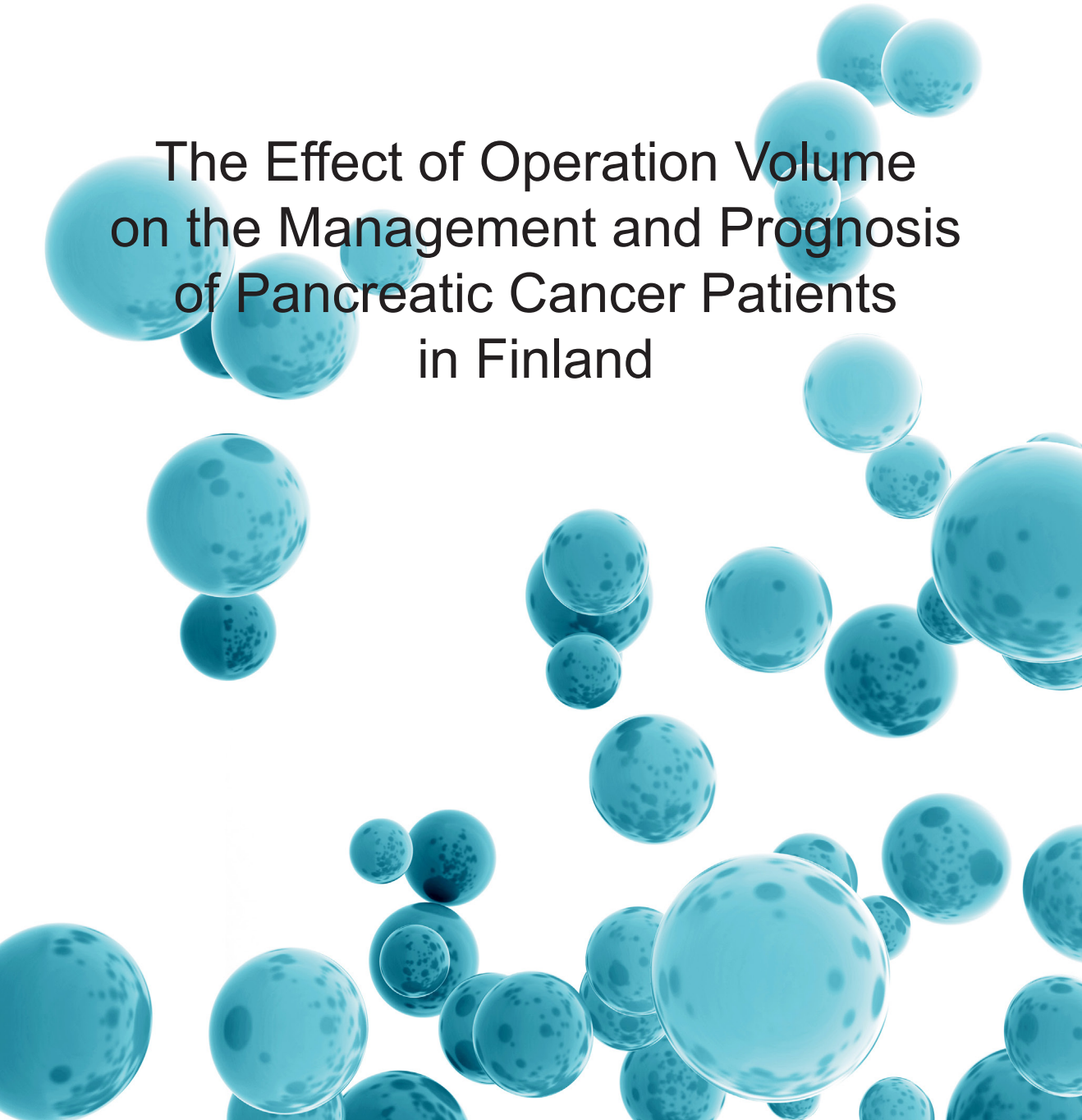
Acta Universitatis Tamperensis 2424

REEA AHOLA

The Effect of Operation Volume on the Management and Prognosis of Pancreatic Cancer Patients in Finland



REEA AHOLA

The Effect of Operation Volume on the Management and Prognosis of Pancreatic Cancer Patients in Finland

■

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty Council of the Faculty of Medicine and Life Sciences
of the University of Tampere,
for public discussion in the Jarmo Visakorpi auditorium
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 26 October 2018, at 12 o'clock.

UNIVERSITY OF TAMPERE

REEA AHOLA

The Effect of Operation Volume on the Management and Prognosis of Pancreatic Cancer Patients in Finland

Acta Universitatis Tamperensis 2424
Tampere University Press
Tampere 2018

UNIVERSITY OF TAMPERE

ACADEMIC DISSERTATION
University of Tampere, Faculty of Medicine and Life Sciences
Tampere University Hospital
Finland

Supervised by
Associate Professor Johanna Laukkarinen
University of Tampere
Finland
Docent Juhani Sand
University of Tampere
Finland

Reviewed by
Docent Esko Kemppainen
University of Helsinki
Finland
Professor Pauli Puolakkainen
University of Helsinki
Finland

The originality of this thesis has been checked using the Turnitin OriginalityCheck service in accordance with the quality management system of the University of Tampere.

Cover design by
Mikko Reinikka

Acta Universitatis Tamperensis 2424
ISBN 978-952-03-0865-0 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 1934
ISBN 978-952-03-0866-7 (pdf)
ISSN 1456-954X
http://tampub.uta.fi

Suomen Yliopistopaino Oy – Juvenes Print
Tampere 2018

ABSTRACT

Pancreatic cancer (PC) is known for poor overall prognosis. Surgery combined with oncologic therapy is currently the best way to improve five-year survival and only 15-20% (Ducreaux et al. 2015) of patients are candidates for surgery. Moreover, pancreatic resections are associated with high mortality and morbidity rates. Internationally it has been reported that a sufficient operation volume has a beneficial effect on the short- and long-term prognosis after surgery. This thesis aimed to study the effect of operation volume on postoperative prognosis and quality of management of PC patients in Finland. A high volume centre (HVC) was defined as a centre performing at least 20 pancreatoduodenectomies (PD) and total pancreatectomies (TP) per year. The thesis comprises four retrospective studies based on national Finnish data.

The first part focuses on long-term survival after pancreatic resection among pancreatic ductal adenocarcinoma (PDAC) patients. The data comprise patients operated on between 2000 and 2008. The study shows that many long-term survivors carried a T3N1-disease. High operation volume was associated with lenghtened survival.

The second part analyses the effect of operation volume on post-operative prognosis among PDAC patients operated on between 2002 and 2008. The study shows that both 30- and 90-day mortalities were lowest in HVCs. Moreover, two- and three-year survivals were highest in the high volume group. Pathological reports seemed more precise in centres with higher operation volumes.

The third part comprises data on patients with PC diagnosed either in 2003 or in 2008. The treatment strategies are analysed in relation to the health care district where the diagnoses was set. The study shows that more patients were selected for surgery in those health care districts having a high volume pancreatic centre.

The fouth part analyses the effect of operation volume on complications, prognosis and resource utilisation after a pancreatic resection during the first 90 days among patients undergoing pancreatic resection between 2012 and 2014. The study showed that a high operation volume was associated with lower 30 and 90-day mortality and lower overall costs.

As a conclusion, this study shows that management of PC differed across health care districts in Finland. The results emphasize the benefits of high operation volume in planning and conducting the surgical care of PC patients. Moreover, pancreatic resections performed in HVCs can result in lower overall treatment costs. These findings support the centralization of pancreatic resections to HVCs.

TIIVISTELMÄ

Haimasyöpä on tunnetusti huonoennusteinen syöpä. Tällä hetkellä kasvaimen poistoleikkaus yhdistettynä solunsalpaajahoitoihin on paras keino parantaa ennustetta merkittävästi. Kuitenkin vain noin 15 - 20% potilaista kuuluu leikkaushoidon piiriin diagnosointihetkellä. (Ducreaux et al. 2015) Haimaleikkauksiin liittyy myös korkeaa kuolleisuutta ja sairastuvuutta. Kansainvälisissä tutkimuksissa on todettu, että riittävä leikkausvolyymi parantaa haimaleikkauksen jälkeistä ennustetta. Tämän väitöskirjatyön tarkoitus oli tutkia leikkausmäärän vaikutusta haimasyöpäpotilaiden hoitolinjoihin ja ennusteeseen leikkauksen jälkeen Suomessa. Tutkimuksessa korkean leikkausmäärän rajana pidettiin 20 haiman ja pohjukaissuolen ja koko haiman poistoa vuosittain. Tutkimus koostui neljästä rekisteripohjaisesta retrospektiivisesta osatyöstä, joiden aineistot olivat valtakunnallisia.

Ensimmäisessä osatyössä käsiteltiin vuosina 2000 - 2008 leikattujen haiman duktaalista adenokarsinoomaa (PDAC) sairastavien potilaiden pitkäaikaisennustetta leikkauksen jälkeen. Tutkimuksessa todettiin että monella pitkäaikaiselossaolijalla tauti oli leikattu T3N1-vaiheessa, ja että korkeat leikkausmäärät vaikuttivat suotuisasti pitkäaikaiselossaoloon.

Toinen osatyö käsitteli leikkausmäärän vaikutusta vuosina 2002 – 2008 leikattujen PDAC-potilaiden ennusteeseen. Tutkimus osoitti, että sekä 30 vuorokauden että 90 vuorokauden kuolleisuus oli matalammillaan, kun leikkausmäärä on suuri. Lisäksi todettiin, että kahden ja kolmen vuoden elossaolot olivat korkeimmat suuren leikkausmäärän ryhmässä. Korkean leikkausmäärän yksiköissä myös patologian raportit vaikuttivat kattavimmilta.

Kolmas osatyö kuvasi vuonna 2003 tai 2008 diagnosoitujen haimasyöpäpotilaiden hoitolinjoja suhteessa sairaanhoitopiiriin, jossa diagnoosi on tehty. Tutkimustulokset kertovat, että alueilla, joissa on korkean leikkausmäärän haimakeskus, suurempi osa haimasyöpäpotilaista päätyy leikkaushoitoon.

Neljäs osatyö käsitteli leikkausmäärien vaikutusta haimaleikkausten jälkeiseen 90 vuorokauden ennusteeseen, komplikaatioihin ja kulutettuihin taloudellisiin voimavaroihin. Aineisto käsitteli vuosina 2012 - 2014 tehtyjä haimaleikkauksia.

Tutkimuksessa todettiin, että korkeat leikkausmäärät johtivat matalampaan 30- ja 90 vuorokauden kuolleisuuteen ja kokonaishoitokustannuksiin.

Johtopäätöksenä voidaan esittää, että haimasyövän hoidossa on eroja sairaanhoitopiirien välillä Suomessa. Tulokset korostavat riittävän leikkausmäärän merkitystä kirurgisen hoidon suunnittelussa ja toteuttamisessa. Lisäksi voidaan todeta, että riittävä leikkausmäärän voi alentaa kokonaishoidon kustannuksia haimasyöpäpotilailla. Tutkimustulokset puoltavat haimaresektioiden keskittämistä yksiköihin, joissa leikkausmäärä on suuri.

TABLE OF CONTENTS

LIST OF ORIGINAL COMMUNICATIONS

1. Patients with resected, histologically re-confirmed pancreatic ductal adenocarcinoma (PDAC) can achieve long-term survival despite T3 tumour or nodal involvement. The Finnish Register Study 2000-2013. R. Ahola, A. Siiki, K. Vasama, M. Vornanen, J. Sand, J. Laukkarinen. *Pancreatology* 2017;9-10:822-826.

2. Effect of centralization on long-term survival after resection of pancreatic ductal adenocarcinoma. R. Ahola, A. Siiki, K. Vasama, M. Vornanen, J. Sand, J. Laukkarinen. *BJS* 2017;104:1532-1538.

3. Access to radical resections of pancreatic cancer is region-dependent despite the public health care system in Finland. R. Ahola, H. Hölsä, S. Kiskola, P. Ojala, A. Pirttilä, J. Sand, J. Laukkarinen. *Journal of Epidemiology and Community Health* 2018;72:803-808.

4. Pancreatic resections are not only safest but also most cost-effective when performed in a high volume centre: A Finnish Register Study. R. Ahola, J. Sand, J. Laukkarinen. Submitted.

ABBREVIATIONS

AJCC	American Joint Committee on Cancer
APACT	trial on adjuvant treatment
ASA	American Society of Anesthesiologists
ASCO	American Society of Clinical Oncology
AUGIS	Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
AUS	abdominal ultrasonography
BMI	body mass index
BRCA1-2	breast cancer genes 1-2CA celiac axis
CA19-9	carbohydrate 19-9 antigen
CAPS	International Cancer of the Pancreas Screening Consortium
CEA	carcinoembryogenic antigen
CE-CT	contrast-enhanced computed tomography
C-D classification	Clavien-Dindo classification
CD-40	cluster of differentiation 40
CDKN2A	cyclin-dependent kinase inhibitor 2A
CFTR	cystic fibrosis transmembrane conductance regulator
CHA	common hepatic artery
COI	confidence interval
CONKO	Charité Onkologie
CRP	C-reactive protein
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte–associated antigen 4
DGE	delayed gastric emptying
DIPLOMA	trial on minimally invasive pancreatectomy
DHo	Costs of a day on a surgical ward
DHo/s	Costs of a day on a surgical ward/ survival
DNA	deoxyribonucleic acid
DP	distal pancreatectomy

EGOC	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ERCP	endoscopic retrograde cholangiopancreatography
ESMO	European Society of Medical Oncology
ESPAC 1-4	European Study Group for Pancreatic Cancer, Studies 1-4
EUS	endoscopic ultrasonography
EUS-FNA	endoscopic ultrasonography assisted fine needle biopsy
FAMMM	familial atypical multiple mole melanoma
FAK	focal adhesion kinase
FAP	familial adenomatous polyposis
FCR	Finnish Cancer Registry
FOLFIRINOX	chemotherapy regimen composed of folinic acid, fluorouracil, irinotecan and oxaplatin
5-FU	5-fluorouracil
Gy	Gray
G-VAX	a vaccine of infiltrated T-cells and lymphoid structures
HLER	high level of experience region
HILMO	procedure and treatment register of Institute of Health and Welfare
HNPCC	hereditary non-polypotic colon cancer
HVC	high volume centre
IBM	International Business Machines Corporation
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IL-2	interleukin-2
IMV	inferior mesenteric vein
INR	throboplastin time
IPMN	intraductal papillary mucinous neoplasm
ISGPS	International Study Group of Pancreatic Surgery
JLC	first letters of pancreatic resection procedure codes
KRAS	Kirsten Rat Sarcoma viral oncogene
LAELAP 1 - 2	a Dutch education programme on laparoscopic pancreatic surgery
LEOPARD-2	Minimally invasive pancreatoduodenectomy trial

LLER	low level of experience region
LTS	long-term survivor
LVC	low volume centre
MCN	mucinous cystic neoplasms
MLER	medium level of experience region
mo	months
MRI	magnetic resonance imaging
MVC	medium volume centre
NAS	non aliter specificatus
NCCN	National Comprehensive Cancer Network
OECD	Organisation for Economic Cooperation and Development
p16	cyclin-dependent kinase inhibitor 2A (CDKNA-2A)
PanIn	pancreatic intraepithelial neoplasia
PARP	poly-adenosine-disphoste ribose polymerase
PC	pancreatic cancer
PD	pancreatoduodenectomy
PDAC	pancreatic ductal adenocarcinoma
POPF	postoperative pancreatic fistula
PPH	postoperative pancreatic haemorrhage
PRODIGE	trial on chemotherapy
PRSS1	cationic trypsinogen gene
PTBD	percutaneous transhepatic biliary drainage
PV	portal vein
RTOG	trial on chemotherapy
R0	no tumour tissue in the margins of a surgical sample
S1	fluoropyrimidine formulation
SCA	serous cystadenomas
SMA	superior mesentery artery
SMAD4	an intracellular protein whichs transduce extracellular signals and activate downstream gene transcription
SMV	superior mesentery vein
SPINK-1	serine protease inhibitor Kazal type 1
SPN	solid pseudopapillary neoplasm
SPSS	Statistical Package for the Social Sciences (analysis programm)

STS	short-term survivor
SUSTENT	trial on gastrojejunostomy
TNM	node, metastasis classification
TP	total pancreatectomy
TP53	tumour protein 53
USD	United States Dollar

1 INTRODUCTION

Pancreatic cancer (PC) is the fourth most deadly (Malvezzi et al. 2014) cancer and its incidence has been rising in recent decades. The prognosis of PC is known to be poor, owing to the asymptomatic, but aggressive nature of the disease. However, there are multiple different subtypes of PC, pancreatic ductal adenocarcinoma (PDAC) forming the largest subgroup. Well timely diagnosis and treatment can increase five-year survival from <1% to circa 30% among PDAC patients (Bilimoria et al. 2007a).

The best means to improve survival is currently surgery combined with oncologic therapy. Pancreatic resections are defined as high-risk surgery with a frequency of major complications of 20-40% (Sheetz et al. 2016; Ansari et al. 2014) and post-operative mortality of 2-15% (Lidsky et al. 2017; Nimptsch et al. 2016; Yoshioka et al. 2014). Moreover, PDAC infiltrates the adjacent tissues, possibly resulting in inoperable disease or necessitating vascular resections. One of the challenges in pancreatic surgery is to select truly operable patients with sufficient performance status for surgery. Nowadays the standard is to assess the treatment options in a multidisciplinary team including surgeons, radiologists, pathologists, anesthesiologists and oncologists (Ducreux et al. 2015).

The quality and safety of the treatment process can be evaluated by the delays to treatments, incidence of post-operative complications, success in rescuing patients after complications, mortality and by long-term survival. In addition, proper survival analysis of operated patients is based on an unbiased evaluation of surgical specimens.

Several studies from Europe have reported that lower mortality rates and longer survival can be achieved with high operation volumes (Farges et al. 2017; van der Geest et al. 2016a; van der Geest et al. 2016b; Gooiker et al. 2014; Ansari et al. 2014; Balzano et al. 2008; Nordback et al. 2002). In Finland centralization of pancreatic surgery has proceeded gradually but slowly during the past decades. Economic pressure, however, has catalysed the re-organisation of the public health care system in recent years in Finland. This study focuses on investigating the effects of hospital volumes on the quality and safety of PC surgery.

2 REVIEW OF THE LITERATURE

2.1 Pancreatic cancer

2.1.1 Epidemiology

According to the Finnish Cancer Registry (FCR), pancreatic cancer was the tenth most common cancer among men and the seventh most common among women in Finland in 2014 (Finnish Cancer Registry, 2015). The mean onset age of the disease is 71 years among men and 75 years among women (Ducreux et al. 2015). The FCR reported an age-standardized PC incidence of 18.9 cases/100,000 women and a slightly greater incidence among men, 23.3/100,000 between 2011 and 2015 (Finnish Cancer Registry, 2015). This is higher than the estimated incidence worldwide 4.9/100,000 among women and 3.6/100,000 among men in 2012 (World Health Organization, 2012). Although the global statistics may contain some biased information, the incidence of PC seems higher in Finland than in most parts of Europe. Ferlay et al. (2013) reported an overall PC incidence of 12.1/100,000 for men and 8.3/100,000 for women in Europe in 2012. This difference of incidences cannot be totally explained by the excellent national registers in Finland, as the incidence at 7.4-6.5/100,000 is lower in Sweden – a country with similar registries (Ferlay et al. 2013).

2.1.2 Risk factors and screening of pancreatic cancer

2.1.2.1 Risk factors

PC is most commonly a sporadic disease with multiple risk factors as shown in Table 1. Smoking doubles the risk for PC. *Helicobacter pylori infection,* non-O-blood-group, diabetes mellitus, obesity and heavy alcohol consumption increase the risk 1.1-2.2-fold. Nutritional factors such as red meat intake and low fruit and folate intake likewise increase the risk (0.5-1.5-fold). Chronic pancreatic accounts for 5%

of pancreas cancers, but is itself associated also with diabetes and alcohol consumption. (Maisonneuve & Lowenfels, 2015)

Only circa 5-10% of the PCs are explained by inherited mutations. The best known mutation resulting in PC is a mutation in *BRCA2*. Other hereditary disorders associated with PC are hereditary pancreatitis (mutations in genes *SPINK1, PRSS1, CFTR*), hereditary non-polyposis colorectal cancer (*HNPCC*), ataxia telangiectasia, Peutz–Jeghers syndrome, familial atypical multiple mole melanoma (*FAMMM*) syndrome, cystic fibrosis, von Hippel-Lindau syndrome and Li–Fraumeni syndrome. (Maisonneuve & Lowenfels 2015; Maher et al. 2011; Torphy & Schulick 2018)

Intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs) and solid pseudopapillary neoplasms (SPNs) are pancreatic cystic neoplasm identified to carry malignant potential. The risk of a lesion progressing to malignancy among patients with main-duct IPMN is 36-100% and among patients with branch-duct IPMN 6.3-46.5%. It has been estimated that under 15% of MCNs have a malignant potential. In addition to mucinous neoplasms, pancreatic intraepithelial neoplasms (PanIn –lesions) are considered high-risk precursors of carcinoma. These small, <0.5cm lesions are difficult to detect with imaging modalities, but secondary features such as lobar chronic pancreatitis may lead to a correct diagnosis. (Torphy & Schulick 2018, Del Chiaro et al. 2013, Keane et al. 2018, Nilsson et al. 2016, European Study Group on Cystic Tumours of the Pancreas 2018)

Table 1. Risk factors for PC and their estimated risk (Torhpy & Schulick 2018, Maisonneuve & Lowenfels 2015, Maher et al. 2014).

Genetic factors	**Estimated risk for PC**
Familial atypical multiple mole melanoma (FAMMM)	17% by 75 years
Peutz-Jeghers syndrome	36% lifetime risk
Hereditary breast-ovarian cancer	BRCA1: 1.5-2.1% by 70 years BRCA2: 3.6 lifetime risk
Hereditary non-polypotic colon cancer (HNPCC)	3.7% by 70 years
Familiar adematous polyposis (FAP)	circa 2% lifetime
Hereditary pancreatitis	40% by 70 years
Familial PC	2 first-degree relative: 8-12% lifetime risk 3 first-degree relative: 16-30% lifetime risk
Ataxia telenangiectasia von Hippel-LIndau syndrome	pancreatic tumours occur among 5-10%
Non-genetic factors	
Tobacco	2- fold
Helicobacter pylori infection	1.5-fold
non-O-blood-group	1.4-fold
Diabetes mellitus	1.4-2.2-fold
Obesity	1.2-1.5-fold
Red meat intake	1.1-1.5-fold
Heavy alcohol intake	1.1-1.5-fold
Low fruit and folate intake	0.5-1.0- fold
Precursor lesions	
Main-duct IPMN	36-100% lifetime risk
Branch-duct IPMN	6.3-46.5% lifetime risk
Mucinous cystic neoplasm (MCN)	<15% lifetime risk, especially if >4cm
Solid pseudopapillary neoplasm (SPN)	16%
PaNin-lesions	100% lifetime risk

2.1.2.2 Screening of pancreatic cancer

Although some risk factors and even genetic mutations for PC have been detected, screening is challenging. It has been proposed that the lifetime overall risk for PDAC is circa 1.49% (Howlander et al. 2010). New-onset diabetes has been associated with PDAC, and it has been proposed as a selection criterion for screening among asymptomatic patients. However, the incidence of diabetes is high and it has been estimated that under 1% of patients with an adult-onset diabetes will be diagnosed with PDAC within three years of the diabetes diagnosis. This has decreased the interest in screening patients with new-onset diabetes. (Becker et al. 2014)

The International Cancer of the Pancreas Screening (CAPS) consortium suggested that individuals should be considered for screening if at least one first-degree relative plus other blood relatives are affected by PC or if the individual carries a mutation or a specific syndrome (p16, BRCA2, PALB2, Peutz-Jeghers syndrome, Lynch syndrome) and has a first-degree relative affected by PC (Canto et al. 2013). DaVee et al. (2018) studied screening modalities among patients with high-risk mutations and reported that PC screening should be focused on patients over 50 years. A new meta-analysis by Signoretti et al. (2018) revealed that high-risk individuals have 0.5% risk for developing a pancreatic lesion requiring resection. In addition, Rubenstein et al. (2007) compared follow-up strategies among familial PC patients and stated that prophylactic pancreatectomy did not lead to higher number of quality-adjusted life years.

In addition, if cystic neoplasms are detected patients are recommended to enrol in surgery or follow-up programs (European Study Group on Cystic Tumours of the Pancreas 2018).

2.1.3 Histopathology

The pancreas has both endocrine and exocrine parenchyma and both can develop a malignant disease. Approximately 95% of malignancies originate in the exocrine parenchyma. The most common cancer subtype is PDAC, which accounts for circa 80% of PCs. The subtypes of PDAC only account for under 10% of all PDACs and they are listed in Table 2. In addition to epithelial tumours, mature teratomas, mesenchymal tumours (sarcomas, lipomas, lymhangiomas, solitary fibrous tumours, perivascular epithelioid cell neoplasms, desmoplastic small round cell tumours), lymphomas, neuroendocrine tumours and secondary tumours may develop in pancreas. The exact histopathological diagnosis of a pancreatic tumour may be verified only after a resection. (Elghazawy & Verbeke 2010; Chen 2017)

PDAC grows infiltratively and dispersed and may have small satellite masses couple of millimetres away from the main mass which challenges histopathological evaluation (Verbeke et al. 2011). The mass is typically yellow or white in colour. Necrosis is uncommon. PDAC causes a strong desmoplastic reaction in the surrounding stroma called the tumour microenvironment. (Esposito et al. 2014) The tumour microenvironment among PDAC patients is considered antioncogenic and immunosuppressive (Zhang et al. 2018). Moreover, it has been reported that in

vivo models PDAC cells even change the inflammatory status of immunologic cells (Salmiheimo et al. 2016a).

Table 2. Epithelial pancreatic malignancies (Chen 2017)

ductal adenocarcinoma	
	adenoquasmos carcinoma
	mucinous adenocarcinoma
	hepatoid carcinoma
	medullary carcinoma
	signet ring cell carcinoma
	undifferentiated carcinoma
	undifferentiated carcinoma with osteoclast-like cells
acinar cell carcinoma	
acinar cell cystadenocarcinoma	
IPMN with an associated invasive carcinoma	
mixed acinar ductal carcinoma	
mixed acinar neuroendocrine carcinoma	
mixed acinar neuroendocrine ductal carcinoma	
mixed ductal neuroendocrine carcinoma	
mucinous cystic neoplasm with an associated invasive carcinoma	
pancreatoblastoma	
serous cystadenocarcinoma	
solid pseudopapillary neoplasm	

In the carcinogenesis of PDAC the normal pancreatic parenchyma progresses to cancer from pancreatic intraepithelial neoplasia. These PanIn lesions are graded from 1 to 3 according to severity of neoplasia (Figure 1). It has been proposed that in addition to carcinogenesis from ductal precursor lesions such as IPMNs, MCNs, SPNs and PanIn-lesions, carcinogenesis may emerge directly among acinar cells without a PanIn step. (Esposito et al. 2014; Murtaugh & Leach 2007)

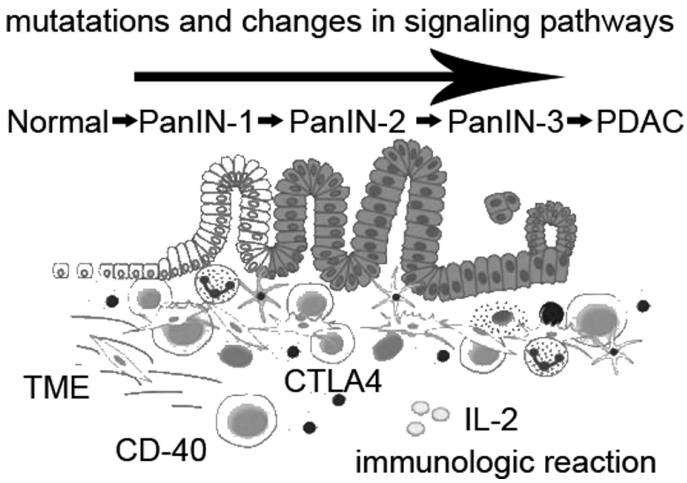


Figure 1. Carcinogenesis of PDAC via PanIN-steps. PDAC causes a strong desmoplastic reaction resulting in an immunosuppressive tumour microenvironment (TME). CD40, CTLA, IL-2 immunological agents. PanIn lesions are considered to be precursors of PDAC. Adapted from the original image by Wörmann & Algul 2013 (License CC-BY).

