Marin, Eran, Tara en Anouk er nu volop de vruchten van plukken. Dank je wel Bengt, voor je geduld.

Marin en Tara, jullie waren nieuwsgierig naar mijn 'geheim'? Haha, the usual suspects denk ik, maar 'weinig stress' lukt echt niet tijdens een PhD-traject, dat weten jullie zelf ook!

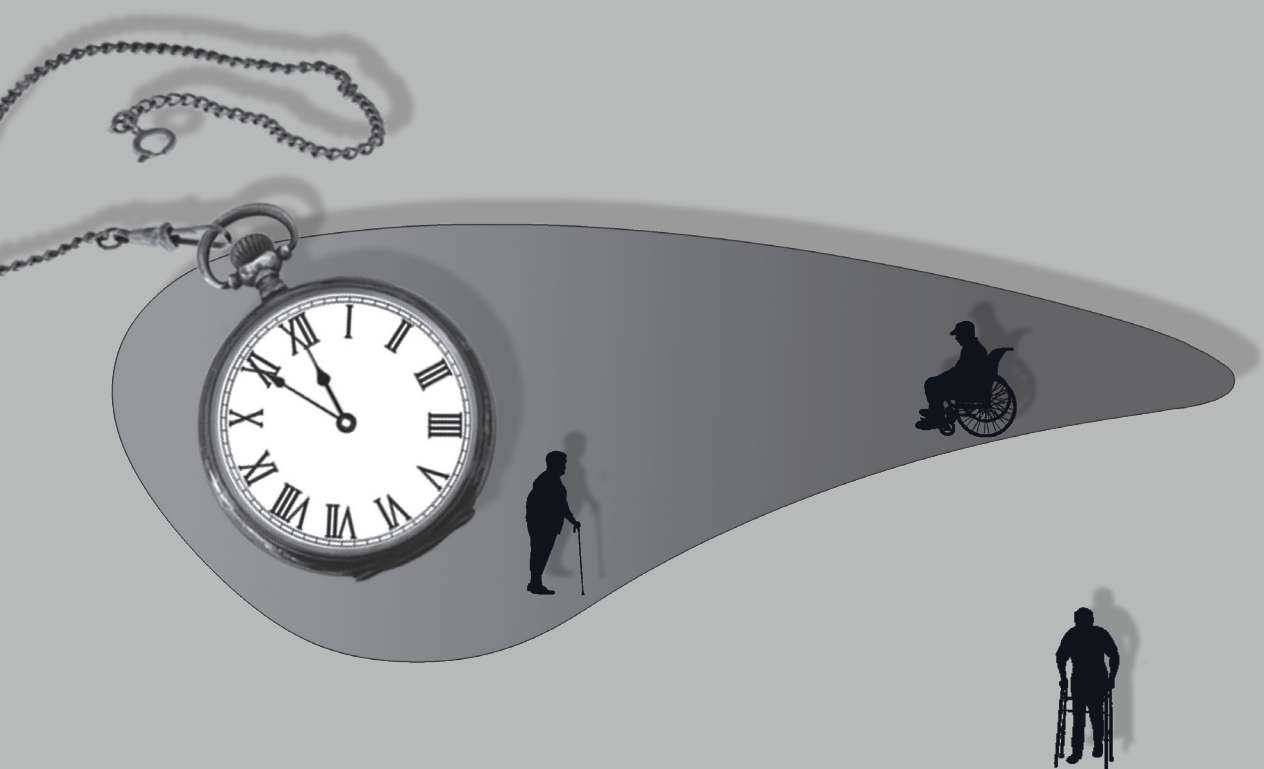
Vriendinnen-van-vroeger, van de studie, wandelmaatjes en alles daartussenin, dank voor jullie geduld wanneer een afspraak maken schier onmogelijk leek in mijn overvolle agenda. Ik heb absoluut genoten van onze uitstapjes, etentjes, wandelingen en fietstochten. Dank vooral aan de zogenoemde 'Bladelgroep' van 11-13 gezinnen, tezamen ruim 50 man/vrouw/kind sterk. De uitstapjes en hele weekenden door de jaren heen, boordevol buitensporten, muziek, spelletjes, toernooien, samen koken, bonte avonden (en nog veel meer), hebben een onuitwisbare indruk gemaakt op ons en onze kinderen. Jullie verstaan de kunst van 'het goede leven'! Guusje, Irma en Hans, ik denk nog dagelijks aan jullie, wat heb ik veel geleerd van hoe jullie omgingen met jullie eigen kanker en we binnen een jaar tijd afscheid moesten nemen van jullie alle drie. De Bladelgroep is niet meer hetzelfde, maar we zullen beslist weer nieuwe activiteiten en nieuwe gezelligheid vinden.

Dank ook aan mijn ouders. Lang geleden zagen jullie een andere toekomst voor mij dan ik zelf, maar ik moest en zou de wijde wereld in. Het aantal diploma's dat ik vergaarde, duizelde jullie en ik kan niet beloven dat ik nu 'uitgeleerd' ben. Pa heeft deze mijlpaal net niet meer kunnen meemaken; maar ma, ik hoop dat u trots bent op wat ik bereikt heb.

Veel jonge PhD-ers bedanken hun ouders voor hun steun, luisterend oor en verzorgende kopjes thee tijdens het promotietraject. Ik heb hetzelfde mogen ontvangen van mijn drie super-kinderen. Dank jullie wel, wat ben ik trots op jullie! Zelfs de jongste, nu 16, weet z'n vrienden en vriendinnen inmiddels te imponeren met zijn kook- en bakkunsten. 'Opvoeden is loslaten', zeg ik altijd, 'stukje bij beetje, en dat begint al bij de navelstreng'! Nu zijn jullie groot en de één na de ander vliegt het nest uit. Ik hoop dat ik jullie met mijn grillige loopbaanpad heb laten zien dat er geen 'foute keuzes' bestaan, alleen maar 'volgende keuzes'. En ik hoop niet dat de dominante herinnering bestaat uit jullie: "Mam? … Mama??! … LYDIA?!!!" op de momenten dat jullie mijn aandacht wilden en ik in diepe diepe concentratie achter m'n computer zat. Jullie hebben me al meerdere malen laten weten hoe trots jullie op me zijn, dus ik hoop maar dat het meevalt.

En last but not least gaat mijn dank uit naar Arie, al meer dan 30 jaar m'n maatje, in goede en slechte tijden. Hoe verschillend we ook in het leven staan, ergens weten we elkaar altijd weer te vinden. Je hebt afgelopen jaren heel veel opgevangen, een eerlijke verdeling van huishouden en zorg was ver te zoeken. Via je grappen-met-serieuze-ondertoon, zoals we die zo goed van je kennen (auwtsz), maakte je al een paar keer duidelijk dat het nu lang genoeg geduurd heeft. Het achterstallig onderhoud van ons huis moet hoognodig aangepakt… Ik ga me beslist niet vervelen!

Curriculum vitae



Curriculum vitae

Lydia van der Geest werd geboren op 13 oktober 1962 in Hoogmade (gemeente Woubrugge). In 1980 behaalde zij haar VWO-diploma aan het Bonaventuracollege te Leiden en begon met de opleiding tot A-verpleegkundige in het Rijnland ziekenhuis (heden Alrijne groep) in Leiderdorp. Na haar diploma deed zij specialisaties in Hartbewaking (Rijnland/MC Haaglanden) en Kinderverpleging (VUMC). Op haar 26ste besloot ze alsnog een universitaire studie te beginnen en studeerde Sociale en Organisatie Psychologie in Leiden. In 1994 rondde zij cum laude haar studie af op een onderzoeksproject over lotsverbondenheid in een twee-generationeel resource dilemma. Kort daarna beviel zij van haar eerste kind, werkte bij TNO Preventie en Gezondheid aan het boekje 'Zelfsturende teams, de praktijk aan het woord' en kon vervolgens aan de slag bij Research voor Beleid in Leiden. In opdracht van overheden en brancheorganisaties voerde Lydia daar onderzoeksprojecten uit op de terreinen Gezondheidszorg en Sociale Zaken. Na diverse jaren projectmatig werken, meer zwangerschappen en een kort uitstapje naar het UWV, kwam Lydia in 2003 terecht bij het Integraal Kankercentrum West (IKW). Daar coördineerde zij onder andere regionale audit-and-feedback projecten, zoals het multidisciplinaire project Kwaliteitsinformatie Colorectaal carcinoom (KIC, tevens pilot voor de landelijke DSCA) en een monitoring project van regionale concentratie-en-spreiding afspraken over slokdarm-, alvleesklier-, grote rectum- en leverchirurgie. In roerige tijden van het IKW was zij één van de oprichters van een personeelsvertegenwoordiging (PVT). Ondertussen volgde ze cursusmodules bij het EpidM (Vrije Universiteit) in Amsterdam en rondde in 2012 haar master Epidemiologie af met een publicatie over het KIC-project. Na de fusies in 2011 en 2014 van de regionale kankercentra tot het Integraal Kankercentrum Nederland (IKNL) werd Lydia de eerste IKNL-onderzoeker met als aandachtsgebied de Hepato-Pancreato-Biliaire (HPB) tumoren. Binnen dit aandachtsgebied ontstonden twee landelijke multidisciplinaire samenwerkingsverbanden: de Dutch Pancreatic Cancer Group (DPCG) voor pancreas- en periampullaire tumoren en de Dutch Hepato & Cholangio Carcinoma Group (DHCG) voor hepato-biliaire tumoren. Een proefschrift stond nog niet op Lydia's CV en ten tijde van de richtlijnevaluatie pancreascarcinoom werd zij prompt benaderd door professor Olivier Busch (AMC) voor een promotietraject over pancreascarcinoom. Tijdens en na afloop van haar promotieonderzoek werkt Lydia binnen IKNL verder aan haar aandachtsgebied, de HPB-tumoren.

DPCG
Dutch Pancreatic Cancer Group