2.1.4 Molecular genetics of PDAC

Several mutations have been associated with PDAC. Mutations typically vary between patients and new mutations may emerge during carcinogenesis. Mutations in KRAS, CDKN2A/p16, SMAD4 and TP53 genes are considered to be the drivers in the carcinogenesis of PDAC. It has been proposed that 90% of low-grade precursor lesions (PanIN) have mutations in the KRAS gene locus while CDKN2A/p16, SMAD4 and TP53 locuses are affected in higher grades of dysplasia and carcinogenesis. (Esposito et al. 2014) In addition to the four loci, 12 core signalling pathways were identified in the first genomic analysis of PDAC carcinogenesis by Jones et al. (2008). These pathways may carry several mutations with a wide variety even in one patient.

Based on the molecular transcriptional profiles three different subtypes (classical, quasimesenchymal and exocrine-like) of PDAC have been proposed. Interestingly, these profiles may respond differently to chemotherapy, but the process is not yet fully understood. (Collisson et al. 2011)

2.1.5 Diagnosis of pancreatic cancer

2.1.5.1 Symptoms

A study by Takeda et al. (2017) reported that 29% of PC patients are asymptomatic at the time of diagnosis and those with symptoms have a more advanced disease. The classical triad of painless jaundice with resistance in the upper quadrant of abdomen is usually encountered only among patients with an advanced disease. Typical symptoms include unspecific pain or discomfort in the upper parts of the abdomen, weight loss, steatorrhea, back pain, nausea or fatigue. Jaundice is encountered when the tumour is located near to the bile duct. It is noteworthy that a PC may also cause acute health problems such as pancreatitis, cholecystitis and gastrointestinal bleeding. (Stapley et al. 2012; Hippisley-Cox & Coupland 2012; Hidalgo et al. 2010; Kimura et al. 2015) Kimura et al. (2015) reported that 6.8% of patients were diagnosed with PC in two years after an acute pancreatitis.

2.1.5.2 Imaging of pancreatic cancer

Imaging is essential for the diagnosis. Contrast-enhanced, multiphase computed tomography (CE-CT) is considered as the gold standard. Its availability overcomes availability of MRI and it feasibly gives information on the local spreading of a tumour and possible metastases. A PDAC is typically seen in CE-CT as a hypodense lesion or sometimes as an unspecific bulge, abrupt cut-off of a bile duct, or typically as s double-duct sign where both bile and pancreatic ducts are enlarged (Figure 2). (Best et al. 2017)

Multiphasial (arterial, pancreatic and hepatic) imaging protocol is crucial for proper CE-CT. The pancreas itself is a highly vascularised organ which is surrounded by large arteries and veins and a vascular liver. The arterial phase is required in the evaluation of vessel involvement of PC. The ability to detect vessel involvement varies from 49-92% depending on the vascular invasion criteria (Wong et al. 2008). A proper evaluation of the surrounding vessels is important when a decision on operability has to be made. The pancreatic phase gives information on the pancreatic parenchyma. It is noteworthy that a small proportion of PDAC is isodense to pancreatic parenchyma and only secondary features, such as abrupt cut-off of the pancreatic duct, distal bile duct stricture or abnormal bulge, can been seen in CE-CT. The hepatic phase is required for

proper detection of possible liver metastasis. The sensitivity of CE-CT for detecting PDAC has been reported to be 89-97%. (Best et al. 2017) There have been concerns about the ability of CT to detect small lesions (<2 cm) (Bronstein et al. 2004), but multiphasial imaging protocol has overcome them. A recent comparison of EUS and CE-CT (Du et al. 2018) reported a parallel mass detection rate for both of 88%.

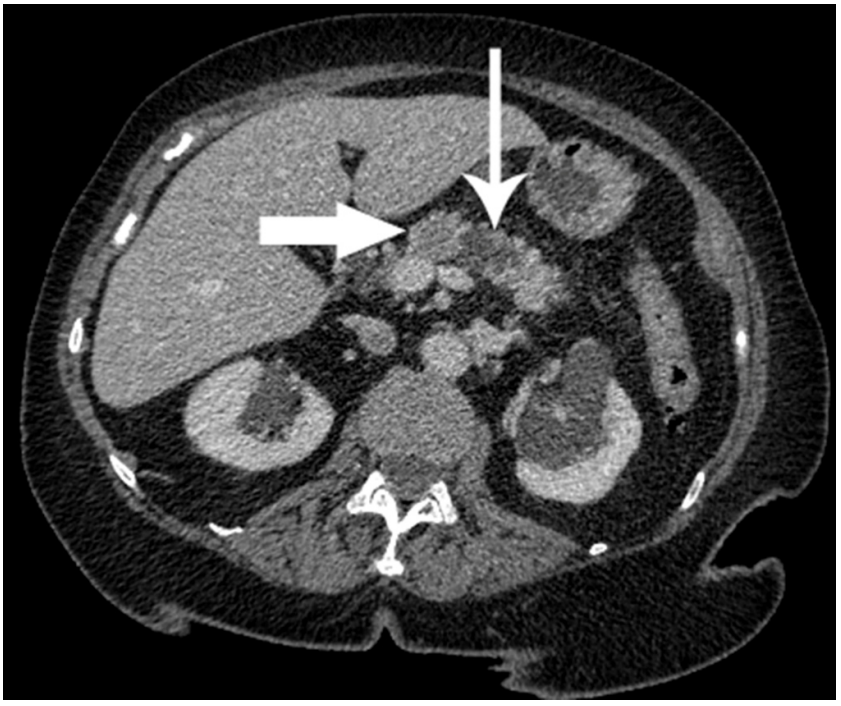


Figure 2. A CE-CT scan of a patient with PDAC. A hypodense, dark bulk in the body of the pancreas (thick arrow) and a dilated pancreatic duct (thin arrow). Courtesy of Dos. Irina Rinta-Kiikka, Tampere University Hospital.

Magnetic resonance imaging (MRI) with contrast medium is used in selective cases in primary diagnostics, but the limited availability decreases its popularity. An informative MRI can also be performed without contrast medium. This is an important property for patients with impaired kidney function. Compared with CE-CT, the particular advantage of MRI is the higher resolution. This is beneficial in the evaluation of ducts and their connections and in the evaluation of small tumours. Its sensitivity and specificity are reportedly 0.69-0.80 and 0.81-0.93 respectively for differentiating cancerous from precancerous lesions. (Best et al. 2017)

Abdominal ultrasonography (AUS) can detect masses of the head of the pancreas, but it is radiologist-dependent and cannot exclude the possibility of PC. The sensitivity of AUS detecting PDAC has been circa 76% (Bipat et al. 2005). The benefit of AUS is its ability to reveal biliary stasis, which can lead to more precise imaging. In recent years there has been a growing interest in endoscopic ultrasonography (EUS). The sensitivity of EUS has been reported to be low, 0.53, but specificity is high, 0.95 (Best et al. 2017). EUS can be combined with a fine needle biopsy (EUS-FNA). The specificity and sensitivity of EUS and EUS-FNA are approximately at the same level, 1.00-0.94 for specificity and 0.79-0.47 for sensitivity for differentiating cancerous or precancerous from benign lesions or distinguishing between cancerous and precancerous lesions (Best et al. 2017; Cazacu et al. 2018). Both EUS methods are endoscopist-dependent and an effective learning curve requires a sufficient case volume. The problems of availability have challenged its routine use in Finland.

PET-TT coupled with fluorodeoxy-glucose marker may offer answers if other imaging modalities are unsuccessful. It is especially useful among patients with chronic pancreatitis. Its sensitivity has been reported to be 0.93 and specificity 0.90 (Santosh et al. 2012). It has not been recommended in staging of PC (Conroy et al. 2016).

Endoscopic retrograde cholangiography (ERCP) is not routinely used in primary diagnostics apart from among patients with a biliary obstruction requiring drainage (Conroy et al. 2016). ERCP makes it possible to take cytometric or tissue samples. Cytometric brush samples have suffered from variable sensitivity (Burnett & Chokshi 2013), but a study by Sethi et al. (2016) demonstrated that the quality can be stabilized with guidance and education, resulting in a sensitivity of 54.7% and specificity of 100%. In 2006 a novel choledocoscope Spyglass (Boston Scientific Corporation, Natick, Massachusetts, United States of America) was presented which offers direct visualization of choledoccal lesions and ease of diagnostics (Woo et al. 2014; Arnelo et al. 2014). Sensitivity of 100% and specificity of 90% has been reported for Spyglass (Woo et al. 2014).

2.1.5.3 Carbohydrate 19-9 antigen (CA19-9)

There are no laboratory tests specific to PC or PDAC. The most informative biomarker is the CA19-9 (carbohydrate 19-9) antigen which is measured from blood. Its sensitivity for PC is 80% and specificity 90% (Steinberg et al. 1990). The

antigen is a sialylated Lewis a blood group antigen which is defined by the monoclonal antibody 1116 NS 19-9.

Elevated CA19-9 levels are associated with more advanced disease stage, unresectability and inferior prognosis (Martin et al. 2012; Bauer et al 2013; van Veldhuisen et al. 2018). However, CA19-9 can be falsely positive in other biliary stasis circumstances than PC. In addition 7-10% of the population are Lewis a or b negative and do not express CA19-9 (Ducreaux et al 2015) and among 15-25% of PC patients CA19-9 levels stay normal despite PC (Tempero et al. 1987).

2.1.6 TNM and stage classifications

The American Joint Committee on Cancer (AJCC) has developed a cancer classification to help to categorise cancers in relation to prognosis. The preoperative stage and the tumour/node/metastasis (TNM) -classification of PC are based on imaging modalities, most commonly on CE-CT.

The TNM classification and staging system published in 2010 (Edge et al. 2010) was recently renewed. The older 7th version categorised pancreatic tumours according to tumour size and peripancreatic tissue involvement, nodal status and distant metastasis. Because of concerns of inconsistency in interpreting the definitions of the 7th version and of new information on the effect of multiple positive nodes on prognosis, a new proposal for an 8th (Allen et al. 2017) version was published in 2017. The key points of the classifications, such as tumour size and vessel involvement, remained unchanged. The term "beyond the pancreas" was removed and a third N-status (N2) added for patients having more than three positive nodes. Details of the classifications are in Table 3.

After defining the TNM-classification of the tumour, the stage can be determined as shown in Table 4. In the 7th version, T1-3 tumours with a nodal involvement were assigned to the stage group (IIB). In the 8th version, tumours with more than three positive nodes where assigned to the stage group III, demonstrating the worse prognosis of tumours with an advanced nodal involvement.

In addition to the TNM-based stage classification, PC can be staged according to surgical staging criteria. The surgical staging categorises patients into three groups: resectable, borderline resectable or locally advanced and metastatic. At the time of diagnosis circa 50% of patients have a metastatic disease and only 10-20% are amenable to resection. Of borderline resectable patients up to 30% end up in

resections after neoadjuvant therapy results. (Evans et al. 2010; Varadhachary et al. 2006).

Table 3. The 7th and 8th Editions of the TNM-classification of PC (Edge et al. 2010; Allen et al. 2017)

Primary tumour (T)	7th edition	8th edition
X	Primary tumour cannot be assessed	
0	No evidence of primary tumour	
	Carcinoma in situ	
1	Tumour limited to the pancreas, ≤2 cm in greatest dimension	Maximum tumour diameter ≤2 cm
2	Tumour limited to the pancreas, >2 cm in greatest dimension	Maximum tumour diameter >2≤4 cm
3	Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery	Maximum tumour diameter >4 cm
4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)
Regional lymph nodes (N)		
X	Regional lymph nodes cannot be assessed	
0	No regional lymph node metastasis	No regional lymph node metastasis
1	Regional lymph node metastasis	Metastasis in 1-3 regional lymph nodes
2	-	Metastasis in ≥ 4 regional lymph nodes
Distant metastasis (M)		
0	No distant metastasis	No distant metastasis
1	Distant metastasis	Distant metastasis

Table 4. Stage classification of PC (Edge et al. 2010; Allen et al. 2017).*row added in the 8th Edition

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1/T2/T3	N1	M0
III	T4	Any N	M0
	Any T*	N2*	M0*
IV	Any T	Any N	M1

2.1.7 Overall survival

PC is recognized as a disease with a poor prognosis. Five-year overall survival has been reported to be as low as < 5%. The prognosis is heavily dependent on stage at the diagnosis and on the histopathological diagnosis of the tumour. (Ducreux et al. 2015) Median survival for PC has been reported to be circa 13 months for resected patients and 4 months for unresected patients (Bilimoria et al. 2007b). Coopermann et al. (2018) reported an overall five-year survival of 21% and 20-year survival of 4% for patients who had had a pancreatic resection. These studies comprised all PCs regardless of the histopathological diagnosis which hampers the generalizability of the results.

The majority of PC comprises PDAC and the five-year survival in the series analysed after revision of the histopathologic diagnoses has been extremely low 0.1 - 0.2% (Carpelan-Holmstrom et al. 2005, Jorgensen et al. 2008). The prognosis for patients undergoing surgery has been reported to be better: five-year survival has been at the level of 10.8-22% and even five-year survival of even 49% has been reported among resected patients with a T1-2N0 tumour (R0-resection) (Birkmeyer et al. 2007; Dusch et al. 2014; Paniccia et al. 2015; Seppänen et al. 2016). Reported median survival has varied between 2.5 and 38 months, one-year survival between 8.8% and 82% and three-year survival between 1.4% and 51.1% depending on the stage as shown in Table 5 (Bilimoria et al. 2007b; Saka et al. 2016).

Table 5. Median survival (months) and 1- and 3-year survival among PDAC patients (*Saka et al. 2016, **Bilimoria et al. 2007).

Stage	Median survival (months)	1 -year survival (%)	3- year survival (%)
IA (T1N0)*	38	82	51.1
IB (T2N0)*	18	72	28
IIA (T3N0)*	12.5	52	10
IIB (T1N1-2)*	26	75	40
IIB (T2N1-2)*	17.5	67	26
IIB (T3N1-2)*	13	51	20
III**	7.7	30.2	4.8
IV**	2.5	8.8	1.4

2.2 Treatment strategies in pancreatic cancer

2.2.1 Surgery

2.2.1.1 Resections

Pancreatic resection is currently essential to achieve lenghtened survival among PC patients. The type of procedure is selected according to the site, size and vessel involvement of the tumour. The aim of the procedure is to achieve total tumour clearance (R0), thus only patients who are candidates for a R0-resection are selected for surgery. The pre-operative evaluation is performed with imaging, typically with CT. It has been reported that only 20% of the patients have a resectable disease. (Ducreux et al. 2015)

Partial pancreatoduodenectomy (PD, classical-Whipple-procedure) was originally described by Kausch (1912) and Whipple et al. (1935) at the beginning of the 20th century. In the Whipple procedure the head of the pancreas, duodenum, gallbladder and the extrahepatic bile ducts are resected. If the gastric antrum is not removed, the procedure is called pylorus preserving pancreatoduodenectomy which was at first presented by Traverso et al. (1980).

The remaining pancreas is connected with the jejunum, forming a pancreatico-jejunal-anastomosis. The proximal bile duct is connected with the jejunum to form hepatico-jejunal anastomosis. The remaining ventricle is connected with the

jejunum to form gastro-jejunostomy. In addition to these anastomoses, one additional entero-entero-anastomosis may be created between the jejunal loops (Figure 3A). This fairly complex reconstruction is required to restore normal digestive function. A recent Cochrane review (Huttner et al. 2016) based on randomized controlled studies summarised the comparison of the pylorus preserving method and the classical Whipple. The review concluded that operating time, intraoperative blood loss and need for blood transfusions were lower in the pylorus-preserving group and less delayed gastric emptying was present in the classical Whipple group. However, no significant differences were found in mortality, morbidity or in survival and no overall superiority could be establised.

For tumours in the distal part of the pancreas, the head of the pancreas, the duodenum as well as the biliary tree remain untouched, and the tail or tail and body are removed. Distal pancreatectomy (DP, Figure 3B) often includes splenectomy, especially when performed for malignancy. In selective cases central pancreatectomy (Figure 3D) can also be performed for lesions in the neck of the pancreas. In central pancreatectomy more pancreatic tissue can be saved, but the risk of grade B or C pancreatic fistula is reportedly higher (60%) than in PD (27%) or in DP (23%) (Pulvirenti et al. 2017). It is recommended only for experienced surgeons. (Bassi 2007; Letton & Wilson 1959).

To maintain as normal endo- and excocrine functions as possible, total pancreatectomies (Figure 3C) are avoided whenever possible. Nevertheless, tumour clearance may sometimes result in total pancreatectomy. These patients need lifelong supplements of insulin and pancreatic enzymes.

During a PD or DP operation, the transsection line of pancreas is usually sent to a pathologist to ensure that there is a clear margin. The surgical margins of the PD specimen itself are recommended to be coloured with tissue ink to facilitate the pathological evaluation of the tumour topography and margins. If tumour tissue on the margins is seen macroscopically, an undesired R2 resection has been achieved. If the clear zone is <1 mm, a R1-resection has been achieved. If the clear zone is ≥1 mm, the desired R0-resection has been accomplished. (Conroy et al. 2016; Ducreux et al. 2015) See also Chapter 2.3.4 Resection success related factors later in this thesis.

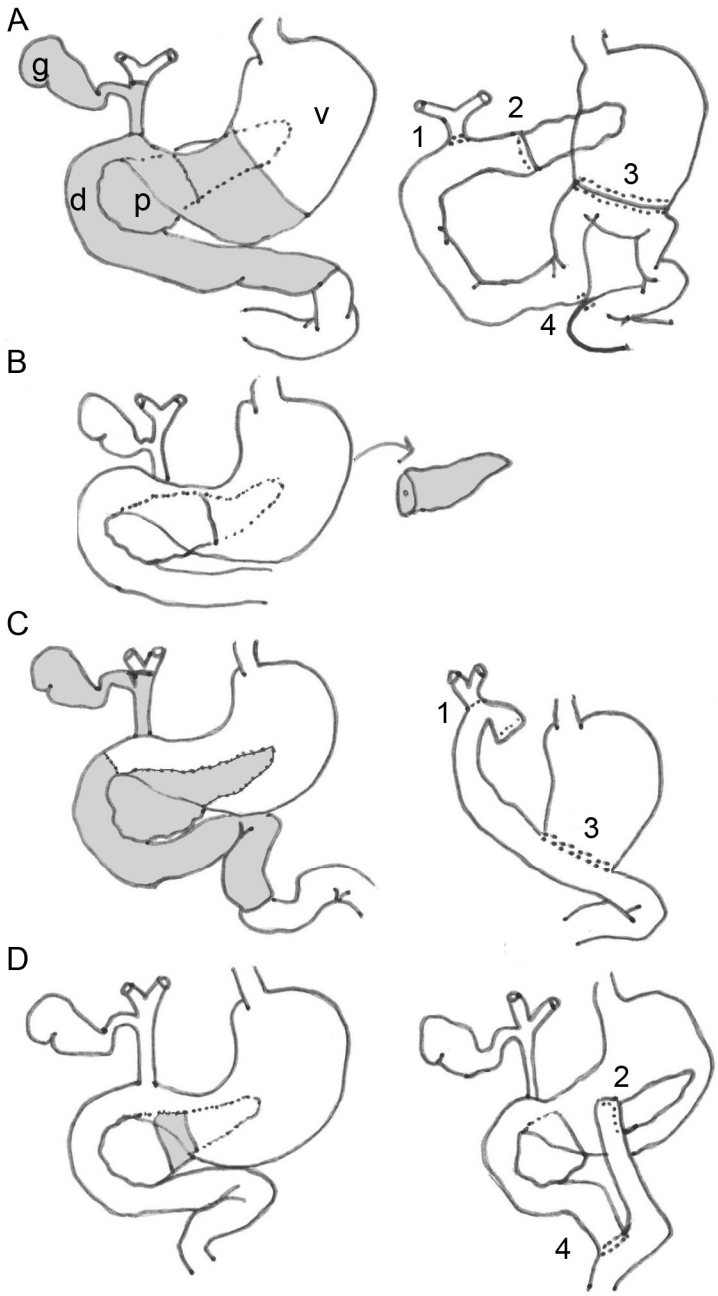


Figure 3. Pancreatic resections and reconstructions. A) pancreatoduodenectomy, B) distal pancreatectomy, C) total pancreatectomy and D) central pancreatectomy. d=duodenum, g=gallbladder, p=pancreas, v=ventricle. Resected parts in gray, anastomosis marked with numbers: 1=hepaticojejunostomy, 2=pancreaticojejunostomy, 3=gastrojejunostomy, 4=enteroenteroanastomosis,

2.2.1.2 Lymphadenectomy

In PD, lymphadenectomy is recommended to cover to lymph nodes in the following stations: suprapyloric (5), infrapyloric (6), anteriosuperior group along the common hepatic artery (8a), along the bile duct and around the cystic duct (12b and c), on the posterior aspect (13a) of the superior and the inferior portion of the head of the pancreas (13b), the anterior surface of the superior portion (17a) and on the inferior portion of the head (17b) and on the right lateral side of superior mesenteric artery (SMA) (14a and b). In distal resection, the lymphoid tissue at the splenic hilum (10) and along the splenic artery (11) and inferior margin of pancreas (18) are included in standard lymphadenectomy (Figure 4). A standard lymphadenectomy should comprise removal of a minimum of 15 nodes. (Ducreux et al. 2015)

In extended lymphadenectomy, nodes along the abdominal aorta to the inferior mesentery artery and nodes around the coeliac trunk and SMA are also removed. This has been reported to lead to excess post-operative morbidity without improved survival, and is, thus, not recommended (Conroy et al. 2016).

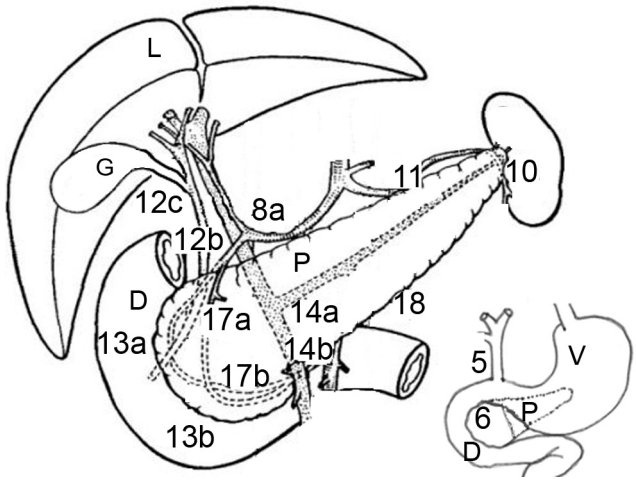


Figure 4. Lymph node stations of pancreas. P= pancreas, L=liver, G= gallbladder, V=ventricle, D=duodenum. Adjusted from the image of Sun et al. (Sun, Leong et al. 2010), with license CC-BY 2.0.

2.2.1.3 Vascular resections

PC easily infiltrates the surrounding vessels: the SMA, the portal vein (PV) and the inferior mesenteric vein (IMV). Approximately 30-40% of patients have borderline or locally advanced disease at the time of diagnosis (Ducreaux et al. 2015). Progression to the coeliac axis or SMA is considered to be unresectable, but a resection of PV/IMV may be technically possible. The resectability of the tumour is typically evaluated with CE-CT. However, it has been reported that EUS may give a better view of vascular invasion than CE-CT (sensitivity 86-95% vs. 58-93% respectively). (Nawaz et al. 2013)

The venal resection can be reconstructed with end-to-end anastomosis, venorraphy/patch or by interposition of a graft. The safety and effect on survival of venal resection is controversial. A meta-analysis by Giovinazzi et al. (2016) reported an increased risk of mortality, more R1/R2-resections, worse long-term-survival and more re-operations and bleeding after a venal resection. The risks for prognosis and costs were also documented by Kantor et al. (2016). A cohort study by Elberm et al. (2015), in contrast, found comparable results for mortality and survival among patients with a T3-disease undergoing venal resection, compared to a standard PD. A study by Del Chiaro et al. (2015) reported promising results after end-to-end anastomosis of the PV and also after the PV in and artery resection. Their series reported 0% mortality and morbidity of 35%, which was comparable with a standard PD. During their follow-up of 22 months no vascular resection related complications occurred.

The most recent guidelines recommend neoadjuvant therapy in venal infiltration (Ducreux et al. 2015; Tempero et al. 2017; Khorana et al. 2017). The treatment guidelines for resectability are presented in Chapter 2.2.5 Deciding on treatment strategy later in this thesis.

2.2.1.4 Laparoscopic resections

Gagner and Pomp (1994) presented laparoscopic PD in 1994 and since then the laparoscopic method has gradually increased popularity. In general, the benefits of laparoscopic techniques have included shorter hospital stay and decreased blood loss during the operation, and the same has been reported of laparoscopic PDs. Compared to other laparoscopic surgery, laparoscopic PD is an extremely challenging operation, and increased post-operative mortality and complication rate as well as operation time and readmissions have been reported (de Rooji et al.

2016a). De Rooji et al. have studied the safety of a specific training program of laparoscopic PD (de Rooji et al. 2017, de Rooji et al 2016b). Despite the promising results in the studies, high mortality rates led to a premature termination of their newest study, LEOPARD-2 trial, comparing open and laparoscopic PD (Abstract, European Pancreas Club meeting 2018 de Rooij et al. 2018).

Cushieri (1994) introduced laparoscopic distal resection of the pancreas in 1994. A recent Cochrane review (Riviere et al. 2016) suggested that a laparoscopic distal resection may result in lower short-term mortality (5% vs. 10%), but in more serious adverse events (8.8% vs. 5.1%) and in an increased number of pancreatic fistula (grade B or C) (7.7% vs. 6.6%). After the review, a report on a pan-European observational study (the DIPLOMA study) (van Hilst et al. 2017) was published. The study reported problems with adequate lymph node retrieval and in the resection of Gerota's fascia in a minimally invasive setting.

All these technical issues have decreased the popularity of laparoscopic PC surgery. In Finland no series on laparoscopic distal resections have been published.

2.2.1.5 Complications after pancreatic resections

Pancreatic surgery is known for high post-operative morbidity. Even HVCs report post-operative morbidity rates of 30-50% and for minor complications 23.1% (Nimptsch et al. 2016). Especially pancreatic resection related complications are leakage of pancreatojejunostomy (POPF), postpancreatectomy haemorrhage (PPH) and delayed gastric emptying (DGE). The International Study Group of Pancreatic Surgery (ISGPS) has published definitions to standardise these complications to facilitate comparison (Bassi et al. 2017; Wente et al. 2007a; Wente et al. 2007b).

The rate of reported POPF has been dependent on the definitions. The earlier definitions of POPF graded the fistulas into three groups A, B and C, but in 2017 the ISGPS published a new version. The new version stated that only pancreatic fistulas which have led to changes in post-operative management are clinically relevant fistulas and these are graded B or C. The earlier grade A is now considered as a biochemical leak, not as a fistula. (Bassi et al. 2017) According to the 2017 definitions, the incidence of POPF is at the level of 20-30% in PDs and DPs. POPF is associated with increased mortality and morbidity. (Pulvirenti et al. 2017)

The incidence of PPHs is up to 8-20% and explains 3-39% of post-operative mortality. DGE is a typical condition after pancreatodudenectomy and its

published incidence has varied from 5 to 60%. (Wente et al. 2007a; Wente et al. 2007b).

2.2.1.6 Classification of complications

Martin et al. (2002) found that the reporting policies of postoperative complications suffer from inconsistency. This hampers comparison between interventions, hospitals and treatment strategies. Clavien and Dindo published a detailed classification for overall surgical complications in 2004 (Dindo et al. 2004). PubMed archive yielded the 1,638 citations to the original article by Clavien and Dindo demonstrating its wide use in the field of surgery. According to this classification, any deviation from the normal post-operative period is defined as grade I. Deviations needing antibiotics, total parenteral nutrition or other medication than pain or nausea comprise grade II. If complications require any procedures with or without anaesthesia they are categorised to grade III. Grade IV complications are life-threatening requiring intensive care. If a complication results in the death of a patient it is defined as a grade V complication.

2.2.2 Oncologic therapy

2.2.2.1 Neoadjuvant therapy

Only 10-20% of PDAC patients have a resectable disease at diagnosis and circa 30% of patients have a borderline resectable disease (Hayasaki et al. 2018). In a meta-analysis by Gillen et al (2010) the resection rate was 32% after neoadjuvant therapy and in a meta-analysis comprising studies using FOLFIRINOX (a composite of folinic acid, fluoro-uracil, irinotecan and oxaplatin) the resection rate was 69% (Gillen et al. 2010). The ESMO guidelines (Ducreaux et al. 2015) suggest that the best option so far is to use gemcitabine or FOLFIRINOX chemotherapy and to continue the treatment with chemoradiation. The latest NCCN guidelines (Tempero et al. 2017) added that gemcitabine+albumin-bound paclitaxel ± chemoradiation is also an option and that gemcitabine +cisplatin +chemoradiation may be iniated among patients with BRCA1/2 mutation.

2.2.2.2 Adjuvant therapy

Several studies have reported survival advantages after postoperative chemotherapy (ESPAC-1 (Neoptolemos et al. 2001), CONKO-001 (Oettle et al. 2007), ESPAC-3 (Neoptolemos et al. 2010), a meta-analysis by Liao et al. (2013)). The ESPAC-4 trial (Neoptolemos et al. 2017) showed that a combination of gemcitabine and cabecitabine results in better outcomes than gemcitabine alone. The impact of combination therapies such as FOLFIRINOX or gemcitabine-nab-paclitaxel is under evaluation in phase III trials (PRODIGE 24/NCIC CTG PA.6, APACT). In future, studies concerning immunologic agents as a part of adjuvant therapy or as solo may also change the protocols.

Regarding adjuvant chemoradiation the study results have not been encouraging. The ESPAC-1 trial (Neoptolemos et al. 2001) reported shorter survival among patients who had received chemoradiation. The EORTC trial 49891 (Smeenk et al. 2007) studied the effect of chemoradiation and found no significant difference compared with simple surveillance. In addition, the meta-analysis by Liao et al. (2013) comprising six randomised controlled studies concluded that chemoradiation has not been proven effective. However, an American study by Rutter et al. (2015) reported improved survival among patients who had received chemoradiation in addition to chemotherapy. The study suggested that the chemoradiation should be started 1-3 months after the initiation of chemotherapy. These results gave rise to further studies (RTOG 0848 and EORTC 40084-22084) the results of which have not yet been published (Conroy et al. 2016).

2.2.2.3 Palliative oncologic therapy

Patients with a locally advanced disease may be offered chemotherapy. Factors influencing the treatment strategy are the patient's performance status, the estimated life-expectancy and bile stasis. FOLFIRINOX or gemcitabine-nab-paclitaxel are the preferred options if performance status is good and the bilirubin value is normal. If bilirubin values are above normal (>26 μmol/l) and performance status is poor (EGOC<2) gemcitabine alone can be considered after relieving of bile stasis. Second-line chemotherapy can be considered in selected cases, especially if gemcitabine-resistance appears during treatment. Chemoradiation may also be beneficial to a selective group of patients (radiotherapy plus capecitabine). Among patients with metastatic disease the

benefits of oncologic therapy on overall quality of life has to be carefully assessed. (Ducreux et al. 2015; Tempero et al. 2017)

2.2.2.4 Immunotherapy

Although traditional chemotherapy has a beneficial effect on survival, more effective therapy modalities for patients are under research. The state of knowledge of immune-oncology and bioinformatics has improved in recent years. Immunological treatment is based on the ability of T-cells to recognise and attack tumour cells. The process is complex and the characteristics vary between patients. The start of an immunologic cascade requires antigens, and the ability of T-cells to recognize them and activate more T-cells. Among PDAC patients, the tumour microenvironment surrounding the cancer is highly immunosuppressive. (Zhang et al. 2018)

Options for immunotherapy include decreasing the immunosuppression of the tumour microenvironment (Beatty et al. 2013 or to increasing the chemosensitivity of PDAC cells. (Zhang et al. 2018) Increase of immunogenicity and immunological response of the cancer cells via tumour vaccines has also been studied (Laheru et al. 2008; Le et al. 2013)

In addition to these attempts, promising results have been reported from studies on DNA repair mechanisms (Michels et al. 2014). The blockage of poly-adenosine-disphoste ribose polymerase (PARP) combined with immune checkpoint inhibitors increased survival among BRCA1 patients with ovarian tumours. Clinical trials among PDAC patients are ongoing. (Zhang et al. 2018)

2.2.3 Symptom relief

2.2.3.1 Biliary stasis

Approximately 60% of PCs lay in the head of the pancreas, which can cause a bile duct obstruction. High bilirubin values are toxic and cause pruritus, fatigue and fat malabsorption. Lowering the bilirubin values is necessary prior to chemotherapy, but it also improves quality of life. When the bilirubin level exceeds 250-300

μmol/L, drainage is indicated (Conroy et al 2016). It has been debated how to approach high bilirubin values among patients selected for surgery. Increased post-operative morbidity among patients with pre-operative biliary stent has been reported. The current recommendation is to use preoperative biliary drainage only in symptomatic patients or if surgery needs to be postponed. (Conroy et al. 2016)

Stent placement in the bile duct via ERCP is the most desired technique to relieve biliary obstruction. Depending on the life expectancy and following treatment, either a plastic or a metallic stent can be used. If no resections are planned, a metallic stent is selected for palliation. The technical success rate is >90% for malignant strictures and risk of complications is under 5%. Mortality rate of 0.2-1% has been reported after ERCP which has to be taken into consideration among patients with a poor performance status. (Stark & Hines 2015; Siiki et al. 2012)

If bile drainage does not succeed via ERCP, percutaneous transhepatic biliary drainage (PTBD) can be attempted. Sometimes a combined technique is the solution. In the rendez-vous technique a percutaneously placed transhepatic drain is encountered in duodenoscopy and an internal ERCP-stent is placed using the other as a guidewire. If the obstruction cannot be passed with PTBD, excess bile can flow via external PTBD into a plastic bag around patient's waist. (Stark & Hines 2015)

The mini-invasive alternatives for relieving biliary stasis have resulted in decreased need for palliative surgery. Hepatico-jejunostomy is an alternative for patients who have been deemed inoperable only during the resection-aimed laparotomy. (Perone et al. 2016)

2.2.3.2 Pain medication

Pancreas lies in the vicinity of the celiac plexus, which is formed by the splanchnic nerves. The splanchnic plexus carries visceral information from the pancreas and senses pain. It has been reported that 75% of patients suffer from pain at the time of diagnosis of PC. (Perone et al. 2016)

Most commonly the pain can be relieved by pharmacological means, such as peroral or transdermal opioids. Opioids may cause side effects such as constipation, sedation, pruritus, nausea, which require additional medical treatment. (Carter et al. 2014)

A celiac plexus blockage can be used on selected patients whose pain or side effects of the pain treatment are not controlled by pharmacological means. A

Cochrane meta-analysis (Arcidiacono et al. 2011) based on six randomized controlled trials estimated that the celiac plexus block can result in reduction of pain during the first eight weeks after the procedure. In addition, the need for opioids and the amount of side effects is reduced.

2.2.3.3 Gastric outlet obstruction

The spread and growth of the cancer in the pancreas may result in obstruction of the upper parts of gastrointestinal tract. It has been reported that 10-25% patients suffer from symptoms (nausea, vomiting, malnutrition, electrolyte imbalance) of gastric outlet obstruction. The obstruction can be relieved either endoscopically or surgically. Measures are recommended only for symptomatic patients and prophylactic procedures can be considered for patients who are confirmed to be inoperable peroperatively. (Perone et al. 2016)

Among patients with a duodenal stent, complications occur in 20% of cases. Typical early complications include perforation, gastrointestinal haemorrhage, aspiration pneumonia and compression of the bile duct. Late complications include stent migration and stent failure. (Stark & Hines 2015) However, gastroenterostomy performed either laparoscopically or openly is not appropriate for every patient. Surgery is recommended if the life expectancy is at least two months and the patients's performance status is suitable for anaesthesia. (Perone et al. 2016) The SUSTENT multicentre randomized controlled trial (Jeurnink et al. 2010) reported that the patients tolerated peroral intake sooner after endoscopic therapy, but the overall oral intake was better in the surgical group, which emphasizes the importance of patient selection. A Cochrane review recommends palliative gastrojejunostomy only for patients undergoing explorative laparoscopy. (Gurusamy et al. 2013)

2.2.3.4 Treatment of pancreatic insufficiency

The pancreas has a key role in the digestion of nutrition. It excretes digestive enzymes and hormones essential in fat, protein and carbohydrate absorption. When cancerous tissue and gland atrophy replace healthy parenchyma, absorption functions are impaired. It has been estimated that 65% of patients with PC suffer from fat malabsorption and 50% of protein malabsorption. The malabsorption

causes appetite loss, malnutrition, hypercatabolism, bloating, steatorrhea resulting in cachexia and weight loss. (Zolghadri et al. 2018)

Patients can be treated with pancreatic enzyme replacement therapy. In a randomized controlled trial (Bruno et al. 1998) the intake of enzyme replacement increased body weight by 1.2% in eight weeks. Dietary intake of pancreatic enzymes is considered safe. Conversely a recently published mice model (Zolghadri et al. 2018) reported tumour growth in terminal stage cancer. Nevertheless, the study summed up a beneficial effect of nutritional supplements on short-term health and median survival.

2.2.4 Deciding on treatment strategy

2.2.4.1 Stage

The decision on treatment strategy of PC should always be made by a multidisciplinary team of at least radiologists, surgeons, pathologists and oncologists. However, a review by Fogel et al. (Fogel et al. 2017), reported that 15% of patients are diagnosed with a benign disease after PD. In addition, a recent Cochrane systematic review (Tamburrino et al. 2016), points out that only 60% of PC patients estimated as having a resectable tumour do indeed have such a tumour in laparotomy. The systematic review was based on studies from the beginning of the 21th century, which probably explains the relatively poor result.

Nevertheless, some 50% of PC patients already have metastatic disease at the time of diagnosis (Ducreaux et al. 2015, Tempero et al. 2017). Their treatment strategy is palliative and personalized depending on the performance status and expected survival. The National Comprehensive Cancer Network Guidelines (NCCN; Tempero, et al. 2017) and The American Society of Clinical Oncology (ASCO; Khorana et al. 2017) recommend only palliative treatment for patients with metastatic disease. The European Society of Medical Oncology (ESMO; Ducreaux et al. 2015) recommends offering palliative oncologic therapy to patients with good performance status and low bilirubin values. For those with very short life expectancy only symptom relief is recommended.

Among 30-40% of patients the tumour has spread to the surrounding tissues and vessels. The NCCN, ASCO and ESMO guidelines (Tempero et al 2017, Khorana et al. 2017, Ducreux et al. 2015; Table 6) recommend preoperative chemotherapy for a borderline resectable disease and enrolling patients in clinical

trials. However, the ASCO and NCCN guidelines present a different definition for a borderline disease: ASCO states that any contact with vessels belongs to the group "borderline resectable" and NCCN has detailed criteria for "borderline" resectable and unresectable. The ESMO guidelines do not define "borderline disease". All in all, the final decision on resectability can be made only after oncologic therapy.

Approximately 10-20% of patients with PC have a primary resectable disease. The NCCN guidelines recommend primary resection only if there are no arterial contacts and or the venous contact is under 180°. The ASCO guidelines recommend considering pre-operative oncologic treatment also for resectable disease. In addition to anatomical findings, the ASCO guidelines take into consideration CA19-9-values, imaging results and the patient's performance status.

Table 6. NCCN (Tempero et al. 2017) and ASCO (Khorana et al. 2017) surgical criteria of resectability for non-metastatic disease

Classification	**NCCN criteria**		**ASCO criteria**		
	Anatomical criteria		Anatomical criteria		Additional criteria
	arterial	venous	arterial	venous	
Resectable	No contact with CA, SMA *or* CHA	No contact with SMV/PV *or* ≤180º contact without vein contour irregularity	No contact	No contact	No evidence of disseminated disease Performance status appropriate for major surgery
Borderline resectable	≤180º contact with SMA/CA *or* contact with CHA *or* >180º contact with CA if resection is safe *or* contact with variant arterial anatomy	>180º contact with SMV/PV *or* ≤180º contact with SMV/PV with contour irregularity *or* contact with IVC	Any contact	Any contact	Findings suspicious for disseminated disease (CA19-9 or imaging findings) Marginal performance status
Unresectable	>180º contact with SMA/CA *or* contact with first jejunal branch of SMA *or* with CA and aorta	Contact with proximal draining jejunal branch of SMV *or* unreconstuctable SMV/PV			

NCCN=National Comprehensive Cancer Network, ASCO= American Society of Cancer Oncologists, PV=portal vein, CA=celiac artery, CHA= common hepatic artery, SMA= superior mesenteric artery, SMV=superior mesenteric vein

2.2.4.2 Patient related factors

PC is a disease of the elderly, when co-morbidities are common or at least probable. A patient's eligibility for pancreatic resection requires sufficient

cardiorespiratory and kidney function. A patient's eligibility for vascular resections has to be taken into consideration preoperatively so the best decisions can be made at the time of the operation.

In addition, the recommended treatment may result in multiple side-effects or complications or impair the quality of life. A recent study by Laitinen et al. (2017) studied the effect of PD on quality of life after PD among PDAC patients. Of these patients 63% reported that quality of life remained the same or improved after PD. Basically, the more advanced the disease diagnosed, the more the patient's own preferences, even to the point of having no treatment at all, have to be taken into consideration.

2.3 Factors associated with prognosis after pancreatic resections

2.3.1 Patient related factors

A recent Japanese study (Aoki et al. 2017) comprising 17,564 patients undergoing PD distinguished factors associated with serious complications (C-D grades IV and V). According to the study preoperative factors predicting severe complications comprised sex, age, co-morbidities, BMI> 25 kg/m^2, activity status in daily living, weight loss >10%, ASA class III-V, smoking status, respiratory distress, cerebrovascular disease within 30 days before surgery, white blood cell >0,11^10^9/l, platelet count <80^10^9/l, INR >1.25, serum albumin level <25 g/l, serum creatinine level >177 μmol/l, serum sodium level >146 mmol/l and serum CRP level >0.01 g/l.

Age, overall performance status, smoking status and comorbidities, such as diabetes, have all been associated with short- and long-term prognosis of the patient (Howard et al. 2006, Dusch et al. 2014, Nimptsch et al. 2016, Kleeff et al. 2016). A multivariate analysis by Salmiheimo et al. (Salmiheimo et al. 2016) showed that elevated preoperative CRP (>0.005 g/l), hypoalbuminea (<36 g/l) and elevated tumour markers (CEA and CA19-9) were associated with worse survival after pancreatic resection among PDAC patients.

2.3.2 Perioperative factors

Drainage of biliary stasis is associated with worsened outcome and survival after surgery (Dusch et al. 2014, Macias et al. 2018). Recent EORTC consensus guidelines (Lutz et al. 2017) recommend avoiding drainage if the tumour is to be resected within a week and otherwise only among patients with cholangitis or decidedly elevated bilirubin values. A review by Conroy et al. (2016) suggests that only bilirubin values ≥300 μmol/l require drainage routinely. Dusch et al. (2014) and Weber et al. (2014) stated that perioperive blood loss is associated with worse prognosis.

2.3.3 Surgical complications

A recent nationwide German study (Nimptsch et al. 2016) documented elevated mortality along with an increase in complications. They reported the highest in-hospital mortality rates among patients with sepsis (43.6%), acute renal failure (55.6%) and prolonged mechanical ventilation (45.3%). Elberm et al. (2015) showed that re-laparotomy is an independent risk factor for poorer survival in multivariate analysis. Weber et al. (2014) reported that postoperative complications impaired short-term survival, but the single-centre study by Dusch et al. (2014) found no association with five-year survival.

2.3.4 Resection success related factors

A standardised pathological report is essential for an accurate survival analysis. Several factors analysed under the pathologist's microscope have been associated with survival, such as tumour size, location within the pancreas, surgical margin status, histologic grade and nodal involvement (Howard et al. 2006; Dusch et al. 2014; Paniccia et al. 2015; Winter et al. 2006; Chen et al. 2010; Strobel et al. 2017). The effect of vascular and perineural invasion has been reported to be controversial (Dusch et al. 2014; Chen et al. 2010; Konstantinidis et al. 2013). Mierke et al. (2016) reported that invasion to PV/SMV is an independent risk factor for survival and results in an increased number of distant metastases. They also reported an association with progression-free survival.

The evaluation of margins is dependent on the slicing technique of the surgical sample. It has been claimed that more reliable evaluation of the margins and

topography of a tumour is achieved with axial slicing technique (Verbeke et al. 2011; Esposito et al. 2008). The Royal College of Pathologists (Campbell et al. 2002) recommended that pancreatic tumours should be resected with a margin of 1 mm. Konstantinidis et al. (2013) used the 1 mm rule and reported that median survival among PDAC patients was 23 months after R0 resection and 14 months after R1 resection. Moreover, they reported longer survival among patients with a R1-resection than among patients with a locally advanced cancer (14 mos. vs. 11 mos.). Strobel et al. agreed with Konstantinidis et al. and reported a median survival of 42 months among patients with R0 resection and 28-23 months among patients with R1 resection (Strobel et al. 2017). Wagner et al. (2004) added that the median survival among patients with R2-resection was 9.8 months. However, the definition of R1-resection has been challenged by new data suggesting that 2 mm would be more beneficial, especially at posterior margins (Chen et al. 2010; Osipov et al. 2017). Osipov et al (2017) reported that even disease-free survival was longer with at least 2 mm posterior margins.

Tummala et al. (2013) pointed out that R0 resection is especially beneficial among patients with tumour size below 25 mm without nodal involvement. Numerous studies have confirmed that tumour size under 20-30 mm is associated with better prognosis. (under 30 mm: Winter et al. 2006, Dusch et al. 2014, Howard et al. 2006; under 20 mm: Paniccia et al. 2015; under 25 mm: Tummala et al 2013).

Both nodal involvement and positive lymph node/lymph node ratio has been strongly associated with poor prognosis (Weber et al. 2014). In addition, the effect of lymph node station on survival has been studied (Hempel et al. 2017, Agalianos et al. 2016, van Rijssen et al. 2016). The role of para-aortic lymph nodes has been under a particular subject of research and no agreement has been reached. A systematic review by van Rijssen et al. (2016) reported that survival among patients with hepatic-artery or para-aortal lymph nodes were comparable to that of patients with positive lymph nodes in other stations. However, another systematic review and meta-analysis by Agalianos et al. (2016) reported that positive para-aortic lymph nodes decrease the chances of survival even as compared with patients with positive lymph nodes elsewhere. A more recent report by Hempel et al. (2017) showed that one third of the patients with positive para-aortic lymph nodes survived over 19 months while median survival was 14 months. The latest ESMO guidelines (Ducreux et al. 2015) recommend removal of at least 15 lymph nodes to achieve proper staging of the tumour. Westgaard et al (2011) reported that the more tissue blocks are sampled, more lymph nodes are studied and the tumour

margins are reported in more detail in a standardised report than in an unstandardised. In addition, more information on tumour size, location of the tumour and microscopical invasion was available if reported routinely. Onete at al. (2015) added that more information was available in pathological reports from HVCs.

2.3.5 Effect of pre- and post-operative oncologic therapy on survival

As the definition of borderline resectable disease faces controversy, the effect of neoadjuvant therapy on survival has also been claimed to be unclear and in need of confirmation from randomized controlled studies. A meta-analysis by Gillen et al. (2010) reported a resection rate of 74% after neoadjuvant therapy. In addition, they reported a median survival of 23 months after neoadjuvant therapy, which was comparable to that of patients who had undergone primary resection. However, the meta-analysis included different neoadjuvant regimens, thus no treatment guideline could be presented.

The effect of postoperative chemotherapy has been explored in several studies. The ESPAC-1 trial (Neoptolemos et al. 2001) compared exclusive adjuvant therapy [bolus 5-fluorouracil (5-FU) and folinic acid], chemoradiation only (40 Gy plus 5-FU), chemoradiation followed by chemotherapy or surveillance alone. The study revealed longer survival among patients who had received chemotherapy (20.1 vs. 15.5 mo, p=0.009). A meta-analysis by Stocken et al. (Stocken et al. 2005) reported that with adjuvant therapy after an operation a 25% reduction can be achieved in the risk of death (hazard ratio 0.75, COI 0.64-0.90). The CONKO-001 trial (Oettle et al. 2007) agreed with the beneficial effect of chemotherapy on both disease-free survival (13.4 vs. 6.9 mos.) and overall survival (22.8 vs. 20.2 mos.). The CONKO trial reported a ten survival rate of 12.2% after gemcitabine vs. 7.7% after surveillance. The ESPAC-3 trial (Neoptolemos et al. 2010) compared six cycles of gemcitabine or 5-FU and found no differences in overall survival, disease-free survival or disease-free quality of life. The ESPAC-3 trial reported that survival is significantly increased even if the adjuvant therapy is iniated up to 12 weeks post-operatively. A recent Japanese study by Uesaka et al. (2016) suggested that adjuvant treatment with oral fluoropyrimidine formulation S1 resulted in a higher two-year survival rate than with gemcitabine treatment (70% vs. 53%). The recently published ESPAC-4 trial (Neoptolemos et al. 2017) reported a significantly longer

median survival in the gemcitabine and capecitabine combination group than in the single gemcitabine group (28 mo vs. 25.5 mo).

2.3.6 Operation volume

The effect of operation volume on the prognosis of PC has been a subject of research since the 1990s. Studies from the Netherlands, the United States, Sweden, Japan, Italy, Belgium, France and Finland (Nordback et al. 2002, Gooiker et al. 2014, Ansari et al. 2014, van der Geest, et al. 2016, Ghaferi et al. 2011, Sutton et al. 2014, Sosa et al. 1998, Balzano et al. 2008, Farges et al. 2017, Lidsky et al. 2017, Yoshioka et al. 2014) have demonstrated an inverse association between volume and mortality rates as shown in Table 7. However, the definition for a HVC has been study-related thereby rendering comparison of the results more difficult. The studies have reported a 30-day mortality rate or an in-hospital mortality rate 0-3.1% in HVCs when the definition is over 20 pancreatic resections per year. The cut-off for low volume centres (LVC) varies as much as the definition of a HVC. The mortality rates in LVCs vary from 3.5% to 15% depending on the study. Despite the heterogeneity of the cut-offs the mortality rates between the volume groups have been comparable. Sutton et al. (Sutton et al. 2014), for example, defined an LVC as a hospital performing under 22 procedures per year and reported an in-hospital mortality rate of 3.5 for LVCs and 1.3 for HVCs which is comparable with lower cut-offs. Topal et al. (2007) concluded that a PD rate of over 10 per year will result in a mortality rate of 6%.

Hata et al. (2016) conducted a pooled meta-analysis of 13 studies and concluded that a strong inverse association exists between mortality and operation volumes. Hata et al. categorised data into three groups in relation to the definition of an HVC. The meta-analysis reported an odds ratio of 4.05 for centres performing over 30 PDs per year, an odds ratio of 2.34 for centres performing over 20 PDs per year and odds ratio 1.94 for HVCs with under 20 PDs per year. Van der Geest et al. (2016) added that the mortality rates are also lower in HVCs among patients who are over 75 years old.

Mamidanna (2016) et al. studied the effect of surgeon volumes on mortality and suggested that each new pancreatectomy served to decrease the mortality by 4.1%, but were unable to set a minimum threshold for a surgeon volume. In Finland Nordback et al. (Nordback et al. 2002) reported that under 3 PDs per year was related to higher mortality and increased number of re-operations. The

Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland published guidelines on minimum surgeon volumes (Clinical Service Committee AUGIS) in 2010 and suggested that the yearly number of pancreatic resections should be 80-100 resections per hospital and 12-16 per surgeon per year.

In addition to the data on mortality, the volume effect has been studied in relation to several hospital parameters such as lengths of hospital stay, complications, readmissions, charges, re-operations and quality of pathology. High operation volumes are associated with shorter stay in hospital (Lidsky et al. 2017, Sosa et al. 1998, Topal et al. 2007). Ansari et al. (2014) and Nordback et al. (2002) reported fewer re-operations in HVCs, and Lidsky et al. suggested that less re-admissions are needed after an operation in a HVC. Ghaferi et al. (2011) demonstrated that there are fewer major complications in HVCs and that LVCs have challenges in rescuing patients after complications.

The effect of volume on long-term survival has not been as widely studied. Lidsky et al. (2017) stated that PC patients have a longer median survival if they have been operated on in an HVC; 20.3 months after being operated in HVCs vs. 15.7 months in LVCs. Gooiker et al. (2014) analysed the Dutsch data and showed that the one- and two-year survivals are better among patients operated on in an HVC (one-year survival 72% vs. 57% and two-year survival 40% vs. 31%). Birkmeyer et al. (2007) showed that pancreatic, stomach, lung, oesophagus, colon and bladder cancer have better Kaplan-Meier curves up to five years if the patients are operated on in a HVC. The exact diagnosis of a pancreatic tumour was not identified in these studies, which may bias the results.

In recent decades, attempts have been made to centralize pancreatic resections. Lemmens et al. (2011) in the Netherlands and Soreide et al (2016) in Norway described the positive effects of centralization in their respective countries. They reported increased numbers of resections and decreased mortality. Soreide et al. added that the changes resulted in a decrease in the median number of days in intensive care and hospital as well as a decreased number of re-operations. Lemmens et al. stated that two-year survival increased from 38% to 50%, but this may also have been influenced by other factors.

As the treatment of pancreatic cancer is teamwork, high operation volume not only increases the experience of surgeons, but also the experience of pathologists who analyse the specimens. Onete et al. (2015) reported that more R0 resections were achieved in HVCs even among T3/T4-tumours. In addition, the quality of pathological reports seemed better as they contain more information than those

produced in LVCs. The small number of lymph nodes detected in LVCs was also confirmed by Lidsky et al. (2017).

Table 7. Reported mortality rates in HVCs and LVCs after pancreatic resection

	Definition of HVC/LVC	In-hospital mortality*/ 30-day mortality/ 90-day mortality**	
		HVC	LVC
Farges et al. 2017 (France)	>65/≤25 pancreatic resections	OR 1**	OR 1.9**
Lidsky et al. 2017 (USA)	≥16/≤3.3 PDs	2.0%	6.3%
van der Geest et al. 2016 (Netherlands)	≥40/<5 PDs	4.3%**	9.7%**
Coupland et al. 2016 (England)	≥30/<15 pancreatic resections	OR 0.78*	OR 1*
Yoshioka et al. 2014 (Japan)	≥18/≤11 PDs	2.8%*	5%*
Gooiker et al. 2014 (Netherlands)	>20/≤9 PDs	3.1%	5.2%
Ansari et al. 2014 (Sweden)	≥25/<10 PDs	0.0%*	4.0%*
Sutton et al. 2014 (USA)	≥97/≤22 PDs	1.3%*	3.5%*
Ghaferi et al. 2011 (USA)	27/≤2 pancreatectomies	3.1%*	13.3%*
Balzano et al. 2008 (Italy)	>14/≤ 6 PDs	5.9%	12.4%
Nordback et al. 2002 (Finland)	>10/<5 PDs	4%*	13%*
Sosa et al. 1998 (USA)	≥20/<5 PC procedures	1.9%*	14.7%*

2.3.7 Tumour biology

The recent progress in bioinformatics has established effect of heterogeneous bioprofile of PDAC on survival. The tumour biology has an impact not only on the aggressiveness of the tumour but also its sensitivity to oncologic therapy. (Marechal et al. 2012; Zhang et al. 2018) It has been suggested that the KRAS mutation is an independent prognostic factor. In addition other driver mutations in CDKN2A/p16, SMAD4 and TP53 are associated with advanced stages of carcinogenesis. (Esposito et al. 2014; Rachakonda et al. 2013; Zhang et al. 2018) Dreyer et al. (2018) reported that tumours in the body or in tail of the pancreas are

more aggressive than those in the head of the pancreas and are associated with a squamous subtype. In addition, the prognosis of PDAC has been associated with differences in tissue expression of different biomarkers and immunologic profile (Saukkonen et al. 2018; Saukkonen et al. 2015; Saukkonen et al. 2013; Tahkola et al. 2018).

2.4 Costs of pancreatic surgery

2.4.1 Cost management in public health care

Finland has a public health care system ensured by the provisions on the Health Care Act (1326/2010) and further stipulated in the Primary Health Care Act (66/1972) and in the Act on Specialised Medical Care (1062/1989). The maximun fees for treatment episodes which can be collected directly from patients are laid down in the Act and Decree on Social and Health Care Client Fees (734/1992 and 912/1992). This means that patients pay only a small proportion of the total costs and the exact costs of a treatment episode are not revealed to patients. In addition, the health care personnel are not involved in the billing process apart from the executive staff.

The actual bill for a treatment episode is paid by the hospital district or the patient's home municipality depending on local arrangements. Hospital districts finance their hospitals though taxation and receive funding from the government. The Finnish Ministry of Social Affairs and Health (Ministry of Health and Social Affairs 2018) estimates that some 5% on the expenditures of health and social affairs are financed by client charges, 30% by government and 65% by regional taxes. The overall costs of public health and social care is estimated to be 30% GDP. However, the results in a recent OECD report were different, suggesting that the costs of the health care system are covered by government (61%), compulsory health insurance (13%), out-of-pocket 20% and by voluntary health insurances (3%). The OECD report (OECD 2017) showed that the share of expenditure of GDP was 9.3% in Finland in 2016, which is about the same as the average among the OECD35 countries (9.0%). The OECD report covered only health related expenditures which explain the difference in the numbers.

It has been estimated that the share of GDP of costs of health and social care will increase during the next years. At the moment the organising and financing of

the social welfare and health care system is undergoing major governmental reform. The aim of the reform is to ensure equality and cost-effectiveness thoughout the country (THL 2018).

2.4.2 Effect of complications on costs

The costs of surgical procedures are dependent on the post-operative course. An uneventful treatment period consumes fewer resources than a complicated one. Vonlanthen et al. (2011) studied the costs of major surgery performed in a tertiary hospital and reported that complication grade is a significant factor in explaining increased costs. They reported that the mean expenditure of an uncomplicated treatment period was 27,946 USD while the mean costs of a patient with organ dysfunction increased to 159,345 USD. In their study, the highest actual mean costs were those for pancreatic surgery with (82,576 USD) or without complications (31,809 USD). Gani et al (2016) studied an American costs database concerning the finances of hepato-pancretico-biliary surgery and stated that both fixed and variable costs increased among patients with postoperative complications. Interestingly, their study reported higher net profits from patients with complications. Santema et al. (2015) concentrated on PDs and reported that a postoperative complication can result in 30-70% increase in costs.

2.4.3 Effect of operation volume on costs

It has been reported that a sufficient procedure volume will lead to better prognosis for patients. Ke et al. (2012) published a systematic review of 19 studies of the economics related to centralization of cancer services. The systematic review stated that increased surgeon volume leads to lower health care costs, but noted that one study suggested that the curve is U-shaped. The analysis of studies concerning the effect of hospital volume did not lead to consistent results: 6/10 studies reported an inverse relationship between hospital volumes and costs, 3/10 a parallel relationship and one study no volume-related relationship. Since the study by Ke et al., more data on a relationship with a volume has been published. Sutton et al. (2014) reported in a retrospective study of 9,883 patients that total costs are lower in HVCs. This was corroborated by large retrospective studies by Yoshioka et al. (2014, 10,625 patients) and Tran et al (2016, 15,599 patients). Balzano et al. (2016) analysed 10,936 patients and reported that hospital volume has an effect on

treatment decisions and low volumes can lead to overuse of expensive treatment modalities.

2.5 Can the management of pancreatic cancer improve prognosis?

All in all, organizing PC treatment is demanding. The decision on treatment strategy needs expertise to select the right patients for neoadjuvant therapy, surgery or palliative treatments. After pancreatic resection, patients are at risk of developing severe complications and even death. International reports have demonstrated the importance of experience and hospital volume on the results of pancreatic resections. Taking into consideration the poor survival from PC reported in earlier studies and the economic pressure facing health care systems, means to minimise adverse effects are needed. Finland has a public health care system. Centralization of pancreatic surgery has proceeded gradually in Finland. Whether the operation volume has an effect on the management, prognosis and treatment costs of PDAC patients in Finland is not known.

3 AIMS OF THE STUDY

The aim of this study was to analyse the effect of operation volume on treatment strategies and prognosis in PC.

The detailed aims were as follows:

1. To study the characteristics of long-term survivors of PDAC in Finland
2. To analyse whether operation volume has an effect on complications, mortality and the costs of pancreatic surgery
3. To study whether the treatment of PC varies in different parts of Finland
4. To analyse whether operation volume has an effect on long-term survival after resection of PDAC

4 PATIENTS AND METHODS

4.1 Study registers

The study consists of four parts and the data is based on the Care Register for Social Welfare and Health Care (HILMO) on pancreatic resections. In the study parts I-III the information from HILMO is encoupled with the information from the Finnish Cancer Registry (FCR) on PC patients. The Nordic Classification of Surgical Procedures code JLC* and the International Classification of Diseases Code (ICD-10) C25.* were used as search terms.

The first part analysed patients undergone a pancreatic resection and diagnosed with PDAC between 2000 and 2008 (n=598 patients) and the second part of PDAC patients undergone a resection between 2002 and 2008 (n=467 patients). The time span was wider in the first part to collect as many long-term survivors (LTSs) as possible. In the second part the first two years were cut off because of uneven distribution of missing data for three-class volumetric analysis. The third part covered all PC patients diagnosed either in 2003 or 2008 (n= 1,546 patients). The third study could not be focused on PDAC patients, because exact histopathological diagnosis was available only among patients undergone a pancreatic resection. The years 2003 and 2008 were selected to be able to analyse 5-year survival at the data retrieval 2015. The fourth part analysed patients undergone a PD or TP on between 2012 and 2014 (n= 501 patients). Patients with any diagnosis were included in the fourth part apart from children and trauma patients. (Figure 5)

The data from national registers was supplemented by detailed information from patient archives. Patients with no records available were excluded.

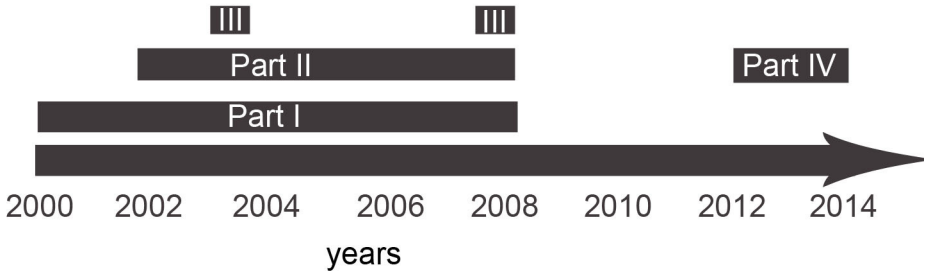


Figure 5. Summary of the time spans in the different parts of the study.

4.2 Methods

4.2.1 Part I: Long-term survivors of PDAC

Considering the well-known poor median survival of less than two years among PDAC patients, survival longer than four years was considered exceptional. This enabled also higher number of patients to be included in the study. The histological diagnosis of PDAC patients surviving over four years after the operation was confirmed by an expert in pancreatic pathology.

TNM, gradus and R-status were determined according to the AJCC 7th Edition (Allen et al. 2017) and updated in the re-analysis whenever the histological slides permitted. Data on patient demographics, pancreatic surgical procedures and oncologic treatment were abstracted from the archives. The cut-point of survival was 31 December 2013.

Hospital volume for demanding pancreatic surgery was calculated from the mean number of PDs performed for any diagnosis per year during the period 2000-2008 and hospitals were defined as HVC;≥ 20 and LVC; <20.

In the statistical analysis patients who had survived over four years were compared with patients surviving under four years in both univariate and multivariate analyses (binary logistic regression analysis). The survival of LTSs was analysed with Kaplan-Meier analysis.

4.2.2 Part II: Effect of operation volumes on survival

The LTSs with a confirmed diagnosis of PDAC were included into this part. To analyse the effect of hospital volume on patient data, operating centres were categorised as HVC; ≥ 20, medium volume centres (MVC); 6-19 and LVC; <6 according to the mean yearly number of PDs performed for any diagnosis during 2002-2008. The 30- and 90-day mortality and survival were analysed between these three categories.

4.2.3 Part III: Accessibility of pancreatic resections

Information on medical history, cancer stage and treatment strategy (radical surgery, palliative surgery, biliary drainage, oncologic therapy, other palliative therapy) was searched from the patient records. In addition, information on the delays from diagnosis to the initiation of each treatment was recorded. The health care districts in Finland were categorised into three groups based on the yearly number of PDs performed between 2002 and 2008 as high level of experience region (HLER; >20 PD/year), medium level of experience region (MLER; 6-19 PD/year), and low level of experience region (LLER; <6 PD/year or only distal resections or no pancreas resections). In the study database the patients were included according to the health care district in which the diagnosis was set.

Proportions of different treatment modalities and time to the onset of treatments were compared between HLER, MLER and LLER.

4.2.4 Part IV: Effect of operation volume on short-term prognosis and resource utilisation

Patient data on medical history, resected tumour (diagnosis, TNM, gradus, R-status, size, number of total and positive lymph nodes), complications, performed procedures and length of hospital stay and stay in intensive care were recorded from the patient records. Patient data was followed up to 90 days postoperatively from the operating hospital as well as from possible other hospitals. The cut-point of survival was 1 February, 2017.

The Clavien-Dindo classification (C-D) (Dindo et al. 2004) was used to categorise complications. For purposes of analysis, a normal, uncomplicated ward stay was classified as grade 0 in this study. Delayed gastric emptying (DGE),

pancreatic fistulas (POPF) and postpancreatectomy haemorrhage (PPH) were classified according to the most recent international guidelines, clinically significant being grades B and C. (Wente et al. 2007a, Wente et al. 2007b, Bassi et al. 2017)

The cost evaluation comprised ward days and intensive care days in all hospitals and in primary health care up to 90 days postoperatively. In addition, costs of relevant interventions, such as reoperations, endoscopies and interventional radiology were included. The costs of the primary operations were not included as it was considered similar in the various centers.

The costs were evaluated according to the 2012 price list of Tampere University Hospital and one local health care centre (Pirkkala) to be able to compare the cost differences unaffected by the possible billing differences between the hospitals. For emergency procedures a mean price was used, because the emergency procedures were personalised to each complication and the original price did not provide detailed prices. For intensive care and ward periods, a mean price of a normal care day and an extra demanding care day was used because it was not possible to separate these retrospectively.

In the cost analysis the costs of different levels of treatment were related to the cost of the "basic unit", which was the costs of one post-operative day on a surgical ward (DHos=day at a hospital) and changed to factors accordingly: factor 1 DHos for a day at any hospital, 5.5 DHos for an intensive care day, 1.1 DHos for endoscopies or interventional radiology, 4.0 DHos for re-operations and radiologic angiographic procedures and 0.3 DHos for a day in primary health care. The benefits of the costs were evaluated in terms of life years gained among cancer patients.

To analyse the effect of hospital volume on patient data, operating centres were grouped as HVC; ≥ 20, MVC; 6-19 and LVC; <6 according to the mean yearly number of PDs or TPs performed for any diagnosis during the period 2012-2014.

5 STATISTICS

Statistical analysis was performed with IBM Statistics SPSS 23. Data are shown as numbers and median (range). Fisher's exact test or Pearson's Chi-squared test for statistical significance was used for categorised variables. Kruskal-Wallis test was used to calculate statistical significance in continuous variables. Survival analysis was performed using Kaplan-Meier analysis or Cox regression analysis. Statistical difference was analysed with Log-rank or Breslow test in Kaplan-Meier analysis. Multivariable analysis was performed with logistic regression analysis. A P-value of ≤ 0.05 was considered statistically significant.

6 ETHICAL ASPECTS

All studies were conducted in accordance with the principles of the Declaration of Helsinki and the guidelines for good clinical practice. The Regional Ethics Committee of Pirkanmaa, Finland (code R12241) approved the study. The data collection for all studies was approved by the National Institute for Health and Welfare in Finland (the decision codes for parts I, II and III: THL/1854/5.05.00/2012 and THL/1681/5.05.00/2013, the decision code for part IV: THL/1619/5.05/2016). For collection and analysing surgical specimens in the first two parts of study, approval was granted by Valvira (code: 10263/06.01/2012). Specific ethical aspects in the studies were as follows: data collection was carried out with caution and no personal data was disclosed beyond the study groups of each part of the study. The analysis was carried out with previously published methods and criteria (hospital volumes, complications).

7 RESULTS

7.1 Part I: Long-term survivors of pancreatic ductal adenocarcinoma

Long-term survivors. After combining information on pancreatic resections and PC patients a list of 883 patients was formed. After exclusion of patients with palliative surgery (14), no available archives (20) or with pancreatic neoplasms other than PDAC (251), a total of 598 patients were further analysed. Out of these patients 94 patients had survived over four years and their slides were collected. The slides of 14 patients were not available and they had to be excluded. The information on the remaining 80 patients was sent for histopathological re-analysis, which confirmed the diagnosis of 52 patients 65%), resulting in a four-year survival rate of 9.4% (52/556) and five-year survival of 7.6% (42/556). A total of 52 LTSs were compared with short-term survivors (STSs).

Demographics. Sex, age or ASA class or distribution of relevant co-morbidities did not differ between STSs and LTSs.

Histopathology. The histopathological diagnosis changed in 23 of the patients (29%) without a statistical significant difference between the HVC and LVC-groups (p=0.461, Fisher's exact test).

Survival. The median survival among all PDAC patients was 1.59 years (range 0.090-13.0, not including patients who died less than 30 days postoperatively). The median survival in LTS was 6.6 years (range 4.0-13 years) and 28 (54%) LTS were still alive at the cut-point of survival. Moreover, a Kaplan-Meier analysis illustrated in Figure 6 showed that 67% of the LTSs survived for over six years and 57% for over eight years.

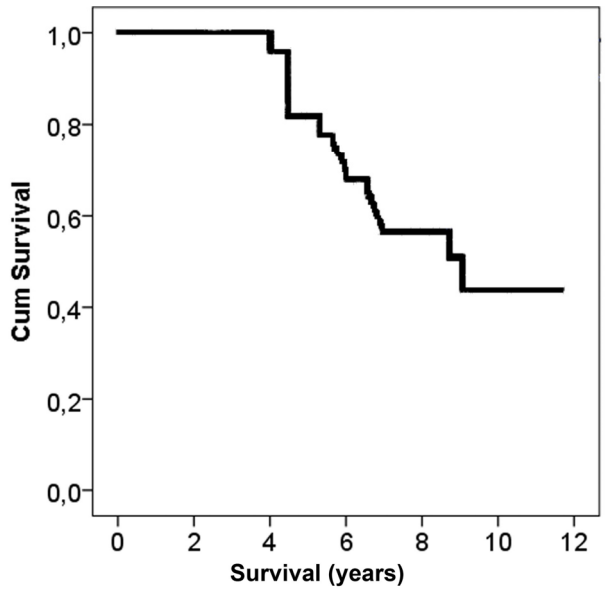


Figure 6. A Kaplan-Meier curve for LTSs. Almost 60% of those patients who survived for over 4 years survived for over 8 years.

In the univariate analysis between STSs and LTSs tumour size, stage and hospital volume showed significant differences (for tumour size: p=0.013 Kruskal-Wallis; stage: p=0.039, Pearson's Chi-squared test). Four-year survival was 13% in HVCs and 6.7% in LVCs (0.017; Fisher's exact test) and five-year survival was 10.4% in HVCs and 5.8% in LVCs (p=0.053, Fisher's exact test). A logistic regression analysis considering age, ASA, hospital volume, nodal involvement, R-status, tumour size and adjuvant therapy showed that tumour size was the only independent prognostic factor for over four-year survival. (Table 8).

Table 8. Factors associated with over four-year survival. According to univariate analysis hospital volume and tumour size were associated with over four-year survival, but after a logistic regression analysis only tumour size persisted as a significant factor.

	Univariate analysis	Multivariate analysis	
	p	p	OR (95% COI)
Sex[1]	0.299	-	-
Age[2]	0.107	0.781	0.993 (0.955-1.032)
ASA[1]	0.295	0.525	ASA2: 1.592 (0.707-3.586)
			ASA3-4: 1.112 (0.500-2.473)
HVC[3]	0.017*	0.147	0.599 (0.299-1.198)
Stage[1]**#**	0.039*	-	-
Nodal involvement[1]	0.454	0.810	0.915 (0.445-1.883
R-status[1]**&**	0.082	0.491	R1: 1.707 (0.859-3.392)
Tumour size[3]**$**	0.013*	0.019*	0.709 (0.533-0.944)
Gradus[1]	0.316	-	-
Adjuvant therapy		0.576	1.460 (0.721-2.958)

**statistically significant difference, [1]Pearson's Chi-squared test, [2]Kruskal-Wallis, [3]Fisher's test, OR=odds ratio, COI=confidence interval #stage III and IV grouped for analysis, &R2 resections exluded, $patients with neoadjuvant therapy excluded, ASA=American Society of Anesthesiologits*

7.2 Part II: Effect of operation volumes on survival

Patients and hospitals. The study registry formed in the first study (above) was searched for PC patients who had undergone pancreatic resection between 2002 and 2008 and a total of 467 PDAC patients were included in the volume based analysis in this study. Between 2002 and 2008 pancreas resections were performed in 22 hospitals in Finland. There were two HVCs, six MVCs and 14 LVCs. The number of hospitals decreased to 17 and the annual number PDAC procedures increased from 59 to 78 by 2008. The mean numbers of PDAC operations performed were 14.4 in HVCs, 3.3 MVCs and 1.3 LVCs between 2002 and 2008.

Demographics. Median age at the time of operation was 67 years, 53% of the patients were male, ASA 1 class accounted for 50%, ASA 2 class 20% and ASA 3-4 class for 31% of the patients. Sex, age or ASA class distributions did not differ between the volume groups (sex: p=0.572, Pearson's Chi-squared test; age: p=0.090, Kruskal-Wallis; ASA: p=0.596, Pearson's Chi-squared test). The distributions of pancreatic resection type (PD: 86%, DP: 7.1% or other: 6.8%) were also similar (p=0.783, Pearson's Chi-squared test).

Histopathology. The stage distribution differed between the volume groups (p<0.01, Pearson's Chi-squared test): stage IIB accounted for 66% of cases in the HVCs and 41-44% in MVCs and LVCs, stage IIA accounted for 14% in HVCs and 19-20% in MVCs and LVCs and stage IB accounted for 6% in HVCs and 12-16% in MVCs and LVCs. The R distribution also showed differences (p=0.001, Pearson's Chi-squared test): R0 accounted for 55% in HVCs and 57-62 % in MVCs and LVCs, R1 accounted for 41% of cases in HVCs and 26-27% in MVCs and LVCs and R2 comprised 2.0% in HVCs and 9.4-13% in MVCs and LVCs. The median size of a tumour was 30 mm in HVCs and LVCs and 35 mm in MVCs with a significant difference (p=0.019, Kruskal-Wallis). The pathological reports were more comprehensive regarding data on lymph nodes, tumour size or TNM in HVCs. (Table 9).

Table 9. Differences in pathological reports. There was more missing information in the pathological reports in medium and lower volume centres than in high volume centres.

	HVC	MVC	LVC	p
Median number of detected nodes in original pathological reports, all patients (range)[1]	20 (2-70)	8 (0-27)	6.5 (0-26)	<0.001*
Missing information in original pathological reports, all patients (%)[2]				
on tumour size	1.0	8.0	12.5	0.002*
on total number of detected nodes	8.0	39.9	53.1	<0.001*
on number of positive nodes	2.5	20.3	21.1	<0.001*
on TNM	28.4	48.6	45.3	<0.001*

*HVC=high volume centres (≥20 PD/yr), MVC=medium volume centres (6-19 PD/yr), LVC=low volume centres (≤5 PD/yr), PD=pancreatoduodenectomy, [1]Kruskal-Wallis, [2]Pearson's Chi-squared test, *statistically significant*

Mortality. The 30-day mortality was 0.0% in HVCs, 2.2% in MVCs and 5.5% in LVCs. The 90-day mortality was 2.5% in HVCs, 4.3% in MVCs and 10.9 in LVCs. Both 30- and 90-day mortality rates were significantly lower in HVCs than in LVCs (p=0.001 and p=0.003, Fisher's exact test).

Survival. The survival analysis shown in Figure 7 was performed without patients who had died during the first 30 days postoperatively. Overall four-year survival was 10.1% and five-year survival was 8.1%. The two-year survival was significantly higher in HVCs and in LVCs (43% vs. 31%, p=0.045, Pearson's Chi-squared test) as well as the three-year survival (25% in HVCs vs. 15% in LVCs, p=0.035, Pearson's Chi-squared test). Four- and five-year survivals did not differ

significantly. In a Cox survival analysis for HVCs and LVCs significant factors for survival were tumour size, nodal involvement, age and hospital volume. (Table 10).

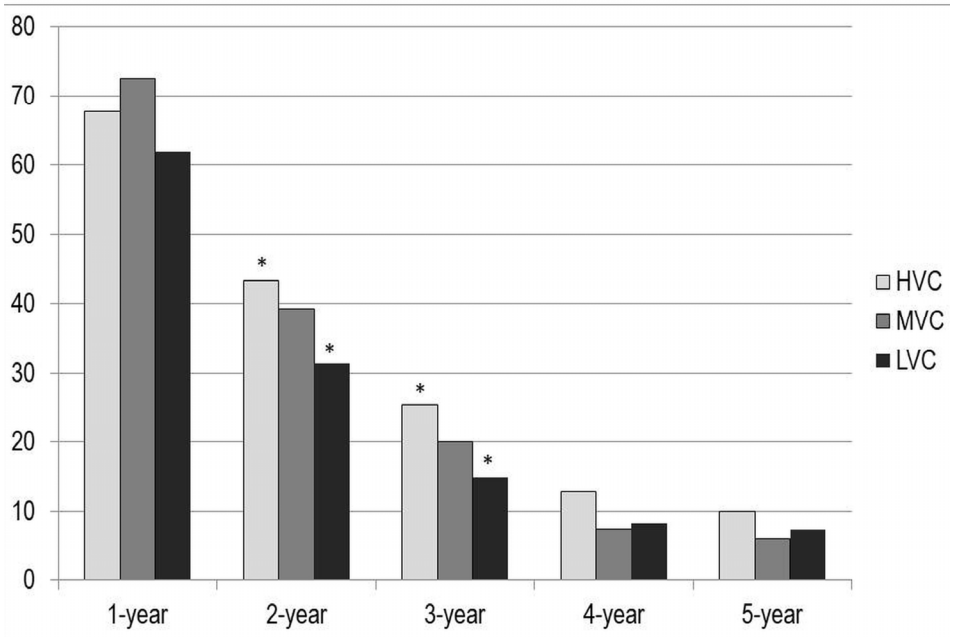


Figure 7. Survival rates after a pancreatic resection among cancer patients. Survival was *significantly better in HVCs than in LVCs 2 and 3 years after the operation (p=0.045 and p=0.035 respectively).

Table 10. A Cox-survival analysis. Tumour size, nodal involvement and low hospital volume were associated with shorter survival.

Factor	p	OR (95% COI)
male	0.913	0.986 (0.767-1.268)
age	0.004*	1.022 (1.007-1.038)
ASA	0.580	
ASA 1		1(refence)
ASA 2	0.340	0.852 (0.613-1.184)
ASA 3-4	0.500	0.901 (0.665-1.220)
tumour size	0.001*	1.135 (1.052-1.225)
R	0.323	
0		1 (reference)
1	0.672	1.061 (0.806-1.398)
2	0.135	1.606 (0.863-2.988)
nodal involvement	0.025*	1.366 (1.040-1.794)
LVC	0.017*	1.422 (1.066-1.896)

*OR=odds ratio, COI=confidence interval, *statistically significant, ASA=American Society of Anesthesiologists classification, LVC= low volume centre*

7.3 Part III: Accessibility of radical resections

Patients and health care districts. The search in the Finnish Cancer Registry found 1,936 PC patients diagnosed in 2003 and 2008. Patient records were available for 90% of patients. After reviewing patients' records, 196 patients were excluded and the remaining 1,546 patients formed the study population. There were two HLERs serving 504 pancreatic patients, six MLERs serving 508 patients and 13 LLERs serving 543 patients. Only one health care district out of 21 did not perform any pancreatic resections during the study period and was grouped with the LLERs. The median yearly incidence of PC was 15.5 per 100,000 population and did not differ between the health care districts (range 23.7 – 12.9/100,000 pop, p=0.458, Kruskal-Wallis test, degree of freedom 20).

Demographic and tumour data. Median age at diagnosis was at its lowest in HLERs (70 years vs. 72 and 73 years, p=0.014, Kruskal-Wallis test, degree of freedom 2). The age group based analysis (<60, 60-75 and >75 years at diagnosis) revealed no significant differences between HLERs, MLERs and LLERs. There ASA-distribution differed between the HLERs, MLERs and LLERs (p= 0.031 Pearson's

Chi squared test, degree of freedom 4). The proportion of stage IV tumours at diagnosis varied between the 21 health care districts (p=0.013, Pearson's Chi-squared test, degree of freedom 4), but no correlation with pancreatic surgery experience (HLER/MLER/LLER) was found (p=0.060, Pearson's Chi-squared test, degree of freedom 2). (Table 11)

Table 11.

	HLER	MLER	LLER	p[1]
Total	504	508	534	
Age (%)				0.062
<60 years	20.2	16.5	15.9	
60-75 years	45.1	43.7	41.4	
>75 years	34.3	39.8	42.7	
ASA (%)				0.031*#
1	37	27	32	
2	34	28	32	
3-4	27	31	33	
NAS	3.2	14.2	3.6	
Stage (%)				0.060#
I-III	29.4	22.0	21.3	
IV	53.6	55.5	51.9	
NAS	17.1	22.4	26.8	

*[1]Pearson's Chi-squared test, *statistically significant, #without patients with unknown data, HLER=high level of experience, MLER=medium level of experience, LLER=low level of experience, ASA=American Society of Anesthesiologists classification, NAS=non aliter specificatus (unknown)*

*Treatment strategies***.** The median incidence of radical surgery, illustrated in Figure 8, was almost twice as high among patients resident in HLERs than in LLERs: 4.9 operations/100,000 vs. 2.5 operations/100,000, but the difference was not statistically significant (p=0.144, Kruskal-Wallis test, degree of freedom 2). More patients had undergone radical resection in HLERs than in MLERs and LLERs (17.9% in HLERs vs. 11.0% in MLERs and 7.7% in LLERs, p<0.001, Pearson Chi-squared test, degree of freedom 10). The difference persisted when analysing only patients with non-metastatic disease (49 % in HLERs, 29% in MLERs and 22% in LLERs; p=0.002, Pearson's Chi-squared test, degree of freedom 2). In the logistic regression analysis also concerning ASA class, age groups and stage (groups I-III, IV, NAS), level of experience in pancreatic surgery persisted as a significant factor for selection for radical surgery. The Odds Ratio for patients with

undefinable stage class was low, demonstrating that their treatment strategies were more likely to be of a palliative nature. Table 12 and 13. Among patients without a defined PC subtype, 1.1% had undergone surgery and the rest palliative treatment strategy.

Table 12. Almost 20 % of the patients were operated on in experienced regions while elsewhere the proportion was 7-11%. The difference was even greater if only patients with stages I-III were analysed. There use of oncologic therapy was more frequent outside the HLERs.

	HLER	MLER	LLER	p[1]
Total	504	508	534	
Radical surgery (%)	90 (17.9)	56 (11.0)	41 (7.7)	<0.001*
Pre-operative biliary drainage	47 (52)	17 (30)	20 (49)	0.137
Only biliary drainage	140 (27.8)	110 (21.8)	130 (24.3)	0.076
Palliative oncologic therapy	122 (24.2)	158 (32.9)	160 (30.0)	0.033*
Palliative surgery	24 (4.8)	36 (7.1)	50 (9.4)	0.016*
Other palliative approaches	128 (25.4)	148 (29.1)	153 (28.7)	0.351
Total, stage I-III	148	112	114	
Radical surgery among stage I-III (%)	79 (49.1)	46 (28.6)	36 (22.4)	0.002*
Palliative oncologic therapy among stage I-III (%)	20 (13.7)	38 (34.2)	39 (34.2)	<0.001*

*[1]Pearson's Chi-squared test, *statistically significant HLER=high level of experience, MLER=medium level of experience, LLER=low level of experience*

Table 13. A logistic regression analysis showed that level of experience in pancreatic surgery was associated with patient selection for surgery as well as age and stage of disease at diagnosis.

Factor	p	degree of freedom	OR	95% COI
Age	**<0.001***	**2**		
Age <60			reference	
Age 60-75	0.131	1	0.690	0.426 – 1.117
Age >75	<0.001	1	0.171	0.093 – 0.314
Stage	**<0.001***	**2**		
Stage I-III			reference	
Stage NAS	<0.001	1	0.092	0.051 – 0.167
Stage IV	<0.001	1	0.016	0.008 – 0.031
ASA	**0.266**	**2**		
ASA 1			reference	
ASA 2	0.480	1	0.847	0.534 – 1.344
ASA 3-4	0.104	1	0.652	0.390 – 1.091
Level of experience in pancreas surgery	**<0.001***	**2**		
high level			reference	
medium level	0.026	1	0.585	0.365 – 0.938
low level	<0.001	1	0.387	0.239 – 0.627

*OR=odds ratio, COI=confidence interval, *statistically significant, ASA=American Society of Anesthesiologists classification, NAS=non aliter specificatus (unknown)*

The proportion of palliative chemotherapy was lowest in HLERs among all patients and among stage I-III disease (p=0.033, Pearson's Chi-squared test, degree of freedom 2 and p=0.000, Pearson's Chi-squared test, degree of freedom 2, respectively). Table 12.

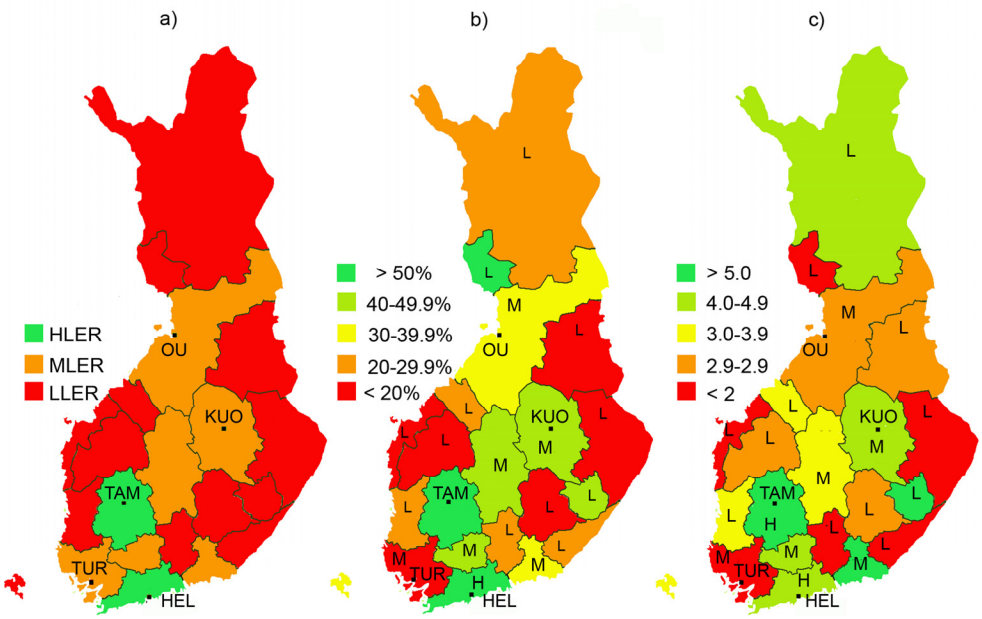


Figure 8. a) Health care districts according to experience in pancreatic surgery in Finland. There are only two health care districts with high-level of experience in pancreatic surgery. b) Proportions of pancreatic resections among patients with a stage I-III PC. More patients are selected for pancreatic resections in experienced districts. c) Incidence of pancreatic resections among cancer patients /100,000 population. Incidence varied between regions and was not related to pancreatic resection experience. HEL= Helsinki, KUO=Kuopio, OU=Oulu, TAM=Tampere, TUR=Turku, H=high level of experience, M=medium level of experience, L=low level of experience.

Time elapsing from diagnosis to initiation of treatment. The median timespan from diagnosis to PC resection varied between the districts in favour of MLERs (18 days in MLERs vs. 27-28 days in LLERs and HLERs, p=0.001, Kruskal-Wallis, degree of freedom 2). The difference persisted if the timespan analysed was cut to 8-60 days (medians 28.0, 20.0 and 27.5 days in HLER, MLER, LLER respectively, p=0.000, Kruskal-Wallis, degree of freedom 2). There were no significant differences between the regions in waiting times to initiation of palliative oncologic therapy (49 to 45.5 days; p=0.290, Kruskal-Wallis, degree of freedom 2). It is noteworthy, 7.4% of the timespan information about radical surgery and 33.5% of the timespan information about the palliative chemotherapy was incomplete.

7.4 Part IV: Effect of operation volume on short-term survival and resource utilisation

Patients and operating centres. The search in the HILMO identified 523 patients having undergone PD or TP. After analysing the patient records, 501 patients were included in the study. There were two HVCs, five MVCs and six LVCs. A total of 284 patients were operated on in HVCs (57%), 184 in MVCs (37%) and 33 in LVCs (6.6%).

Demographic and surgical data. The median age at the time of operation was 67-64 years in the volume groups without a significant difference (p=0.475, Kruskal-Wallis). The proportion of patients over 75 seemed higher in HVCs and MVCs without a statistically significant difference (19% in HVCs, 22% in MVCs and 12% in LVCs, p=0.358, Pearson's Chi-squared test). The ASA distributions among patients over 75 years did not differ (p=0.890). Most of the patients had a malignant disease (82-86%) without a significant difference between the volume groups (p=0.542, Pearson's Chi-squared test). Significantly more vascular resections were performed in HVCs (16% in HVCs and 3-4% in LVCs and MVCs, p<0.01, Pearson's Chi-squared test).

Complications. Overall complications according to C-D classification did not differ between volume groups except in post-operative (C-D V: 1.1/8.7/12% in HVCs/MVCs/LVCs; p=0.000, Pearson's Chi-squared test). (Table 14) The incidence of PD-related complications showed no statistically significant difference between the volume groups; DGE gradus B-C (6.6-6.5-15%), POPF gradus B-C (5.6 - 9.2 - 9.1%) and PPH gradus B-C (5.3-6.0-9.1%) in HVC, MVC and LVC respectively. More unspecified infections were present in the MVC group (20% vs. 12% in HVC and 6.1% in LVC, p=0.034, Pearson's Chi-squared test). More leakages in gastro-enterostomies/enteroenterostomies were present in the MVC group, but the total number was low (5, 2.7%).

Table 14. Distribution of complication grades among different volume groups.

Complication grade	HVC	MVC	LVC	p[1]
0	35	33	49	0.216
I	10	6.5	6.1	0.279
II	32	30	18	0.263
III	13	15	9.1	0.813
IV	9.2	7.1	6.1	0.814
V	1.1	8.7	12	<0.01*

*[1]Pearson's Chi-squared test, *statistically significant, HVC=high volume centre, MVC=medium volume centre, LVC=low volume centre*

Postoperative short-term survival. Thirty day mortality was lowest in HVCs (0.7% in HVCs vs. 8.8% in MVCs and 12% in LVCs; p<0.01, Pearson's Chi-squared test). The difference was also significant in 90-day mortality (1.8% in HVCs vs. 10 in MVCs and 15% in LVCs, p<0.01, Pearson's Chi-squared test). In a logistic regression analysis considering sex, ASA, malignant/benign disease, age and operation volume, age and operation volume persisted as significant variables in 30- and 90-day mortality rates. In addition, the nature (benign/malignant) of the disease was potentially significant in the 90-day mortality analysis (p=0.049), when metastasis surgery was excluded. Analysing logistic regression analysis inside each volume subgroup (HVC, MVC, LVC), it could be stated that not a single operating hospital was a significant factor for 30-day and 90-day mortality (considering sex, ASA, malignant/benign, age and hospital).

Use of health care resources for 90 days postoperatively. The median number of ward days either in hospitals or in primary health care centres did not differ between volume groups (14 in the HVCs, 16 in the MVCs and 15 LVC, (range 1-90 days). Analysing different C-D groups there was a significant difference in C-D class 3 (p=0.018, Kruskal-Wallis). The number of reoperations, endoscopies or radiological drainage procedures was the same in the different volume groups. Radiological procedures for vascular complications were only performed in HVCs.

Cost analysis. Median costs were lowest in the HVC group (14 DHos vs. 16 DHos in MVC and 16 DHos in LVC; p=0.019, Kruskal-Wallis) both analysing the data as a whole and considering only patients who survived longer than five days (p=0.010, Kruskal-Wallis). Among patients over 75 years, median costs were

lowest in the HVC group (14 DHos in the HVC group and 25 DHos in the MVC group, p=0.002, Kruskal-Wallis). There were only four patients over 75 years in the LVC group thus the LVC group was not analysed in this subset.

The absolute median costs in C-D grades 0, I, II and IV were higher in the LVC group, but the differences between the volume groups were not statistically significant (p=0.139, p=0.129, p=0.353, p=0.761 respectively, Kruskal-Wallis). However, the median costs for patients with grade III complications were lowest in the HVC group (p=0.015, Kruskal-Wallis). When costs/survival (Dhos/s) were calculated among PC patients, the costs were significantly lower in C-D classes 0-I (p=0.013 and 0.026 respectively, Kruskal-Wallis). (Table 15)

Table 15. Median costs (DHos) among all patients vs. median costs per survival (DHos/s) among PC patients (up to two years after surgery). The costs were the lowest in the HVC group among all patients and in complication grade III.

		HVC	MVC	LVC	p[1]
Total, DHos (range) vs. DHos/s (range)		14 (6.0-203) vs. 8.0 (3.0-1,500)	16 (5.5-285) vs. 9.8 (3.5-2,590)	16 (6-92) vs. 11 (3.0-1,460)	0.019 vs. <0.001
According to complication grade					
	0	10 (6.0-24) vs. 6.0 (3.5-46)	13 (7.0-37) vs. 7.5 (3.5-300)	13 (6.0-49) vs. 8.0 (3.0-28)	0.139 vs. 0.013*
	1	11 (7.0-59) vs. 6.5 (3.5-32)	13 (9.0-27) vs. 11 (4.5-91)	21 (13-28) vs. 40 (14-65)	0.129 vs. 0.026*
	2	15 (7.0-43) vs. 8.3 (3.5-222)	17 (7.0-57) vs. 9.0 (3.5-120)	17.8 (9.0-33) vs. 10 (7,8-15)	0.353 vs. 0.494
	3	21 (9.1-89) vs. 16 (4.6-71)	30 (11-100) vs. 21 (7.5-480)	46 (40-51) vs. 23 (21-26)	0.015* vs. 0.346
	4	57 (19-203) vs. 38 (9.5-1,250)	66.6 (17-285) vs. 42 (8.5-230)	80.6 (6.0-92) vs. 41 (35-49)	0.761 vs. 0.997

[1]*Kruskal-Wallis, *statistically significant, HVC=high volume centre, MVC=median volume centre, LVC=low volume centre*

Factors associated with costs in different cost quartiles were analysed with logistic regression analysis considering sex, age, operation volume and ASA class. The costs were analysed in relation to survival (five days to two years). In the logistic regression analysis both hospital volume and ASA class were associated with the highest cost quartile (>18 DHos/s) as well as with higher costs than

median costs (>8.6 DHos/s). Hospital volume and ASA class were also significant factors in the lowest cost quartile (<6.25 DHos/s), but the impact was the opposite. (Table 16) The model did not reveal any significant factors among C-D grades 0-II patients and among III-IV patients too few patients were available for the multivariate model.

Table 16. A logistic regression analysis demonstrating factors associating with costs per survival in different cost quartiles. High hospital volume and ASA class were significant factors in all cost groups.

	Costs/survival <25%		**Costs/survival >50%**		**Costs/survival >75%**	
Variable	p	OR (95% COI)	p	OR (95% COI)	p	OR (95% COI)
Sex male	reference		reference		reference	
female	0.345	1.226 (0.803-1.873)	0.296	0.823 (0.571-1.186)	0.194	0.754 (0.492-1.155)
Age	0.238	0.988 (0.968-1.008)	0.322	1.009 (0.991-1.028)	0.207	1.015 (0.992-1.038)
ASA	0.001*		0.005*		0.043*	
ASA1	reference		reference		reference	
ASA 2	0.037	0.586 (0.355-0.967)	0.251	1.305 (0.828-2.056)	0.583	1.169 (0.669-2.044)
ASA 3-4	<0.001	0.367 (0.212-0.637)	0.002	2.130 (1.334-3.400)	0.021	1.897 (1.101-3.270)
Operation volume	0.014*		0.009*		0.016*	
HVC	reference		reference		reference	
MVC	0.022	0.585 (0.369-0.927)	0.005	1.731 (1.175-2.550)	0.012	1.756 (1.130-2.729)
LVC	0.035	0.308 (0.103-0.920)	0.071	2.010 (0.941-4.291)	0.047	2.254 (1.012-5.023)

*OR=odds ratio, COI=confidence interval, *statistically significant, ASA=American Society of Anesthesiologists classification, HVC=high volume centre, MVC=median volume centre, LVC=low volume centre*

8 DISCUSSION

8.1 Main results

This thesis summarizes data on the effect of hospital volumes on the treatment and prognosis of PC in Finnish population reported in four original articles. All the articles are based on nationwide information analysed retrospectively. Our findings show that a high operation volume led to statistically lower post-operative mortality and longer survival among PDAC patients. Although, the complication distribution revealed no significant differences, our data suggests that more patients are saved from severe complications in higher-volume centres and overall costs are at lowest in them. In addition, our data reveals that more surgical experience also leads to better access to pancreatic resections for patients and the evaluation of surgical specimens.

8.2 Survival among PDAC patients

The first study described the factors associated with long-term survival. Earlier studies (Carpelan-Holmstrom et al. 2005, Jorgensen et al. 2008) have demonstrated difficulties in the histopathologic diagnostics of pancreatic specimens and stated that re-analysing the samples may change the original diagnosis. Our study corroborates this. Furthermore histopathology has adavanced since the series from 1996 and we can present a lower proportion (35% vs. 49% reported by Carpelan-Holmström et al. 2005) of changed diagnoses. In addition to the developments in histopathology, centralization has also taken small steps in Finland since the 1990 which may have had an effect on the diagnostics. Our second study supports this as the pathological reports were more detailed in HVCs between 2002 and 2008.

The first study suggested that high hospital volumes can lead to long survival among PDAC-patients. Traditionally long-term survival has been associated with small tumours without nodal involvement (Howard et al. 2006, Winter et al. 2006, Chen et al. 2010, Dusch et al. 2014, Paniccia et al. 2015, Strobel et al. 2017, Seppänen et al. 2017). Our study shows that actually the distribution of the most

common stage, IIB, accounts for circa 50% of cases both among patients with under or over four-year survival. In addition, we can confirm that tumour size is a risk factor for poor prognosis. The role of tumour size is also emphasized in the most recent TNM classification (Allen et al. 2017). The new TNM classification also attributed a more significant role to positive lymph nodes. The analysis of our first study did not confirm the effect of nodal status at four years after surgery, but a continuous Cox regression analysis in our second study showed that nodal status is indeed associated with survival.

In addition, both the first and second study demonstrated the beneficial effect of hospital volume on survival. The study by Gooiker et al. 2014 reported a volume-based survival advantage in one and two-year survival rates among PC patients. This study, as well as the studies by Birkmeyer et al. (2007) and Lidsky et al. (2017) included all PC patients. Analysis of the patient records and re-confirmation of the diagnoses of LTSs allowed us to exclude at least most of the patients without a PDAC diagnosis. This is important, because some pancreatic tumours have a significantly better prognosis than PDAC and the distribution of tumours with a better prognosis could result in biased results. Nevertheless, this data concentrating on PDAC patients confirmed the earlier published benefits of hospital volume on survival.

8.3 Operation volume and post-operative mortality

The second study also revealed a wide variation in post-operative mortalities between HVCs, MVCs and LVCs in favour of HVCs. Thirty day mortality ranged from 0-5.5% between 2002 and 2008 to 0.7% to 12% between 2012 and 2014. One may wonder whether the quality of treatment deteriorated between 2002 and 2014 despite centralization. However, the results are not fully comparable: the first study comprised only PDAC patients and also included distal pancreatectomies while the data from the years 2012 -2014 included all patients undergoing PD or TP. Volume-dependency in post-operative mortality rates has also been reported in other studies and our results concur with these (Nordback et al. 2002, Gooiker et al. 2014, Ansari et al. 2014, van der Geest et al. 2016, Ghaferi et al. 2011, Sutton et al. 2014, Sosa et al. 1998, Balzano et al. 2008, Farges et al. 2017, Lidsky et al. 2017, Yoshioka et al. 2014).

No universal classification for high, medium or low volme centre exists. The most commonly used cut-off for a high volumehigh volume centre has been

around 20-30 PDs per year in Europe (Gooiker et al. 2014, van der Geest et al. 2016, Ansari et al. 2014). The recent French study (Farges et al. 2017) set the lower limit at 25 PDs per year. Despite the differences in cut-offs the results appear parallel: high volume centres can achieve post-operative mortality rates from 0 to 3% and low volume centres from 6 to 15%. The French study reported a two-fold risk for 90-day mortality in low volume centres, which concurs with a study by van der Geest et al. (2016). We set the cut-off level for high volume centre at 20 PDs or total pancreatectomies per year which concurs with the results of studies published in Europe up to 2014 (Ansari et al. 2014, Gooiker et al. 2014, Balzano et al. 2008, Nordback et al. 2002). Despite a lower cut-off for HVCs than in the French study (Farges et al. 2017), our second and fourth studies reported much greater differences between HVCs and LVCs: 90-day mortality of 2.5%/1.8% in HVCs and 10.9/15% in LVCs in 2002-2008 and 2012-2014 respectively. On the other hand, a population based study from England (Coupland et al. 2016) set the upper limit to 30 pancreatic resections per year, but found no significant benefit for mortality rates. It seems that the beneficial effect of centralization on post-operative mortality is a result of multiple factors associated with post-operative facilities in the hospitals. Wong et al. (2015) reported that low and high mortality hospitals do not differ in the number of complications (21% vs. 17%, retrospectively) and emphasized attention to the follow-up of patients after surgery.

8.4 Failure to rescue

Failure to rescue is a concept describing the ability of a hospital to avoid death after a complication. Our fourth study revealed that among patients who have had an episode in the ICU, more patients were lost in low volume centres than in high volume centres. Because the total number of these patients was low, no multivariate analysis could be performed. Sheetz et al. (2016) attempted to analyse factors explaining failure to rescue. Their study suggested that the microsystem factors inside a hospital play a major role. This was also noticed by Wakeam et al. (2016), who reported variation in the incidence of and mortality from common post-operative complications: pneumonia, surgical site infection, urinary tract infection, myocardial infarct and post-operative haemorrhage.

8.5 Accessibility to pancreatic resections

The cornerstone of surgical and medical services is safe treatment. Finland has a public health care system intended to offer evidence-based, safe treatment equally to all. Our studies have revealed that post-operative mortalities after pancreatic resection vary in Finland. Furthermore, we wanted to ascertain whether access to treatments is equal. Our third study discussed the incidence of pancreatic resections among PC patients. A population based study by Sharp et al. (2009) from Ireland suggested that there may be some undertreatment among PC patients while only 7% of patients were resected and 39% received chemotherapy. Among patients with loco-regional disease 15-23% underwent surgery. Accessibility to treatment was also associated with patient-related factors such as age and marital status (Bilimoria et al. 2007a). A study by Coupland et al. 2016 used English data and reported an overall resection rate of 8.1%. Our study revealed that in Finland 18% of patients were operated on in experienced health care districts while in districts with less experience the proportion was 7.7%. Moreover, the proportion more than doubled when only non-metastatic diseases were analysed. The wide differences in access to pancreatic resection may be caused by differences in experience in pancreatic surgery or by differences in local treatment paths. Patient-related issues may also explain some of the differences, but it is noteworthy that the challenges in accessing pancreatic surgery did not totally follow the population density chart or geographic boundaries in Finland.

8.6 Operation volume and costs

Studies (Balzano et al. 2016, Sutton et al. 2014, Yoshioka et al. 2014, Tran et al. 2016) have reported that higher hospital volumes may result in more cost-effective treatment of patients. In a public health care system costs are planned to cover the expenditures of care and vice versa. How to analyse the costs per treatment per patient in public health care whose economies are not based on open market rules. Our fourth study sought to describe the cost differences based on the billing list of Tampere University Hospital (Pirkanmaan sairaanhoitopiiri, 2012). Finnish patient records contain all care and treatment information on a ward stay but the information is recorded scatterly and recording policies vary between hospitals. Taking this into consideration, we decided to concentrate on macrolevel factors in cost analysis, such as ward days in different levels of care (intensive care, hospital,

primary health care) and procedures performed. This kind of analysis does not take into consideration variation between ward days at the same level of care, but it offers a functional analysis of the resources consumed resulting in the costs per patient.

Gerard et al. (2017) (2017) analysed cost analysis among PC patients according to Drummond score (Drummond & Jefferson 1996) and stated that only 30% of the analyses were high-quality (Drummond score ≥7). Drummond score fits best for comparing different interventions, especially in randomized controlled studies and Gerard et al. also concentrated on studies comparing different treatment options, not hospital volume. The Drummond score nevertheless highlights important features in cost-analysis. Our study succeeded in question formulation, describing alternatives and in including relevant costs. We analysed the costs in terms of life years gained and presented the results in relation to cost-benefits (life-years) which is emphasized in Drummond score. We also reported confidence intervals for the differences for each volume group. However, it was not possible to separate incremental costs and fixed costs. Because the analysis was based on the variation between resources required, the role of incremental costs was more dominant in our analysis. The fixed costs of maintaining the hospital services were not taken into consideration. Nor did our study include information on quality of life and we found no single specific billing price for each procedure. All in all, the cost analysis reveals the differences in resource use in different volume groups. The cost-quartile analysis showed that lower hospital volumes are associated with higher costs. On the other hand, the analysis also demonstrated that high ASA class was also associated with low costs. The results of the lowest cost-quartile may be explained by the significantly higher mortality rates in lower volume hospitals.

8.7 Weaknessess, advatages and generalisability of the study

The thesis is based on data searches in the national registries in Finland. Hospitals are obligated to send information on their treatment episodes to the Care Register for Social Welfare and Health Care (HILMO) and the information is most commonly transferred from the patient records to the register on the discharge of a patient. The national register is considered reliable. Our study used pancreatic resection and pancreatic diagnoses codes as search terms, because they are unambiguous and routinely marked in the patient records. The register is currently the only objective source of national care information. Naturally the process of

transferring information to the national register may be influenced by human error. Sporadic errors are unlikely to have had a significant impact on the results. The patient data was recorded manually and retrospectively. A prospective, multicentre study would have made data records uniform in all study centres, which would have had a benefical effect on the data retrieval. All in all, the analysis in this study concentrated on variables such as survival, mortality, ASA and age, which are unaffected by the way the original information is recorded. In addition, the re-procedure information was retrieved from several records: surgical, anaesthesiological, radiological or endoscopic, which gave us a reliable overview of the care of the complications.

Despite the advanges of a prospective study on hospital volume, the result of a statistical power calculation is discouraging: If we expected that the mortality in a high volume centre would be half of the mortality in a low volume centre, 2.5% vs. 5%, for example, and we used 90% for power (1-β) and 5% significance (α), we would need a total of 2,415 patients to find a significant difference. This would mean a long longitudinal study in Finland to enroll enough patients even from high volume centres and especially from lower volume centres. Furthermore, to find a siginifcant difference between 10% and 2.5% mortality rates is possible with a total of only 427 patients, which is in concordance with our retrospective results. From the patient's perspective, the lower the mortality rates are, the better, but to find statistical significance to support that, is complex.

The study results concerning survival and mortality can be generalized to other populations with high level health care systems. The features of long-term term survivors concur well with earlier published data. However, the binary analysis suggests that longer prognosis needs more detailed assessment tools than traditional stage classification. Although, the tumour size persisted as a significant factor, the absolute difference was low, 4 mm, between short- and long-term survivors. The results on accessibility of pancreatic resections can be generalized to societies providing public health care. The cost analysis gives information on resource expenditure 90 days post-operatively for every health care system.

It has been calculated that the health care costs will increase rapidly over the next few years, because larger population groups are ageing and enjoy longer life expectancy. This has prompted the politicians to seek to establish a more effective health care system. When it comes to pancreatic surgery even uncomplicated cases demand hospital resources both pre- and post-operatively. This means that re-organizing pancreatic surgery may affect the hospital services as whole. Our results show that increasing surgical experience leads to benefits in treatment selection,

surgery success, cancer prognosis and post-operative costs among PC patients and these favour centralization of pancreatic surgery.

9 SUMMARY OF CONCLUSIONS

This study contributes information on the benefits of sufficient hospital volumes in centres performing pancreatic surgery. In addition, the data reveals that long-term survival is also possible among patients with T3-disease and nodal involvement. The detailed conclusions were as follows:

1. Long-term survival (over four-years) among PDAC patients was associated with tumour size in a multivariate analysis. Stage IIB (T3N1) was the most common stage class among the LTSs. More patients survived over five years in HVCs than in LVCs in a univariate analysis (10.4% in HVCs and 5.8% in LVCs).

2. The 30-day and 90-day mortality rates were lowest in the HVCs among PDAC patients. Survival was significantly higher at two and three years after surgery in the HVCs. Low operation volume (≤5 PDs per year) persisted as a significant factor in multivariate analysis for mortality. Pathological reports on surgical specimens were more detailed in HVCs.

3. Access to radical resections differed across health care districts among PDAC patients in Finland. The proportion of PC patients undergoing surgery was related to the surgical experience available in the particular health care district. More palliative oncologic therapy was offered in areas with less experience available in pancreatic surgery.

4**.** High hospital volume was associated with lower 30- day and 90-day mortality rates after PD or TP. Complication distribution did not differ between the volume groups HVC, MVC and LVC. Overall costs were lowest if a patient was operated on in an HVC.

ACKNOWLEDGEMENTS

This thesis was conducted in Tampere University Hospital and at the Faculty of Medicine and Life Sciences in Tampere University between 2013 and 2018.

I warmly thank Professor Teuvo Tammela for supporting active research in the Tampere University and University Hospital.

I wish to sincerely thank both my supervisors, Associate Professor, Chief of Alimentary Tract Surgery Johanna Laukkarinen and Docent, Medical Director Juhani Sand for commenting and guiding me through the study. It has been an honour to have a chance to study a national database and in a well-planned study.

I am grateful to all co-authors Antti Siiki, MD, PhD, Kaija Vasama, MD, Martine Vornanen, MD, Heini Hölsä MD, Pirkka Ojala MD, Aino Pirttilä MD and Samuli Kiskola MD for their contributions to the study. I warmly thank Mika Helminen, MSc, for explaining and reviewing my statistics.

I warmly thank the research co-ordinator and research nurse Mrs. Satu Järvinen and research nurse Mrs. Katriina Hietanen for the excellent data managing. I would also like to thank THL and FCR for proving us base-line patient registers and hospitals for providing us medical histories of the study patients. The study would not have been possible without their help.

I would also like to acknowledge the Tampere Pancreas Group for listening and commenting preliminary results, posters and presentations of this thesis. I would especially thank Associate Professor Johanna Laukkarinen for giving an oral presentation on my behalf and other group members for taking care of my posters when I have not been able to attend myself. I wish to warmly thank Docent, Development Director Isto Nordback for organizing and starting active pancreatic research in Tampere University Hospital.

I warmly thank Docent Irina Rinta-Kiikka for her efforts in supplying a proper CT scan image for this thesis and her comments on the imaging of the pancreas. I would also like to express thanks to senior consultant, oncologist Tapio Salminen for reviewing the facts on oncologic therapy.

I wish to sincerely thank the official reviewers of my thesis, Professor Pauli Puolakkainen and Professor Esko Kemppainen for sparing time to meet with me and giving excellent comments and tips. With their comments the thesis could be

further improved. I am indebted to Virginia Mattila, MA, for the excellent and fast proofreading.

I owe my gratitude to all colleagues I have to worked with during this thesis. Their support, questions and criticisms have helped to increase my knowledge of my research theme. I warmly thank fantastic Sannamari for help and support during this project.

I warmly thank the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital, the Sigrid Juselius Foundation, the Central Fund of the Finnish Cultural Foundation for funding this study.

I express my warmest gratitude to my parents Paula and Hannu for their support during the study. Finally, I want to thank my husband Antti for listening and supporting me and our children Liina and Tiitus for reminding me of life without research.

REFERENCES

ACT ON SPECIALISED MEDICAL CARE, issued 1.1.1991. Available: https://www.finlex.fi/fi/laki/smur/1989/19891062

ACT ON SOCIAL AND HEALTH CARE CLIENT FEES, issued 3.8.1992. Available: https://www.finlex.fi/fi/laki/ajantasa/1992/19920734?search%5Btype%5D=pika&search%5Bpika%5D=sairaanhoito

AGALIANOS, C., GOUVAS, N., PAPAPARASKEVA, K. and DERVENIS, C., 2016. Positive para-aortic lymph nodes following pancreatectomy for PC. Systematic review and meta-analysis of impact on short term survival and association with clinicopathologic features. HPB, **18**(8), pp. 633-641.

ALLEN, P.J., KUK, D., CASTILLO, C.F., BASTURK, O., WOLFGANG, C.L., CAMERON, J.L., LILLEMOE, K.D., FERRONE, C.R., MORALES-OYARVIDE, V., HE, J., WEISS, M.J., HRUBAN, R.H., GONEN, M., KLIMSTRA, D.S. and MINO-KENUDSON, M., 2017. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma. Annals of Surgery, **265**(1), pp. 185-191.

ANSARI, D., WILLIAMSSON, C., TINGSTEDT, B., ANDERSSON, B., LINDELL, G. and ANDERSSON, R., 2014. Pancreaticoduodenectomy--the transition from a low- to a high volume center. Scandinavian Journal of Gastroenterology, 49(4), pp. 481-484.

ARNELO, U., SIIKI, A., SWAHN, F., SEGERSWÄRD, R., ENOCHSSON, L., DEL CHIARO, M., LUNDELL, M., VERBEKE, C. S. and LÖHR, J.M., 2014. Single – operator pancreatoscopy is helpful in the evaluation of suspected intraductal papillary mucinous neoplasms (IPMN). Pancreatology, 14(6), pp. 510-514.

AOKI, S., MIYATA, H., KONNO, H., GOTOH, M., MOTOI, F., KUMAMARU, H., WAKABAYASHI, G., KAKEJI, Y., MORI, M., SETO, Y. and UNNO, M., 2017. Risk factors of serious postoperative complications after pancreaticoduodenectomy and risk calculators for predicting postoperative complications: a nationwide study of 17,564 patients in Japan. Journal of Hepato-biliary-pancreatic Sciences, 24(5), pp. 243-251.

ARCIDIACONO, P.G., CALORI, G., CARRARA, S., MCNICOL, E.D. and TESTONI, P.A., 2011. Celiac plexus block for pancreatic cancer pain in adults. The Cochrane Database of Systematic Reviews, (3):CD007519. doi(3), pp. CD007519.

BALZANO, G., CAPRETTI, G., CALLEA, G., CANTU, E., CARLE, F. and PEZZILLI, R., 2016. Overuse of surgery in patients with pancreatic cancer. A nationwide analysis in Italy. HPB, 18(5), pp. 470-478.

BALZANO, G., ZERBI, A., CAPRETTI, G., ROCCHETTI, S., CAPITANIO, V. and DI CARLO, V., 2008. Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. The British journal of surgery, 95(3), pp. 357-362.

BASSI, C., 2007. Middle segment pancreatectomy: a useful tool in the management of pancreatic neoplasms. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, **11**(6), pp. 726-729.

BASSI, C., MARCHEGIANI, G., DERVENIS, C., SARR, M., ABU HILAL, M., ADHAM, M., ALLEN, P., ANDERSSON, R., ASBUN, H.J., BESSELINK, M.G., CONLON, K., DEL CHIARO, M., FALCONI, M., FERNANDEZ-CRUZ, L., FERNANDEZ-DEL CASTILLO, C., FINGERHUT, A., FRIESS, H., GOUMA, D.J., HACKERT, T., IZBICKI, J., LILLEMOE, K.D., NEOPTOLEMOS, J.P., OLAH, A., SCHULICK, R., SHRIKHANDE, S.V., TAKADA, T., TAKAORI, K., TRAVERSO, W., VOLLMER, C.R., WOLFGANG, C.L., YEO, C.J., SALVIA, R., BUCHLER, M. and INTERNATIONAL STUDY GROUP ON PANCREATIC SURGERY (ISGPS), 2017. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery, 161(3), pp. 584-591.

BAUER, T.M., EL-RAYES, B.F., LI, X., HAMMAD, N., PHILIP, P.A., SHIELDS, A.F., ZALUPSKI, M.M. and BEKAII-SAAB, T., 2013. Carbohydrate antigen 19-9 is a prognostic and predictive biomarker in patients with advanced pancreatic cancer who receive gemcitabine-containing chemotherapy: a pooled analysis of 6 prospective trials. Cancer 119(2), pp. 285-92

BEATTY, G.L., TORIGIAN, D.A., CHIOREAN, E.G., SABOURY, B., BROTHERS, A., ALAVI, A., TROXEL, A.B., SUN, W., TEITELBAUM, U.R., VONDERHEIDE, R.H. and O'DWYER, P.J., 2013. A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. Clinical Cancer, 19(22), pp. 6286-6295.

BECKER, A.E., HERNANDEZ, Y.G., FRUCHT, H. and LUCAS, A.L., 2014. Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. World journal of gastroenterology, **20**(32), pp. 11182-11198.

BEST, L.M., RAWJI, V., PEREIRA, S.P., DAVIDSON, B.R. and GURUSAMY, K.S., 2017. Imaging modalities for characterising focal pancreatic lesions. The Cochrane Database of Systematic Reviews, 4, pp. CD010213.

BILIMORIA, K.Y., BENTREM, D.J., KO, C.Y., STEWART, A.K., WINCHESTER, D.P. and TALAMONTI, M.S., 2007a. National failure to operate on early stage pancreatic cancer. Annals of Surgery, **246**(2), pp. 173-180.

BILIMORIA, K.Y., BENTREM, D.J., KO, C.Y., RITCHEY, J., STEWART, A.K., WINCHESTER, D.P. and TALAMONTI, M.S., 2007b. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. Cancer, 110(4), pp. 738-744.

BIPAT, S., PHOA S., VAN DELDEN, O. M., BOSSUYT, P. M.M, GOUMA, D.J., LAME, J.S. and STROKER J., 2005. Ultrasonography, Computed Tomography and Magnetic Resonance Imaging for Diagnosis and Determining Resectability of Pancreatic Adenocarcinoma A Meta-Analysis. Journal of Computer Assisted Tomography, 29(4), pp. 438-445.

BIRKMEYER, J.D., SUN, Y., WONG, S.L. and STUKEL, T.A., 2007. Hospital volume and late survival after cancer surgery. Annals of Surgery, 245(5), pp. 777-783.

BRONSTEIN, Y.L., LOYER, E.M., KAUR, H., CHOI, H., DAVID, C., DUBROW, R.A., BROEMELING, L.D., CLEARY, K.R. and CHARNSANGAVEJ, C., 2004.

Detection of small pancreatic tumors with multiphasic helical CT. AJR, 182(3), pp. 619-623.

BURNETT, A. and CHOKSHI, R. 2013. Sensitivity of ERCP standard cytology: 10 year review of the literature. Journal of Surgical Research, 184(1), pp. 304-11.

CAMPBELL, F., BENNETT, M. and FOULIS, A.J. 2002, Minimum Dataset for Histopathological Reporting of Pancreatic, Ampulla of Vater and Bile Duct Carcinoma . Royal College of Pathologists: London

CANTO, M.I, HARINCK, F., HRUBAN R. H., OFFERHAUS, G.J., POLEY, J-W., KAMEL, I., NIO, Y., SCHULICK, R.S., BASSI, C., KLUIJT, I., LEVY, M.J., CHAK, A., FOCKENS, P., GOGGINS, M. AND BRUNO, M., 2013. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer Consortium. Gut, 62, pp.339-347

CARPELAN-HOLMSTROM, M., NORDLING, S., PUKKALA, E., SANKILA, R., LUTTGES, J., KLOPPEL, G. and HAGLUND, C., 2005. Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry. Gut, 54(3), pp. 385-387.

CARTER, G.T., DUONG, V., HO, S., NGO, K.C., GREER, C.L. and WEEKS, D.L., 2016, Side effects of commonly prescribed analgesic medications, Physical Medicine & Rehabilitation Clinics of North America, 25(2), pp. 457-70.

CAZACU, I.M., LUZURIAGA, A.A., SAFTOIU, A., VILMANN, P. and BHUTANI, M.S., 2018. A quarter century of EUS-FNA: Progress, milestones, and future directions. Endoscopic Ultrasound, 7(3), pp. 141–160.

CHEN, W. WHO classification of tumors. 2017. [updated 08/2017, visited 07/05/2018].Available: http://www.pathologyoutlines.com/topic/pancreaswho.html

CHEN, J.W., BHANDARI, M., ASTILL, D.S., WILSON, T.G., KOW, L., BROOKE-SMITH, M., TOOULI, J. and PADBURY, R.T., 2010. Predicting patient survival after pancreaticoduodenectomy for malignancy: histopathological criteria based on perineural infiltration and lymphovascular invasion. HPB, 12(2), pp. 101-108.

CLINICAL SERVICE COMMITTEE AUGIS, Guidance on minimum surgeon volumes 2010. [updated 2010, visited 27/11/2017] Available: http://www.augis.org/wp-content/uploads/2014/ 5/AUGIS_recommendations_on_Minimum

COLLISSON, E.A., SADANANDAM, A., OLSON, P., GIBB, W.J., TRUITT, M., GU, S., COOC, J., WEINKLE, J., KIM, G.E., JAKKULA, L., FEILER, H.S., KO, A.H., OLSHEN, A.B., DANENBERG, K.L., TEMPERO, M.A., SPELLMAN, P.T., HANAHAN, D. and GRAY, J.W., 2011. Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. Nature Medicine, 17(4), pp. 500-503.

CONROY, T., BACHET, J.B., AYAV, A., HUGUET, F., LAMBERT, A., CARAMELLA, C., MARECHAL, R., VAN LAETHEM, J.L. and DUCREUX, M., 2016. Current standards and new innovative approaches for treatment of pancreatic cancer. European Journal of Cancer, 57, pp. 10-22.

COOPERMAN, A.M., BRUCKNER, H., SNADY, H., HAMMERMAN, H., FADER, A., FELD, M., GOLIER, F., RUSH, T., SIEGAL, J., KASMIN, F., COHEN, S., WAYNE, M.G., ISKANDAR, M.E. and STEELE, J.G., 2018. Cancer of the Pancreas-Actual 5, 10, and 20+Year Survival: The Lucky and Fortunate Few. The Surgical clinics of North America, 98(1), pp. 73-85.

CUSCHIERI, A., 1994. Laparoscopic surgery of the pancreas. Journal of the Royal College of Surgeons of Edinburgh, 39(3), pp. 178-184.

COUPLAND, V.H., KONFORTION, J., JACK, R.H., ALLUM, W., KOCHER, H.M., RIAZ, S.P., LUCHTENBORG, M. and MOLLER, H., 2016. Resection rate, hospital procedure volume and survival in pancreatic cancer patients in England: Population-based study, 2005-2009. European Journal of Surgical Oncology, **42**(2), pp. 190-196.

DAVEE, T., CORONEL, E., PAPAFRAGKAKIS, C., THAIUDOM, S., LANKE, G., CHAKINALA, R.C., NOGUERAS GONZALEZ, G.M., BHUTANI, M.S., ROSS, W.A., WESTON, B.R. and LEE, J.H., 2018. Pancreatic cancer screening in high-risk individuals with germline genetic mutations. Gastrointestinal Endoscopy, 87(6), pp. 1443-1450.

DECREE ON SOCIAL AND HEALTH CARE CLIENT FEES, issued 1.1.1993. Available: https://www.finlex.fi/fi/laki/smur/1992/19920912?search%5Btype%5D=pika&search%5Bpika%5D=erikoissairaanhoito

DE ROOIJ, T, LU, M.Z., STEEN, M.W., 2016a.Minimally invasive versus open pancreatoduodenectomy: systematic review and meta-analysis of comparative cohort and registry studies. Annals of Surgery, 264, pp. 257–267.

DE ROOIJ T., VAN HILST J., BOERMA D., BONSING, B.A., DAAMS, F., VAN DAM, R.M., DIJKGRAAF, M.G., VAN EIJCK, C.H., FESTEN, S., GERHARDS, M.F., KOERKAMP, B.G., VAN DER HARST, E., DE HINGH, I.H., KAZEMIER, G., KLAASE, J., DE KLEINE, R.H., VAN LAARHOVEN, C.J., LIPS, D.J., LUYER, M.D., MOLENAAR, I.Q., PATIJN, G.A., ROOS, D., SCHEEPERS, J.J., VAN DER SCHELLING, G.P., STEENVOORDE, P., VRIENS, M.R., WIJSMAN, J.H., GOUMA, D.J., BUSCH, O.R., HILAL, M.A., and BESSELINK, M.G., 2016b.Impact of a Nationwide Training Program in Minimally Invasive Distal Pancreatectomy (LAELAPS). Annals of Surgery 264(5), pp. 754–762.

DE ROOIJ, T., VAN HILST, J., TOPAL, B., BOSSCHA, K., BRINKMAN, D.J., GERHARDS, M.F., DE HINGH, I.H., KARSTEN, T.M., LIPS, D.J., LUYER, M.D., MARSMAN, H.A., VAN RIJSSEN, L.B., STEEN, M.W., BUSCH, O.R., FESTEN, S., BESSELINK, M.G. and DUTCH PANCREATIC CANCER GROUP, 2017. Outcomes of a Multicenter Training Program in Laparoscopic Pancreatoduodenectomy (LAELAPS-2). Annals of Surgery, epub ahead of print.

DE ROOIJ, T., VAN HILST, J., BOSSCHA, K., DIJKGRAAF, M.G., GERHARDS, M.F., GROOT KOERKAMP, B., HAGENDOORN, J., DE HINGH, I.H., KARSTEN, T.M., LIPS, D.J., LUYER, M.D., MOLENAAR, I.Q., VAN SANTVOORT, H.C., TRAN, T.C.K., BUSCH, O.R., FESTEN, S., BESSELINK, M.G. and DUTCH PANCREATIC CANCER GROUP, 2018. Minimally invasive versus open pancreatoduodenectomy (LEOPARD-2): study protocol for a randomized controlled trial. Trials, 19(1), pp. 1-017-2423-4.

DEL CHIARO, M., SEGERSVARD, R., RANGELOVA, E., COPPOLA, A., SCANDAVINI, C.M., ANSORGE, C., VERBEKE, C. and BLOMBERG, J., 2015. Cattell-Braasch Maneuver Combined with Artery-First Approach for Superior Mesenteric-Portal Vein Resection During Pancreatectomy. Journal of Gastrointestinal Surgery, 19(12), pp. 2264-2268.

DEL CHIARO, M., VERBEKE, C., SALVIA, R., KLOPPEL, G., WERNER, J., MCKAY, C., FRIESS, H., MANFREDI, R., VAN CUTSEM, E., LOHR, M., SEGERSVARD, R. and EUROPEAN STUDY GROUP ON CYSTIC TUMOURS OF THE PANCREAS, 2013. European experts consensus statement on cystic tumours of the pancreas. Digestive and Liver Disease, 45(9), pp. 703-711.

DINDO, D., DEMARTINES, N. and CLAVIEN, P.A., 2004. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of Surgery, 240(2), pp. 205-213.

DREYER, S.B., JAMIESON, N.B., UPSTILL-GODDARD, R., BAILEY, P-J., MCKAY, C.J., AUSTRALIAN PANCREATIC CANCER GENOME INITIATIVE, BIANKIN, A.C., AND CHANG, D.K., 2018. Defining the molecular pathology of pancreatic body and tail adenocarcinoma. BJS, 105, pp. e183–e191

DRUMMOND, M.F. and JEFFERSON, T.O., 1996. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal, **313**(7052), pp. 275-283.

DU, T., BILL, K.A., FORD, J., BARAWI, M., HAYWARD, R.D., ALAME, A. and BERRI, R.N., 2018. The diagnosis and staging of pancreatic cancer: A comparison of endoscopic ultrasound and computed tomography with pancreas protocol. American Journal of Surgery, 215(3), pp. 472-475.

DUCREUX, M., SA. CUHNA, A., CARAMELLA, C., HOLLEBECQUE, A., BURTIN, P., GOÉRÉ, D., SEUFFERLEIN, T., HAUSTERMANS, K., VAN LAETHEM, J., CONROY, T. and ARNOLD, D., 2015. Cancer of the Pancreas: ESMO Clinical Practice Guidelines. Annals of Oncology, 26(suppl 5), pp. v56.

DUSCH, N., WEISS, C., STROBEL, P., KIENLE, P., POST, S. and NIEDERGETHMANN, M., 2014. Factors predicting long-term survival following pancreatic resection for ductal adenocarcinoma of the pancreas: 40 years of experience. Journal of Gastrointestinal Surgery, 18(4), pp. 674-681.

EDGE, S.B. and COMPTON, C.C., 2010, The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of Surgical Oncology, 17(6), pp. 1471-4

ELBERM, H., RAVIKUMAR, R., SABIN, C., ABU HILAL, M., AL-HILLI, A., AROORI, S., BOND-SMITH, G., BRAMHALL, S., COLDHAM, C., HAMMOND, J., HUTCHINS, R., IMBER, C., PREZIOSI, G., SALEH, A., SILVA, M., SIMPSON, J., SPOLETINI, G., STELL, D., TERRACE, J., WHITE, S., WIGMORE, S. and FUSAI, G., 2015. Outcome after pancreaticoduodenectomy for T3 adenocarcinoma: A multivariable analysis from the UK Vascular Resection for Pancreatic Cancer Study Group. European Journal of Surgical Oncology, 41(11), pp. 1500-1507.

ELGHAZAWY, R.M. and VERBEKE, C.S., 2010. Pathology of pancreatic tumours. Surgery, **28**(5), pp. 189.

ESPOSITO, I., KLEEFF, J., BERGMANN, F., REISER, C., HERPEL, E., FRIESS, H., SCHIRMACHER, P. and BUCHLER, M.W., 2008. Most pancreatic cancer resections are R1 resections. Annals of Surgical Oncology, 15(6), pp. 1651-1660.

ESPOSITO, I., KONUKIEWITZ, B., SCHLITTER, A.M. and KLOPPEL, G., 2014. Pathology of pancreatic ductal adenocarcinoma: facts, challenges and future developments. World Journal of Gastroenterology, 20(38), pp. 13833-13841.

EUROPEAN STUDY GROUP ON CYSTIC TUMOURS OF THE PANCREAS, 2018. European evidence-based guidelines on pancreatic cystic neoplasms. Gut, **67**(5), pp. 789-804.

EVANS, D.B., ERICKSON, B.A. and RITCH, P., 2010. Borderline resectable pancreatic cancer: definitions and the importance of multimodality therapy. Annals of Surgical Oncology, 17(11), pp. 2803-2805.

FARGES, O., BENDERSKY, N., TRUANT, S., DELPERO, J.R., PRUVOT, F.R. and SAUVANET, A., 2017. The Theory and Practice of Pancreatic Surgery in France. Annals of Surgery, 266(5), pp. 797-804.

FERLAY, J., STELIAROVA-FOUCHER, E., LORTET-TIEULENT, J., ROSSO, S., COEBERGH, J.W., COMBER, H., FORMAN, D. and BRAY, F., 2013. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. European Journal of Cancer, 49(6), pp. 1374-1403.

FINNISH CANCER REGISTRY, 2015. Syöpätilastot. [updated 2015, visited 12/15, 2017]. Available: https://syoparekisteri.fi/tilastot/tautitilastot/

FOGEL, E.L., SHAHDA, S., SANDRASEGARAN, K., DEWITT, J., EASLER, J.J., AGARWAL, D.M., EAGLESON, M., ZYROMSKI, N.J., HOUSE, M.G., ELLSWORTH, S., EL HAJJ, I., O'NEIL, B.H., NAKEEB, A. and SHERMAN, S., 2017. A Multidisciplinary Approach to Pancreas Cancer in 2016: A Review. The American Journal of Gastroenterology, 112(4), pp. 537-554.

GAGNER, M. and POMP, A., 1994. Laparoscopic pylorus-preserving pancreatoduodenectomy. Surgical Endoscopy, 8(5), pp. 408-410.

GANI, F., HUNDT, J., MAKARY, M.A., HAIDER, A.H., ZOGG, C.K. and PAWLIK, T.M., 2016. Financial Impact of Postoperative Complication Following Hepato-Pancreatico-Biliary Surgery for Cancer. Annals of Surgical Oncology, 23(4), pp. 1064-1070.

GERARD, C., FAGNONI, P., VIENOT, A., BORG, C., LIMAT, S., DAVAL, F., CALAIS, F., VARDANEGA, J., JARY, M. and NERICH, V., 2017. A systematic review of economic evaluation in pancreatic ductal adenocarcinoma. European Journal of Cancer, 86, pp. 207-216.

GHAFERI, A.A., BIRKMEYER, J.D. and DIMICK, J.B., 2011. Hospital volume and failure to rescue with high-risk surgery. Medical care, 49(12), pp. 1076-1081.

GILLEN, S., SCHUSTER, T., MEYER ZUM BUSCHENFELDE, C., FRIESS, H. and KLEEFF, J., 2010. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS medicine, 7(4), pp. e1000267.

GIOVINAZZO, F., TURRI, G., KATZ, M.H., HEATON, N. and AHMED, I., 2016. Meta-analysis of benefits of portal-superior mesenteric vein resection in pancreatic resection for ductal adenocarcinoma. BJS, 103(3), pp. 179-191.

GOOIKER, G.A., LEMMENS, V.E., BESSELINK, M.G., BUSCH, O.R., BONSING, B.A., MOLENAAR, I.Q., TOLLENAAR, R.A., DE HINGH, I.H. and WOUTERS, M.W., 2014. Impact of centralization of pancreatic cancer surgery on resection rates and survival. BJS, 101(8), pp. 1000-1005.

GURUSAMY, K.S., KUMAR, S. and DAVIDSON, B.R., 2013. Prophylactic gastrojejunostomy for unresectable periampullary carcinoma. The Cochrane Database of Systematic Reviews, (2):CD008533. doi(2), pp. CD008533.

HATA, T., MOTOI, F., ISHIDA, M., NAITOH, T., KATAYOSE, Y., EGAWA, S. and UNNO, M., 2016. Effect of Hospital Volume on Surgical Outcomes After

Pancreaticoduodenectomy: A Systematic Review and Meta-analysis. Annals of Surgery, 263(4), pp. 664-672.

HAYASAKI, A., SHUJI. I., KISHIWADA, M., FUJII, T., IIZAWA, Y., KATO, H., TANEMURA, A., MURATA,. Y., YOSHINORI, A., KURIYAMA, N., MIZUNO., S., USUI., M., and SAKURAI. H., 2018. Survival analysis in Patients with Pancreatic Ductal Adenocarcinoma undergoing chemoradiotherapy followed by surgery according to the international consensus on the 2017 definition of borderline resectable cancer. Cancers (Basel), 10(3), pp. 65.

HEMPEL, S., PLODECK, V., MIERKE, F., DISTLER, M., AUST, D.E., SAEGER, H.D., WEITZ, J. and WELSCH, T., 2017. Para-aortic lymph node metastases in pancreatic cancer should not be considered a watershed for curative resection. Scientific reports, **7**(1), pp. 7688-017-08165-w.

HEALTH CARE ACT, issued in Helsinki on 30 December 2010. Available: https://www.finlex.fi/en/laki/kaannokset/2010/en20101326_20131293.pdf

HIDALGO, M.D., 2010. Pancreas Cancer. New England Journal of Medicine, 362, pp.1605-17.

HIPPISLEY-COX, J. and COUPLAND, C. 2012. Identifying patients with suspected pancreatic cancer in primary care derivation and validation of an algorithm, British Journal of General Practice, pp. e38-45

HOWARD, T.J., KRUG, J.E., YU, J., ZYROMSKI, N.J., SCHMIDT, C.M., JACOBSON, L.E., MADURA, J.A., WIEBKE, E.A. and LILLEMOE, K.D., 2006. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. Journal of Gastrointestinal Surgery, 10(10), pp. 1338-45; discussion 1345-6.

HOWLADER, N.,NOONE, A.M.,KRAPCHO, M.,GARSHELL, J.NEYMAN, N.,ALTERKRUSE, S.F.,KOSARY, C.L.,YU, M., RUHL, J.,TATALOVISH, Z., CHO, H., MARIOTTO, A.,LEWIS, D. R.,CHEN, H.S., FEUER, E.J.,CRONIN, K.A., SEER Cancer Statistics Review, 1975-2010. [updated 2013, visited 31/7/2018]. Available: http://seer.cancer.gov/csr/1975_2010

HUTTNER, F.J., FITZMAURICE, C., SCHWARZER, G., SEILER, C.M., ANTES, G., BUCHLER, M.W. and DIENER, M.K., 2016. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. The Cochrane Database of Systematic Reviews, 2, pp. CD006053.

JEURNINK, S.M., STEYERBERG, E.W., VAN HOOFT, J.E., VAN EIJCK, C.H., SCHWARTZ, M.P., VLEGGAAR, F.P., KUIPERS, E.J., SIERSEMA, P.D. and DUTCH SUSTENT STUDY GROUP, 2010. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointestinal Endoscopy, 71(3), pp. 490-499.

JONES, S., ZHANG, X., PARSONS, D.W., LIN, J.C., LEARY, R.J., ANGENENDT, P., MANKOO, P., CARTER, H., KAMIYAMA, H., JIMENO, A., HONG, S.M., FU, B., LIN, M.T., CALHOUN, E.S., KAMIYAMA, M., WALTER, K., NIKOLSKAYA, T., NIKOLSKY, Y., HARTIGAN, J., SMITH, D.R., HIDALGO, M., LEACH, S.D., KLEIN, A.P., JAFFEE, E.M., GOGGINS, M., MAITRA, A., IACOBUZIO-DONAHUE, C., ESHLEMAN, J.R., KERN, S.E., HRUBAN, R.H., KARCHIN, R., PAPADOPOULOS, N., PARMIGIANI, G., VOGELSTEIN, B., VELCULESCU, V.E. and KINZLER, K.W., 2008. Core signaling pathways in

human pancreatic cancers revealed by global genomic analyses. Science, 321(5897), pp. 1801-1806.

JORGENSEN, M.T., FENGER, C., KLOPPEL, G. and LUTTGES, J., 2008. Long-term survivors among Danish patients after resection for ductal adenocarcinoma of the pancreas. Scandinavian Journal of Gastroenterology, 43(5), pp. 581-583.

KANTOR, O., TALAMONTI, M.S., STOCKER, S.J., WANG, C.H., WINCHESTER, D.J., BENTREM, D.J., PRINZ, R.A. and BAKER, M.S., 2016. A Graded Evaluation of Outcomes Following Pancreaticoduodenectomy with Major Vascular Resection in Pancreatic Cancer. Journal of Gastrointestinal Surgery, 20(2), pp. 284-292.

KAUSCH, W., 1912. Carsinoma of the duodenal papilla and its radical excision. Beitrage zur klinischen Chirurgie, 78, pp. 439.

KE, K.M., HOLLINGWORTH, W. and NESS, A.R., 2012. The costs of centralization: a systematic review of the economic impact of the centralization of cancer services. European Journal of Cancer Care, 21(2), pp. 158-168.

KEANE, M.G., SHAMALI, A., NILSSON, L.N., ANTILA, A., MILLASTRE BOCOS, J., MARIJINISSEN VAN ZANTEN, M., VERDEJO GIL, C., MAISONNEUVE, P., VAALAVUO, Y., HOSKINS, T., ROBINSON, S., CEYHAN, G.O., ABU HILAL, M., PEREIRA, S.P., LAUKKARINEN, J. and DEL CHIARO, M., 2018. Risk of malignancy in resected pancreatic mucinous cystic neoplasms. BJS, **105**(4), pp. 439-446.

KHORANA, A.A., MANGU, P.B., BERLIN, J., ENGEBRETSON, A., HONG, T.S., MAITRA, A., MOHILE, S.G., MUMBER, M., SCHULICK, R., SHAPIRO, M., URBA, S., ZEH, H.J. and KATZ, M.H.G., 2017. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology, 35(20), pp. 2324-2328.

KIMURA, Y., KIKUYAMA, M., KODAMA, Y., 2015. Acute Pancreatitis as a Possible Indicator of Pancreatic
Cancer: The Importance of Mass Detection. Internal Medicine, 54(17), pp. 2109-14.

KLEEFF, J., COSTELLO, E., JACKSON, R., HALLORAN, C., GREENHALF, W., GHANEH, P., LAMB, R.F., LERCH, M.M., MAYERLE, J., PALMER, D., COX, T., RAWCLIFFE, C.L., STROBEL, O., BUCHLER, M.W. and NEOPTOLEMOS, J.P., 2016. The impact of diabetes mellitus on survival following resection and adjuvant chemotherapy for pancreatic cancer. British Journal of Cancer, 115(7), pp. 887-894.

KONSTANTINIDIS, I.T., WARSHAW, A.L., ALLEN, J.N., BLASZKOWSKY, L.S., CASTILLO, C.F., DESHPANDE, V., HONG, T.S., KWAK, E.L., LAUWERS, G.Y., RYAN, D.P., WARGO, J.A., LILLEMOE, K.D. and FERRONE, C.R., 2013. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? Annals of Surgery, 257(4), pp. 731-736.

LAHERU, D., LUTZ, E., BURKE, J., BIEDRZYCKI, B., SOLT, S., ONNERS, B., TARTAKOVSKY, I., NEMUNAITIS, J., LE, D., SUGAR, E., HEGE, K. and JAFFEE, E., 2008. Allogeneic granulocyte macrophage colony-stimulating factor-secreting tumor immunotherapy alone or in sequence with cyclophosphamide for metastatic pancreatic cancer: a pilot study of safety, feasibility, and immune activation. Clinical Cancer Research, 14(5), pp. 1455-1463.

LAITINEN, I., SAND, J., PEROMAA, P., NORDBACK, I. and LAUKKARINEN, J., 2017. Quality of life in patients with pancreatic ductal adenocarcinoma undergoing pancreaticoduodenectomy. Pancreatology, **17**(3), pp. 445-450.

LE, D.T., LUTZ, E., URAM, J.N., SUGAR, E.A., ONNERS, B., SOLT, S., ZHENG, L., DIAZ, L.A.,Jr, DONEHOWER, R.C., JAFFEE, E.M. and LAHERU, D.A., 2013. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. Journal of Immunotherapy, 36(7), pp. 382-389.

LEMMENS, V.E., BOSSCHA, K., VAN DER SCHELLING, G., BRENNINKMEIJER, S., COEBERGH, J.W. and DE HINGH, I.H., 2011. Improving outcome for patients with pancreatic cancer through centralization. BJS, 98(10), pp. 1455-1462.

LETTON, A.H. and WILSON, J.P., 1959. Traumatic secerance of pancreas treated by Roux-Y anastomosis. Surgical Gynecology and Obstetrics, **109**(473).

LIAO, W.C., CHIEN, K.L., LIN, Y.L., WU, M.S., LIN, J.T., WANG, H.P. and TU, Y.K., 2013. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. The Lancet.Oncology, 14(11), pp. 1095-1103.

LIDSKY, M.E., SUN, Z., NUSSBAUM, D.P., ADAM, M.A., SPEICHER, P.J. and BLAZER, D.G.,3rd, 2017. Going the Extra Mile: Improved Survival for Pancreatic Cancer Patients Traveling to High volume Centers. Annals of Surgery, 266(2), pp. 333-338.

LUTZ, M.P., ZALCBERG, J.R., DUCREUX, M., AUST, D., BRUNO, M.J., BUCHLER, M.W., DELPERO, J.R., GLOOR, B., GLYNNE-JONES, R., HARTWIG, W., HUGUET, F., LAURENT-PUIG, P., LORDICK, F., MAISONNEUVE, P., MAYERLE, J., MARTIGNONI, M., NEOPTOLEMOS, J., RHIM, A.D., SCHMIED, B.M., SEUFFERLEIN, T., WERNER, J., VAN LAETHEM, J.L. and OTTO, F., 2017. 3rd St. Gallen EORTC Gastrointestinal Cancer Conference: Consensus recommendations on controversial issues in the primary treatment of pancreatic cancer. European Journal of Cancer, 79, pp. 41-49.

MACIAS, N., SAYAGUES, J.M., ESTEBAN, C., IGLESIAS, M., GONZALEZ, L.M., QUINONES-SAMPEDRO, J., GUTIERREZ, M.L., CORCHETE, L.A., ABAD, M.M., BENGOECHEA, O. and MUNOZ-BELLVIS, L., 2018. Histologic Tumor Grade and Preoperative Bilary Drainage are the Unique Independent Prognostic Factors of Survival in Pancreatic Ductal Adenocarcinoma Patients After Pancreaticoduodenectomy. Journal of Clinical Gastroenterology, 52(2), pp. e11-e17.

MAISONNEUVE, P. and LOWENFELS, A.B.,2015. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. International Journal of Epidemiology, 44(1), pp. 186 – 198.

MAHER, E.R., NEUMANN, H.P., RICHARDS, S., 2011. Von Hippel-Lindau disease: a clinical and scientific review. European Journal of Genetics, 19(6), pp. 617-623.

MALVEZZI M, BERTUCCIO P, LEVI F ET AL., 2014. European cancer mortality predictions for the year 2014. Annals of Oncology, 25, pp. 1650 – 1656.

MAMIDANNA, R., NI, Z., ANDERSON, O., SPIEGELHALTER, S.D., BOTTLE, A., AYLIN, P., FAIZ, O. and HANNA, G.B., 2016. Surgeon Volume and Cancer Esophagectomy, Gastrectomy, and Pancreatectomy: A Population-based Study in England. Annals of Surgery, 263(4), pp. 727-732.

MARECHAL, R., BACHET, J.B., MACKEY, J.R., DALBAN, C., DEMETTER, P., GRAHAM, K., COUVELARD, A., SVRCEK, M., BARDIER-DUPAS, A.,

HAMMEL, P., SAUVANET, A., LOUVET, C., PAYE, F., ROUGIER, P., PENNA, C., ANDRE, T., DUMONTET, C., CASS, C.E., JORDHEIM, L.P., MATERA, E.L., CLOSSET, J., SALMON, I., DEVIERE, J., EMILE, J.F. and VAN LAETHEM, J.L., 2012. Levels of gemcitabine transport and metabolism proteins predict survival times of patients treated with gemcitabine for pancreatic adenocarcinoma. Gastroenterology, 143(3), pp. 664-74.e1-6.

MARTIN, L. K., WEI, L., TROLLI, E. and BEKAII-SAAB T. 2012.Elevated baseline CA19-9 levels correlate with adverse prognosis in patients with early- or advanced-stage pancreas cancer. Medical Oncology, 29(5), pp.3101-7

MARTIN, R.C.,2nd, BRENNAN, M.F. and JAQUES, D.P., 2002. Quality of complication reporting in the surgical literature. Annals of Surgery, **235**(6), pp. 803-813.

MICHELS, J., VITALE, I., SAPARBAEV, M., CASTEDO, M. and KROEMER, G., 2014. Predictive biomarkers for cancer therapy with PARP inhibitors. Oncogene, 33(30), pp. 3894-3907.

MIERKE, F., HEMPEL, S., DISTLER, M., AUST, D.E., SAEGER, H.D., WEITZ, J. and WELSCH, T., 2016. Impact of Portal Vein Involvement from Pancreatic Cancer on Metastatic Pattern After Surgical Resection. Annals of Surgical Oncology, 23(Suppl 5), pp. 730-736.

MINISTRY OF HEALTH AND SOCIAL AFFAIRS, 2018. Palvelujen meno ja rahoitus. [updated 2013, visited 16/8/2018]. Available: https://stm.fi/talous-ja-toiminta/palvelujen-menot-ja-rahoitus

MURTAUGH, L.C., LEACH, S.D., 2007. A case of mistaken identity? Non-ductal origins of pancreatic "ductal" cancers. Cancer Cell 11(3), pp. 211-3.

NAWAZ, H., FAN, C.Y., KLOKE, J., KHALID, A., MCGRATH, K., LANDSITTEL, D. and PAPACHRISTOU, G.I., 2013. Performance characteristics of endoscopic ultrasound in the staging of pancreatic cancer: a meta-analysis. JOP, 14(5), pp. 484-497.

NEOPTOLEMOS, J.P., STOCKEN, D.D., DUNN, J.A., ALMOND, J., BEGER, H.G., PEDERZOLI, P., BASSI, C., DERVENIS, C., FERNANDEZ-CRUZ, L., LACAINE, F., BUCKELS, J., DEAKIN, M., ADAB, F.A., SUTTON, R., IMRIE, C., IHSE, I., TIHANYI, T., OLAH, A., PEDRAZZOLI, S., SPOONER, D., KERR, D.J., FRIESS, H., BUCHLER, M.W. and EUROPEAN STUDY GROUP FOR PANCREATIC CANCER, 2001. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. Annals of Surgery, 234(6), pp. 758-768.

NEOPTOLEMOS, J.P., STOCKEN, D.D., BASSI, C., GHANEH, P., CUNNINGHAM, D., GOLDSTEIN, D., PADBURY, R., MOORE, M.J., GALLINGER, S., MARIETTE, C., WENTE, M.N., IZBICKI, J.R., FRIESS, H., LERCH, M.M., DERVENIS, C., OLAH, A., BUTTURINI, G., DOI, R., LIND, P.A., SMITH, D., VALLE, J.W., PALMER, D.H., BUCKELS, J.A., THOMPSON, J., MCKAY, C.J., RAWCLIFFE, C.L., BUCHLER, M.W. and EUROPEAN STUDY GROUP FOR PANCREATIC CANCER, 2010. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA, 304(10), pp. 1073-1081.

NEOPTOLEMOS, J.P., PALMER, D.H., GHANEH, P., PSARELLI, E.E., VALLE, J.W., HALLORAN, C.M., FALUYI, O., O'REILLY, D.A., CUNNINGHAM, D., WADSLEY, J., DARBY, S., MEYER, T., GILLMORE, R., ANTHONEY, A.,

LIND, P., GLIMELIUS, B., FALK, S., IZBICKI, J.R., MIDDLETON, G.W., CUMMINS, S., ROSS, P.J., WASAN, H., MCDONALD, A., CROSBY, T., MA, Y.T., PATEL, K., SHERRIFF, D., SOOMAL, R., BORG, D., SOTHI, S., HAMMEL, P., HACKERT, T., JACKSON, R., BUCHLER, M.W. and EUROPEAN STUDY GROUP FOR PANCREATIC CANCER, 2017. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet, 389(10073), pp. 1011-1024.

NILSSON, L.N., KEANE, M.G., SHAMALI, A., MILLASTRE BOCOS, J., MARIJINISSEN VAN ZANTEN, M., ANTILA, A., VERDEJO GIL, C., DEL CHIARO, M. and LAUKKARINEN, J., 2016. Nature and management of pancreatic mucinous cystic neoplasm (MCN): A systematic review of the literature. Pancreatology, 16(6), pp. 1028-1036.

NIMPTSCH, U., KRAUTZ, C., WEBER, G.F., MANSKY, T. and GRUTZMANN, R., 2016. Nationwide In-hospital Mortality Following Pancreatic Surgery in Germany is Higher than Anticipated. Annals of Surgery, 264(6), pp. 1082-1090.

NORDBACK, L., PARVIAINEN, M., RATY, S., KUIVANEN, H. and SAND, J., 2002. Resection of the head of the pancreas in Finland: effects of hospital and surgeon on short-term and long-term results. Scandinavian Journal of Gastroenterology, 37(12), pp. 1454-1460.

OECD, Health at a Glance 2017: OECD Indicators, OECD Publishing, Paris. [visited 02/16, 2017, updated 2017]. Available: http//dx.doi.org/10.1787/health_glance-2017-en.

OETTLE, H., POST, S., NEUHAUS, P., GELLERT, K., LANGREHR, J., RIDWELSKI, K., SCHRAMM, H., FAHLKE, J., ZUELKE, C., BURKART, C., GUTBERLET, K., KETTNER, E., SCHMALENBERG, H., WEIGANG-KOEHLER, K., BECHSTEIN, W.O., NIEDERGETHMANN, M., SCHMIDT-WOLF, I., ROLL, L., DOERKEN, B. and RIESS, H., 2007. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA, 297(3), pp. 267-277.

ONETE, V.G., BESSELINK, M.G., SALSBACH, C.M., VAN EIJCK, C.H., BUSCH, O.R., GOUMA, D.J., DE HINGH, I.H., SIEDERS, E., DEJONG, C.H., OFFERHAUS, J.G., MOLENAAR, I.Q. and DUTCH PANCREATIC CANCER GROUP, 2015. Impact of centralization of pancreatoduodenectomy on reported radical resections rates in a nationwide pathology database. HPB, 17(8), pp. 736-742.

OSIPOV, A., NISSEN, N., RUTGERS, J., DHALL, D., NAZIRI, J., CHOPRA, S., LI, Q., HENDIFAR, A.E. and TULI, R., 2017. Redefining the Positive Margin in Pancreatic Cancer: Impact on Patterns of Failure, Long-Term Survival and Adjuvant Therapy. Annals of Surgical Oncology, 24(12), pp. 3674-3682.

PANICCIA, A., HOSOKAWA, P., HENDERSON, W., SCHULICK, R.D., EDIL, B.H., MCCARTER, M.D. and GAJDOS, C., 2015. Characteristics of 10-Year Survivors of Pancreatic Ductal Adenocarcinoma. JAMA surgery, 150(8), pp. 701-710.

PERONE, J.A., RIALL, T.S. and OLINO, K., 2016. Palliative Care for Pancreatic and Periampullary Cancer. The Surgical clinics of North America, 96(6), pp. 1415-1430.

PIRKANMAAN SAIRAANHOITOPIIRI, 2012. Tuotteet ja hinnat 2012, pp. 18-22

PRIMARY HEALTH CARE ACT, issued 28.1.1972. Available: https://www.finlex.fi/fi/laki/ajantasa/1972/19720066?search%5Btype%5D=pika&search%5Bpika%5D=sairaanhoito

PULVIRENTI, A., MARCHEGIANI, G., PEA, A., ALLEGRINI, V., ESPOSITO, A., CASETTI, L., LANDONI, L., MALLEO, G., SALVIA, R. and BASSI, C. 2017, Clinical Implications of the 2016 International Study Group on Pancreatic Surgery Definition and Grading of Postoperative Pancreatic Fistula on 775 Consecutive Pancreatic Resections. Annals of Surgery, [Epub ahead of print]

RIVIERE, D., GURUSAMY, K.S., KOOBY, D.A., VOLLMER, C.M., BESSELINK, M.G., DAVIDSON, B.R. and VAN LAARHOVEN, C.J., 2016. Laparoscopic versus open distal pancreatectomy for pancreatic cancer. The Cochrane Ddatabase of Systematic Reviews, 4, pp. CD011391.

RUBENSTEIN, J.H., SCHEIMAN, J.M. and ANDERSON, M.A., 2007. A clinical and economic evaluation of endoscopic ultrasound for patients at risk for familial pancreatic adenocarcinoma. Pancreatology, 7(5-6), pp. 514-525.

RUTTER, C.E., PARK, H.S., CORSO, C.D., LESTER-COLL, N.H., MANCINI, B.R., YEBOA, D.N. and JOHUNG, K.L., 2015. Addition of radiotherapy to adjuvant chemotherapy is associated with improved overall survival in resected pancreatic adenocarcinoma: An analysis of the National Cancer Data Base. Cancer, 121(23), pp. 4141-4149.

SAKA, B., BALCI, S., BASTURK, O., BAGCI, P., POSTLEWAIT, L.M., MAITHEL, S., KNIGHT, J., EL-RAYES, B., KOOBY, D., SARMIENTO, J., MURAKI, T., OLIVA, I., BANDYOPADHYAY, S., AKKAS, G., GOODMAN, M., REID, M.D., KRASINSKAS, A., EVERETT, R. and ADSAY, V., 2016. Pancreatic Ductal Adenocarcinoma is Spread to the Peripancreatic Soft Tissue in the Majority of Resected Cases, Rendering the AJCC T-Stage Protocol (7th Edition) Inapplicable and Insignificant: A Size-Based Staging System (pT1: 2-4 cm) is More Valid and Clinically Relevant. Annals of Surgical Oncology, 23(6), pp. 2010-2018.

SALMIHEIMO, A., MUSTONEN, H., VAINIONPÄÄ, S., SHEN, Z., KEMPPAINEN, E., SEPPÄNEN, H. and PUOLAKKAINEN, P., 2016a. Increasing the Inflammatory Competence of Macrophages with IL-6 or with Combination of IL-4 and LPS Restrains the Invasiveness of Pancreatic Cancer Cells. J Cancer. 7(1): 42–49.

SALMIHEIMO, A., MUSTONEN, H., STENMAN, U-H, PUOLAKKAINEN, P., KEMPPAINEN, E., SEPPÄNEN, H. and HAGLUND, C., 2016b. Systemic Inflammatory Response and Elevated Tumour Markers Predict Worse Survival in Resectable Pancreatic Ductal Adenocarcinoma. PLoS One. 11(9): e0163064.

SANTEMA, T.B., VISSER, A., BUSCH, O.R., DIJKGRAAF, M.G., GOSLINGS, J.C., GOUMA, D.J. and UBBINK, D.T., 2015. Hospital costs of complications after a pancreatoduodenectomy. HPB, 17(8), pp. 723-731.

SANTHOSH, S., MITTAL, B.R., BHASIN, D., SRINIVASAN, R., RANA, S., DAS, A., NADA, R., BHATTACHARYA, A., GUPTA, R. and KAPOOR, R., 2012, Role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the characterization of pancreatic masses: Experience from tropics. Journal of Gastroenteroly and Hepatology, 28 (2), pp. 255-261.

SAUKKONEN, K., HAGSTRÖM, J., MUSTONEN, H., JUUTI, A., NORDLING, S., FERMÉR, C., NILSSON, O., SEPPÄNEN, H., HAGLUND, C., 2015. Podocalyxin Is a Marker of Poor Prognosis in Pancreatic Ductal Adenocarcinoma. PLoS One, 10(6), pp. e0129012.

SAUKKONEN, K., HAGSTRÖM, J., MUSTONEN, H., JUUTI, A., NORDLING, S., KALLIO, P., ALITALO, K., SEPPÄNEN, H., HAGLUND, C.,2016. PROX1 and

β-catenin are prognostic markers in pancreatic ductal adenocarcinoma. BMC Cancer, 16(7), pp. 472. doi: 10.1186/s12885-016-2497-5.

SAUKKONEN, K, HAGSTRÖM, J., MUSTONEN, H., LEHTINEN, L., CARPEN, O., ANDERSSON, L.C., SEPPÄNEN, H., and HAGLUND, C., 2018. Prognostic and diagnostic value of REG4 serum and tissue expression in pancreatic ductal adenocarcinoma. Tumour Biology, 40(3), pp. 1010428318761494.

SEPPÄNEN, H., JUUTI, A., MUSTONEN, H., HAAPAMÄKI, C., NORDLING, S., CARPELAN-HOLMSTRÖM, M., SIRÉN, J., LUETTGES, J., HAGLUND, C. and KIVILUOTO, T.2017. The Results of Pancreatic Resections and Long-Term Survival for Pancreatic Ductal Adenocarcinoma: A Single-Institution Experience. Scandinavian Journal of Surgery. 106(1), pp. 54-61.

SHARP, L., CARSIN, A.E., CRONIN-FENTON, D.P., O'DRISCOLL, D. and COMBER, H., 2009. Is there under-treatment of pancreatic cancer? Evidence from a population-based study in Ireland. European Journal of Cancer, **45**(8), pp. 1450-1459.

SHEETZ, K.H., DIMICK, J.B. and GHAFERI, A.A., 2016. Impact of Hospital Characteristics on Failure to Rescue Following Major Surgery. Annals of Surgery, **263**(4), pp. 692-697.

SIIKI, A., TAMMINEN, A., TOMMINEN, T., KUUSANMÄKI, P., 2012, Scandinavian Journal of Surgery, 101(1), pp. 45-50.

SIGNORETTI, M., BRUNO, M.J, ZERBONI, G., POLEY, J-W., DELLE FAVE, G. and CAPURSO, G., 2018. Results of surveillance in individuals at high-risk of pancreatic cancer: A systematic review and meta-analysis. United European Gastroenterology Journal, 6(4), pp. 489-499.

SMEENK, H.G., VAN EIJCK, C.H., HOP, W.C., 2007. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Annals of Surgery, 246, pp. 734–40.

SOREIDE, J.A., SANDVIK, O.M. and SOREIDE, K., 2016. Improving pancreas surgery over time: Performance factors related to transition of care and patient volume. International Journal of Surgery, 32, pp. 116-122.

SOSA, J.A., BOWMAN, H.M., GORDON, T.A., BASS, E.B., YEO, C.J., LILLEMOE, K.D., PITT, H.A., TIELSCH, J.M. and CAMERON, J.L., 1998. Importance of hospital volume in the overall management of pancreatic cancer. Annals of Surgery, 228(3), pp. 429-438.

STAPLEY, S., PETERS, T.J., NEAL, R.D., ROSE, P.W., WALTER, F. M., HAMILTON, W., 2012. The risk of pancreatic cancer in symptomatic patients in primary care: a large case–control study using electronic records. British Journal of Cancer, 106(12), pp. 1940-1944.

STARK, A. AND HINES, O.J., 2015, Endoscopic and operative palliation strategies for pancreatic ductal adenocarcinoma. Seminars of Oncology, 42(1):163–176.

STEINBERG, W., 1990, The clinical utility of the CA19-9 tumor-associated antigen. American Journal of Gastroenterology, 85(4), pp. 350-5.

STOCKEN, D.D., BUCHLER, M.W., DERVENIS, C., BASSI, C., JEEKEL, H., KLINKENBIJL, J.H., BAKKEVOLD, K.E., TAKADA, T., AMANO, H., NEOPTOLEMOS, J.P. and PANCREATIC CANCER META-ANALYSIS GROUP, 2005. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. British Journal of Cancer, 92(8), pp. 1372-1381.

STROBEL, O., HANK, T., HINZ, U., BERGMANN, F., SCHNEIDER, L., SPRINGFELD, C., JAGER, D., SCHIRMACHER, P., HACKERT, T. and BUCHLER, M.W., 2017. Pancreatic Cancer Surgery: The New R-status Counts. Annals of Surgery, 265(3), pp. 565-573.

SUN, W., LEONG, C.N., ZHANG, Z. and LU, J.J., 2010. Proposing the lymphatic target volume for elective radiation therapy for pancreas cancer: a pooled analysis of clinical evidence. Radiation Oncology, 5, 28. http://doi.org/10.1186/1748-717X-5-28

SUTTON, J.M., WILSON, G.C., PAQUETTE, I.M., WIMA, K., HANSEMAN, D.J., QUILLIN, R.C.,3rd, SUSSMAN, J.J., EDWARDS, M.J., AHMAD, S.A., SHAH, S.A. and ABBOTT, D.E., 2014. Cost effectiveness after a pancreaticoduodenectomy: bolstering the volume argument. HPB, 16(12), pp. 1056-1061.

TAHKOLA, K., MECKLIN, J.P., WIRTA, E.V., AHTIAINEN, M., HELMINEN, O., BOHM, J. and KELLOKUMPU, I., 2018. High immune cell score predicts improved survival in pancreatic cancer. Virchows Archiv, 472(4), pp. 653-665

TAKEDA, Y., SAIURA, A, TAKAHASHI, Y., INOUE, Y., ISHIZAWA, T., MISE, Y., MATSUMURA, M., ICHIDA, H., MATSUKI, R., TANAKA, M., ITO, M., 2017. Asymptomatic Pancreatic Cancer: Does Incidental Detection Impact Long-Term Outcomes? Journal of Gastrointestinal Surgery, 21, pp. 1287 – 1295.

TAMBURRINO, D., RIVIERE, D., YAGHOOBI, M., DAVIDSON, B.R. and GURUSAMY, K.S., 2016. Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. The Cochrane Database of Systematic Reviews, 9, pp. CD011515.

TEMPERO, M.A., UCHIDA, E., TAKASAKI, H., BURNETT, D.A., STEPLEWSKI, Z., and POUR, P.M., 1987, Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. Cancer Research, 47(20), 5501-3

TEMPERO, M. A., MALAFA, M.P., AL-HAWARY, M., ASBUN, H., BAIN, A., BEHRMAN, S.W., BENSON III, A.B., BINDER, E., CARDIN, D.B., CHA, C., CHIOREAN, E.G., CHUNG, V., CZITO, B., DILLHOFF, M., DOTAN, E., FERRONE, C.R., HARDACRE, J. AND HAWKINS, W.G.,2017. Pancreatic Adenocarcinoma, Version 2.201, Clinical Practice Guidelines in Oncology. Journal of National Comprehensive Cancer Network, 15(8), pp.1028–1061

THL, 2018, Suomen virallinen tilasto: Sosiaaliturvan menot ja rahoitus 2016, Tilastoraportti 13/2018, 14.5.2018. [updated 15/5/2018, visited 16/8/2018]. Available: https://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/sosiaali-ja-terveydenhuollon-talous/sosiaaliturvan-menot-ja-rahoitus

TOPAL, B., VAN DE SANDE, S., FIEUWS, S. and PENNINCKX, F., 2007. Effect of centralization of pancreaticoduodenectomy on nationwide hospital mortality and length of stay. BJS, 94(11), pp. 1377-1381.

TORPHY, R.J. and SCHULICK, R.D., 2018. Screening of Patients at Risk for Familial Pancreatic Cancer: What Is Beneficial? The Surgical clinics of North America, 98(1), pp. 25-35.

TRAN, T.B., DUA, M.M., WORHUNSKY, D.J., POULTSIDES, G.A., NORTON, J.A. and VISSER, B.C., 2016. An economic analysis of pancreaticoduodenectomy: should costs drive consumer decisions? American Journal of Surgery, 211(6), pp. 991-997.e1.

TRAVERSO, L. and LONGMIRE, W., 1980. Preservation of the pylorus in pancreaticoduodenectomy a follow-up evaluation. Annals of Surgery, 192, pp. 306.

TUMMALA, P., HOWARD, T. and AGARWAL, B., 2013. Dramatic Survival Benefit Related to R0 Resection of Pancreatic Adenocarcinoma in Patients With Tumour ≤25 mm in Size and ≤1 Involved Lymph Nodes. Clinical and Translational Gastroenterology, 4(3), pp. e33-.

UESAKA, K., BOKU, N., FUKUTOMI, A., OKAMURA, Y., KONISHI, M., MATSUMOTO, I., KANEOKA, Y., SHIMIZU, Y., NAKAMORI, S., SAKAMOTO, H., MORINAGA, S., KAINUMA, O., IMAI, K., SATA, N., HISHINUMA, S., OJIMA, H., YAMAGUCHI, R., HIRANO, S., SUDO, T., OHASHI, Y. and JASPAC 01 STUDY GROUP, 2016. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet, 388(10041), pp. 248-257.

VAN DER GEEST, L. G., BESSELINK, M., G, BUSCH, O., R, DE HINGH, I., H, VAN EIJCK, C., H, DEJONG, C., H and LEMMENS, V., E, 2016a. Elderly Patients Strongly Benefit from Centralization of Pancreatic Cancer Surgery: A Population-Based Study. Annals of Surgical Oncology, 23, pp. 2002.

VAN DER GEEST, L.G., VAN RIJSSEN, L.B., MOLENAAR, I.Q., DE HINGH, I.H., GROOT KOERKAMP, B., BUSCH, O.R., LEMMENS, V.E., BESSELINK, M.G. and DUTCH PANCREATIC CANCER GROUP, 2016b. Volume-outcome relationships in pancreatoduodenectomy for cancer. HPB, 18(4), pp. 317-324.

VAN DER ZEE, J.A., VAN EIJCK, C.H., HOP, W. J., VAN DEKKEN, H., DICHEVA, B.M., SEYNHAEVE, A.L., KONING, G.A., EGGERMONT, A.M. AND HAGEN, T., 2011.Angiogenesis: A prognostic determinant in pancreatic cancer? European Journal of Cancer, 47, pp. 2576–2584

VAN HILST, J., DE ROOIJ, T., KLOMPMAKER, S., RAWASHDEH, M., ALEOTTI, F., AL-SARIREH, B., ALSEIDI, A., ATEEB, Z., BALZANO, G., BERREVOET, F., BJORNSSON, B., BOGGI, U., BUSCH, O.R., BUTTURINI, G., CASADEI, R., DEL CHIARO, M., CHIKHLADZE, S., CIPRIANI, F., VAN DAM, R., DAMOLI, I., VAN DIEREN, S., DOKMAK, S., EDWIN, B., VAN EIJCK, C., FABRE, J.M., FALCONI, M., FARGES, O., FERNANDEZ-CRUZ, L., FORGIONE, A., FRIGERIO, I., FUKS, D., GAVAZZI, F., GAYET, B., GIARDINO, A., BAS GROOT, K., HACKERT, T., HASSENPFLUG, M., KABIR, I., KECK, T., KHATKOV, I., KUSAR, M., LOMBARDO, C., MARCHEGIANI, G., MARSHALL, R., MENON, K.V., MONTORSI, M., ORVILLE, M., DE PASTENA, M., PIETRABISSA, A., POVES, I., PRIMROSE, J., PUGLIESE, R., RICCI, C., ROBERTS, K., ROSOK, B., SAHAKYAN, M.A., SANCHEZ-CABUS, S., SANDSTROM, P., SCOVEL, L., SOLAINI, L., SOONAWALLA, Z., SOUCHE, F.R., SUTCLIFFE, R.P., TIBERIO, G.A., TOMAZIC, A., TROISI, R., WELLNER, U., WHITE, S., WITTEL, U.A., ZERBI, A., BASSI, C., BESSELINK, M.G., ABU HILAL, M. and EUROPEAN CONSORTIUM ON MINIMALLY INVASIVE PANCREATIC SURGERY (E-MIPS), 2017. Minimally Invasive versus Open Distal Pancreatectomy for Ductal Adenocarcinoma (DIPLOMA): A Pan-European Propensity Score Matched Study. Annals of Surgery, epub ahead of print.

VAN RIJSSEN, L.B., NARWADE, P., VAN HUIJGEVOORT, N.C., TSENG, D.S., VAN SANTVOORT, H.C., MOLENAAR, I.Q., VAN LAARHOVEN, H.W., VAN EIJCK, C.H., BUSCH, O.R., BESSELINK, M.G. and DUTCH

PANCREATIC CANCER GROUP, 2016. Prognostic value of lymph node metastases detected during surgical exploration for pancreatic or periampullary cancer: a systematic review and meta-analysis. HPB, **18**(7), pp. 559-566.

VAN VELDHUISEN, E., VOGEL, J.A., KLOMPMAKER, S., BUSCH, O.R., VAN LAARHOVEN, H.W.M., VAN LIENDEN, K.P., WILMINK, J.W., MARSMAN, H.A. and BESSELINK, M.G., 2018. Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy. HPB 20(7), pp. 605-611.

VARADHACHARY, G.R., TAMM, E.P., ABBRUZZESE, J.L., XIONG, H.Q., CRANE, C.H., WANG, H., LEE, J.E., PISTERS, P.W., EVANS, D.B. and WOLFF, R.A., 2006. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Annals of Surgical Oncology, 13(8), pp. 1035-1046.

VERBEKE, C.S., KNAPP, J. and GLADHAUG, I.P., 2011. Tumour growth is more dispersed in pancreatic head cancers than in rectal cancer: implications for resection margin assessment. Histopathology, 59(6), pp. 1111-1121.

VONLANTHEN, R., SLANKAMENAC, K., BREITENSTEIN, S., PUHAN, M.A., MULLER, M.K., HAHNLOSER, D., HAURI, D., GRAF, R. and CLAVIEN, P.A., 2011. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. Annals of Surgery, 254(6), pp. 907-913.

WAGNER, M., REDAELLI, C., LIETZ, M., SEILER, C.A., FRIESS, H. and BUCHLER, M.W., 2004. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. BJS, 91(5), pp. 586-594.

WAKEAM, E., HYDER, J.A., LIPSITZ, S.R., COHEN, M.E., ORGILL, D.P., ZINNER, M.J., KO, C.Y., HALL, B.L. and FINLAYSON, S.R., 2016. Hospital-level Variation in Secondary Complications After Surgery. Annals of Surgery, **263**(3), pp. 493-501.

WEBER, C.E., BOCK, E.A., HURTUK, M.G., ABOOD, G.J., PICKLEMAN, J., SHOUP, M. and ARANHA, G.V., 2014. Clinical and pathologic features influencing survival in patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma. Journal of Gastrointestinal Surgery, 18(2), pp. 340-347.

WENTE, M.N., BASSI, C., DERVENIS, C., FINGERHUT, A., GOUMA, D.J., IZBICKI, J.R., NEOPTOLEMOS, J.P., PADBURY, R.T., SARR, M.G., TRAVERSO, L.W., YEO, C.J. and BUCHLER, M.W., 2007a. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery, 142(5), pp. 761-768.

WENTE, M.N., VEIT, J.A., BASSI, C., DERVENIS, C., FINGERHUT, A., GOUMA, D.J., IZBICKI, J.R., NEOPTOLEMOS, J.P., PADBURY, R.T., SARR, M.G., YEO, C.J. and BUCHLER, M.W., 2007b. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery, 142(1), pp. 20-25.

WESTGAARD, A., CLAUSEN, O.P. and GLADHAUG, I.P., 2011. Survival estimates after pancreatoduodenectomy skewed by non-standardized histopathology reports. APMIS: Acta Pathologica, Microbiologica, et Immunologica Scandinavica, 119(10), pp. 689-700.

WHIPPLE, A., PARSONS, W. and MULLINS, C., 1935. Treatment of carcinoma of the ampulla of Vater. Annals of Surgery, 102, pp. 763.

WINTER, J.M., CAMERON, J.L., CAMPBELL, K.A., ARNOLD, M.A., CHANG, D.C., COLEMAN, J., HODGIN, M.B., SAUTER, P.K., HRUBAN, R.H., RIALL, T.S., SCHULICK, R.D., CHOTI, M.A., LILLEMOE, K.D. and YEO, C.J., 2006. 1423

pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. Journal of Gastrointestinal Surgery, 10(9), pp. 1199-210; discussion 1210-1.

WONG, J.C. and LU, D.S., 2008. Staging of pancreatic adenocarcinoma by imaging studies. Clinical gastroenterology and hepatology, 6(12), pp. 1301-1308.

WONG, S.L., REVELS, S.L., YIN, H., STEWART, A.K., MCVEIGH, A., BANERJEE, M. and BIRKMEYER, J.D., 2015. Variation in hospital mortality rates with inpatient cancer surgery. Annals of Surgery, 261(4), pp. 632-636.

WOO, Y.S., LEE, J., K., OH, S.H, KIM, M. J., JUNG, J.G, LEE, K. H. and LEE K. T., 2014. Role of SpyGlass Peroral Cholangioscopy in the Evaluation of Indeterminate Biliary Lesions. Digestive Disease and Sciences, 59(10), PP. 2565-70.

WORLD HEALTH ORGANIZATION, 2012. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012, [updated 2012, visited 01/08, 2018]. Available: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx

WÖRMANN, S.M. and ALGUL, H., 2013. Risk factors and therapeutic targets in pancreatic cancer. Frontiers in Oncology, 3, pp. 282.

YOSHIOKA, R., YASUNAGA, H., HASEGAWA, K., HORIGUCHI, H., FUSHIMI, K., AOKI, T., SAKAMOTO, Y., SUGAWARA, Y. and KOKUDO, N., 2014. Impact of hospital volume on hospital mortality, length of stay and total costs after pancreaticoduodenectomy. The British journal of surgery, 101(5), pp. 523-529.

ZHANG, J., WOLFGANG, C.L. and ZHENG, L., 2018. Precision Immuno-Oncology: Prospects of Individualized Immunotherapy for Pancreatic Cancer. Cancers (Basel), 10(2), pp. 10.3390/cancers10020039.

ZOLGHADRI, Y., PAL CHOUDHURI, S., OCAL, O., LAYEGHI-GHALEHSOUKHTEH, S., BERHE, F., HALE, M.A. and WILKIE, T.M., 2018. Malnutrition in Pancreatic Ductal Adenocarcinoma (PDA): Dietary Pancreatic Enzymes Improve Short-Term Health but Stimulate Tumor Growth. The American Journal of Pathology, 188(3), pp. 616-626.

ORIGINAL COMMUNICATIONS

Pancreatology 17 (2017) 822–826

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Patients with resected, histologically re-confirmed pancreatic ductal adenocarcinoma (PDAC) can achieve long-term survival despite T3 tumour or nodal involvement. The Finnish Register Study 2000–2013

Reea Ahola [a], Antti Siiki [a], Kaija Vasama [b], Martine Vornanen [b], Juhani Sand [a], Johanna Laukkarinen [a, *]

[a] Dept. of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Finland, PL 2000, 33521 Tampere, Finland
[b] Dept. of Pathology, Fimlab Laboratories, Tampere University Hospital, Tampere, Finland, PL 66, 33101 Tampere, Finland

ARTICLE INFO

Article history:
Received 6 November 2016
Received in revised form
30 June 2017
Accepted 27 July 2017
Available online 29 July 2017

Keywords:
Carcinoma
Pancreatic ductal
Pancreas neoplasms
Survival
Pathology
Surgical

ABSTRACT

Background: Long-term survival of patients with operated pancreatic ductal adenocarcinoma (PDAC) has been associated with resection status, disease stage and centralisation. However, no previous reports are available about long-term survivors of PDAC with confirmed histology covering an entire nation. Our aim was to analyze retrospectively confirmed long-term survivors of PDAC operated on in Finland 2000–2008.

Method: PDAC patients operated between 2000 and 2008 were selected from Finnish patient registers and archives. Histological slides of patients with over four-year survival were re-evaluated by an expert pancreatic pathologist. From the confirmed PDAC patients, demographic, oncologic and operative parameters were recorded. The cut-point of survival was 31.12.2013.

Results: Out of the 598 patients operated on and originally diagnosed with PDAC, 52 of the long-term survivors (LTS) were confirmed as having had true PDAC. The four-year survival rate in high volume centres (HVC) was 13.0% and 6.7% elsewhere ($p = 0.017$). Five-year survival rate was 7.2%. After multivariate analysis only the size of the tumour persisted as prognostic factor for over four-year survival. Among LTSs, 50% of patients had stage IIB tumour and 40% had a R1 resection without difference with patients with shorter survival. The use of adjuvant therapy did not differ between the groups.

Conclusion: This is the largest single-nationwide cohort of long-term survivors with confirmed PDAC. Comprehensive pathological evaluation is mandatory for an adequate PDAC diagnosis and true survival analysis. Long-term survival can be achieved even in T3 patients with nodal involvement and may be explained by favorable tumour biology.

Introduction

The reported five-year survival for operated pancreatic ductal adenocarcinoma (PDAC) is 11–24% [1,2]. However, assessment of pancreatic specimens requires experience in pancreatic histopathology. In most reports the histopathology was not reconfirmed in long-term survivors, suggesting there were other diagnoses with better natural prognoses than in PDAC [4,5]. Long-term survival of patients with operated PDAC has traditionally been associated with tumour-free resection margins, small tumour size, zero nodal involvement and centralisation [1,2,6,7]. Yet some patients seem not to evince such characteristics and research on tumour biology has been a subject of growing interest [15]. More information about the characteristics of the tumours with a favorable prognosis is needed to identify the patients who would benefit the most from neoadjuvant therapy and super-radical surgery [3]. No reports on long-term PDAC survivors with confirmed histology are available covering entire nations. Our aim was to analyse the characteristics of long-term surviving PDAC patients with confirmed histology who had been operated on in Finland between 2000 and 2008.

Abbreviations: PDAC, Pancreatic Ductal Adenocarcinoma; HVC, high-volume centre; LVC, low volume centre.

* Corresponding author. Dept. of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Teiskontie 35, 33521 Tampere, Finland.
E-mail address: johanna.laukkarinen@fimnet.fi (J. Laukkarinen).

http://dx.doi.org/10.1016/j.pan.2017.07.192
1424-3903/

Methods

The Finnish Cancer Registry was searched for all potential patients diagnosed with PDAC (ICD-10 codes C25.*) and the Care Register for Social Welfare and Health Care (HILMO) for all pancreatic resections according to the Nordic Classification of Surgical Procedures (JLC*). These two lists of patients were used to create a list of potential PDAC patients operated on between 2000 and 2008. Patient records were then searched for all available data. Patients with final diagnoses other than PDAC, with a palliative procedure or with no records available were excluded.

Patients with over four-year survival were identified from the study register. These apparent long-term survivors of PDAC were further evaluated and their histological slides were re-analysed by an expert in pancreatic pathologist. All the patients who were not confirmed to have had PDAC as well as those for whom no slides were available were excluded.

TNM, gradus and R-status were determined according to the international classifications[1] and updated in the re-analysis whenever the histological slides permitted; otherwise the original assessments were used. R-status was categorized as R0: free margins, R1: margin <1 mm, R2: macroscopic tumour in margins or left in the patient. Data on patient demographics, pancreatic surgical procedures and oncologic treatment were abstracted from the archives. The cut-point of survival was 31 December 2013.

Hospital volume for demanding pancreatic surgery was calculated from the yearly number of pancreaticoduodenectomies (PDs) performed for any diagnosis during the period 2000–2008. Hospitals were defined as high (HVC; $\geq$ 20; 2 hospitals) and low (LVC; <20; 22 hospitals) volume pancreatic centres.

Data are shown as median (range) or mean (±sem). Fisher's exact test, Chi-square test and Mann-Whittney-U test were used to calculate the statistical significances. Survival analysis was done using Kaplan-Meier. Kaplan-Meier- curves were analysed with log rank or Breslow-test. Logistic regression analysis was performed for multivariate analysis. A p-value of $\leq$0.05 was considered statistically significant.

The study is approved by the Regional Ethics Committee of Pirkanmaa (code R12241).

Results

Long-term survivors. The search identified 883 possible pancreatic cancer patients who underwent pancreatic resection in Finland between 2000 and 2008. Of these patients, the final diagnosis set in the operating hospital was PDAC in 598 patients. Out of these, 94 patients with minimum survival of four years were detected. After histopathological re-analysis by an experienced pancreatic pathologist, 28 of the patients were excluded. Another 14 patients had to be excluded due to missing slides. Thus 52 patients with a survival of a minimum of four years (52/556; 9.4%) were ultimately considered to be confirmed long-term survivors (Fig. 1). Five-year survival was achieved by 42 (42/556; 7.6%) patients. The histopathological diagnosis changed in 10 of the patients operated on in

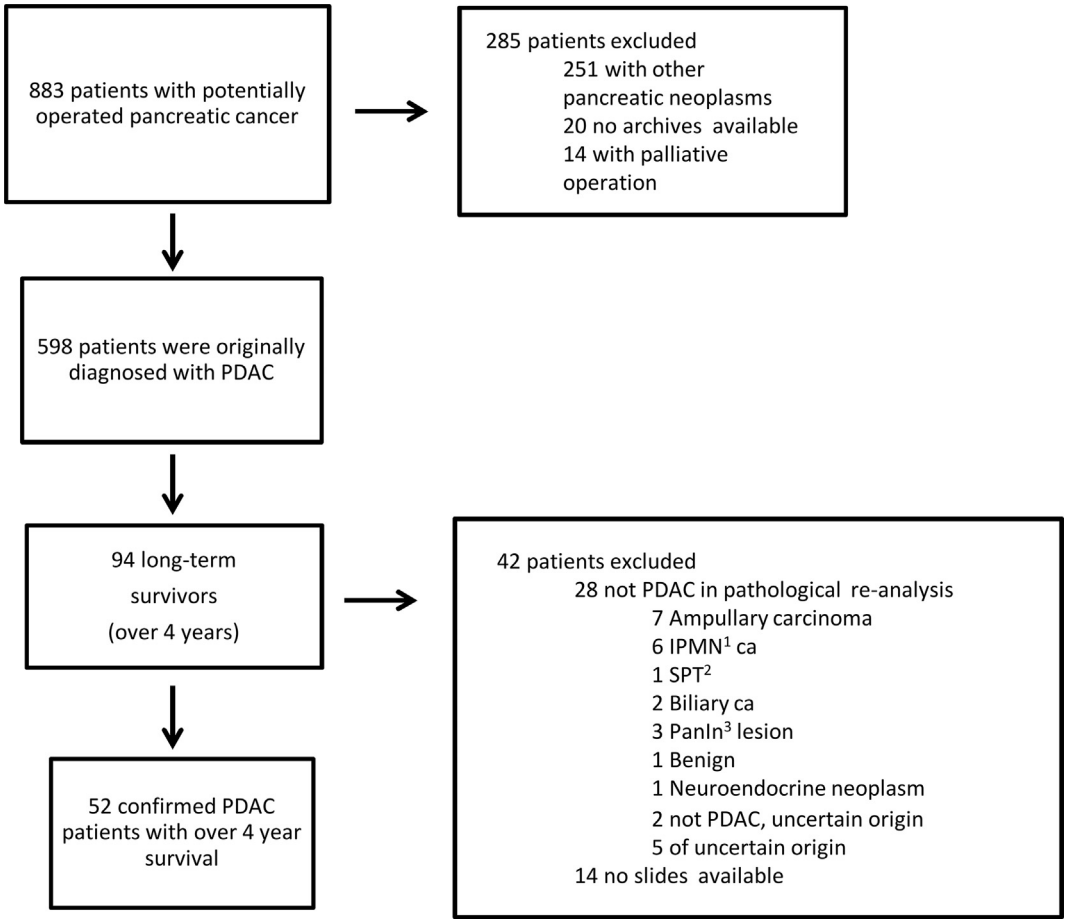


Fig. 1. Combined search of the Care Registers for Social Welfare and Health Care (HILMO) and the Cancer Registry in Finland resulted in 883 potentially radically operated PDA patients. After archive-based exclusions, 94 LTSs were selected. Pathological re-analysis was possible for 80 patients, of whom 52 were confirmed with a diagnosis of PDAC. [1]Intraductal papillary mucinous neoplasm,[2]Solid pseudopapillary tumour, [3]Pancreatic intraepithelial neoplasia.

HVCs and in 13 of those operated on in other hospitals (p = 0.461, Fisher's exact test). The precise diagnosis of five patients was still uncertain after the re-evaluation. The number of patients excluded after histopathological re-evaluation was higher in other hospitals than in HVCs, but not statistically significantly (11 vs. 17, p = 0.116, Pearson Chi-square, degree of freedom 1).

Operation and demographic data. Demographics or ASA-classes did not differ between long-term and short-term survivors. Patients were operated on in two high volume centres (HVC) and 13 low volume centres (LVC). Two hundred thirty (41.4%) patients were operated on in HVCs. Details of the procedures and demographics are reported in Table 1.

Histology. Overall status distribution differed significantly between long-term and short-term survivors (p = 0.041, Pearsons's chi-squared test). Stage IIB was found in 50% and 48.6% of the cases among long-term and short-term survivors without significant differences (0.383). Gradus or resection status distribution did not differ significantly (p = 0.316 and 0.082 respectively, Pearson's chi-squared test). Median tumour size was 4 mm lower among long-term survivors (p = 0.019, Mann-Whittney-U test). Nodal involvement was found in ca 60% of the cases both among long-term and short-term survivors (p = 0.454). (Table 2). More nodes were detected in HVCs (median 20 vs 7 in LVCs; p = 0.000, Mann-Whitney U- test) and less R2-resections (1.7% vs 9.5%, p = 0.000, Pearson Chi-Squared test) than in LVCs.

Chemotherapy. Twenty-five (48.1%) of the LTS and 230 (45.6%) of the STS received adjuvant therapy (p = 0.401, Fischer's exact test). Three patients (5.9%) of the LTS and seven (1.5%) patients of the STS received neoadjuvant chemoradiation therapy.

Survival. Median survival of the patients was 1.59 years (range 0.090–13.0; without patients who died in 30 days postoperatively). The overall five-year survival was 7.2%.The steep decrease of survival started to diminish after four-year of survival in the Kaplan-Meier curve (Fig. 2a). The median survival of confirmed long-term survivors was 6.6 years (range 4.0–13 years) during the study period. Twenty-eight patients (54% of the LTS) were still alive at the cut-point of survival on 31 December 2013 suggesting even longer survival potential among the long-term survivors. The Kaplan-Meier survival analysis of LTS demonstrated survival over six years in 67% of the patients and over eight years in 57% of the patients (Fig. 2b). After histopathological re-evaluation the four-year survival rates were 13.0% in HVCs and 6.7% in LVCs (p = 0.017; Fisher's exact test) and the five-year survival rates were 10.4% in HVCs and 5.8% in LVCs (p = 0.053; Fisher's exact test). In the logistic regression analysis describing factors resulting in over four-year survival only tumour size persisted as a significant factor. Information on gradus could not been included into the analysis because of the proportion of missing data. Table 3.

Comparing Kaplan- Meier survival analysis of R0 and R1 groups among patients with tumours >25 mm (95 patients) and <25 mm (318 patients), R0 group had significantly better survival only if the tumour size was under 25 mm (p = 0.043, Breslow).

Table 1
Demographic data. The profile of long-term survivors did not differ from the short-term survivors.

	survival >4 years	survival <4 years	p
Total (%)	52	504	
Male/Female (%)	25 (48.1)/27 (51.9)	267 (53.0)/237 (47.0)	0.299*
Median age, years (range)	62.2 (43.9–82.0)	67.4 (37.0–85.9)	0.107**
ASA (%)			0.295*** without ASA NAS
ASA 1	24 (46.2)	229 (45.4)	
ASA 2	14 (26.9)	85 (16.7)	
ASA 3-4	14 (26.9)	153 (30.4)	
ASA NAS	0	37 (7.3)	
Comorbidities			
Diabetes	10 (19.2)	80 (15.8)	0.552*
High blood pressure	12 (23.1)	122 (24.2)	0.508*
Rheumatoid disease or IBD	5 (9.6)	11 (2.2)	0.012*
Thyroid disease	1 (1.9)	13 (2.6)	1.000*
Neurological or psychiatric disease	2 (3.8)	11 (2.2)	0.346*
Cardiac disease or ASO	6 (11.5)	100 (19.8)	0.100*
Previous stroke	2 (3.8)	5 (1.0)	0.133*
Respiratory disease	2 (3.8)	29 (5.7)	0.758*
Nephropathy	1 (1.9)	5 (1.0)	0.446*
Operated in HVC (%)#	29 (56.9)	199 (40.6)	0.076***

*Fischer's exact test, **Mann-Whitney-U- test, *** Pearson's chi-squared test, # without patients who deceased in 30 days postoperatively.
IBD = inflammatory bowel disease, ASO = arteriosclerosis, HVC = high volume centre.

Table 2
IIB accounted for the majority of cases in both groups. Nodal status was positive in ca. 60% of the cases and R1 resection status was also met among long-term survivors.

		survival over 4 years	survival under 4 years	p
Stage (%)			0.041*#	
IA	T1N0	4 (7.7)	19 (3.8)	
IB	T2N0	1 (1.9)	57 (11.3)	
IIA	T3N0	15 (28.8)	57 (15.2)	
IIB		26 (50.0)	245 (48.6)	0.383**
	T1N1	0	1 (0.04)	
	T2N1	3 (11.5)	65 (26.5)	
	T3N1	23 (88.5)	173 (70.6)	
III	T4N0-1M0	1 (1.9)	32 (6.3)	
IV	M1	3 (5.8)	13 (2.6)	
NAS		2 (3.8)	62 (12.3)	
Gradus				0.316*
1		14 (26.9)	76 (15.1)	
2		25 (48.1)	232 (46.0)	
3		11 (21.2)	91 (18.1)	
NAS		2 (3.8)	105 (20.8)	
Median size, mm (range)		28 (15–70)	32 (8–100)	0.019***
R				0.082*
R0		29 (55.8)	266 (52.8)	
R1		21 (40.4)	148 (29.4)	
R2		0	35 (6.9)	
R NAS		2 (3.8)	55 (10.9)	
Nodal involvement		30 (60.0)	279 (57.6)	0.454**

*Pearson's chi-squared test, without missing data; **Fischer's exact test; *** Mann-Whitney-U-test, without patients after neoadjuvant therapy; # stage III and IV grouped for stage analysis.

Discussion

Earlier studies have considered nodal involvement, resection margins, tumour size, gradus, adjuvant therapy, serum albumin levels, intraoperative blood loss, postoperative complications and operation in high volume centres to be factors affecting the long-term survival of operated PDAC-patients [1–3,6,7]. This study aimed to characterise long-term survivors of operated PDAC with reconfirmed histopathology. We found that nodal involvement and T3-tumour status were surprisingly common features among the long-term survivors and both R1 and R0-resection status may result in long-term survival, suggesting that patient-specific tumour biology plays a key role in the prognosis.

Earlier studies have been sceptic regarding the long-term survival of PDAC patients [3–5]. Carpelan-Holmström et al. [3]

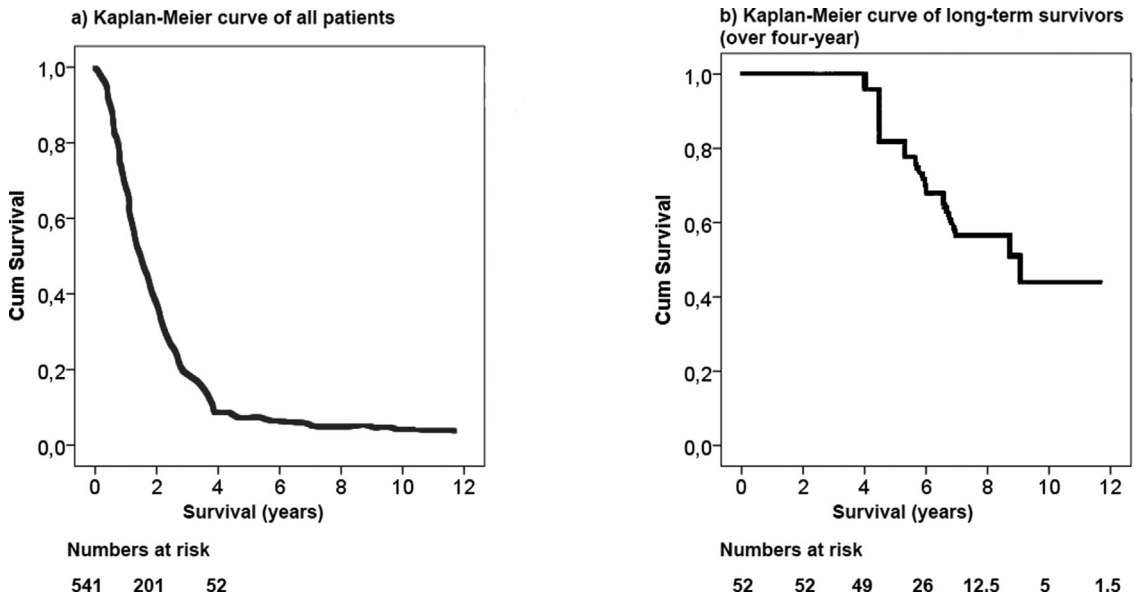


Fig. 2. A) Overall Kaplan-Meier curve shows the curve shape changing after ca. Four-years post-operatively. B) Kaplan-Meier curve of long-term survivors demonstrating that over 8-year survival is achievable for about 40% of patients who survived over 4 years.

reviewed Finnish long-term survivors diagnosed in 1990–1996 and stated that only few long-surviving patients had true PDAC. The diagnosis of 49% patients changed in the re-evaluation. A Danish register [4] study evaluating patients diagnosed 1990–1996 demonstrated that after re-evaluation the original diagnoses of only 27% of patients persisted. In the present study the precise diagnosis altered in only 35% of cases showing improvements in the histopathological evaluation. However, in our study three tumours originally diagnosed as PDAC showed no invasive components and one was re-analysed as a benign lesion demonstrating persisting challenges in histopathological evaluation of pancreas specimens.

Although small, local tumours without nodal involvement have traditionally been classified as potential long-term survivors, stage IIB accounted for 50% of the long-term survivors. However, due to variability of original nodal analysis, the number of stage IIB cases must be considered the minimum level. Insufficient nodal analysis is a typical weakness in unstructured histopathological reports [6] which were common in Finland during the study period. This could have had an effect on stage classifications, especially between stages IIA and IIB.

An earlier retrospective survival analysis [7] of 246 patients pointed out that low nodal involvement, preoperative hypertension, abdominal pain on presentation, operating time and positive margins influenced survival after five years. A multivariate analysis, however, did not confirm the effect of positive margins. In the present study both nodal involvement and R1 resections were found among the long-term survivors and after multivariate analysis they did not appear to be as prognostic factors. Moreover, also other recent studies have been debating the weight of R0 versus R1 resection status on prognosis [8,9]. However, these studies have emphasised the nodal involvement or positive node ratio as a prognostic factor. Our study demonstrated that nodal status was not a factor explaining long-term survival. A study by Paniccia et al. [10] recently published in JAMA demonstrated characteristics of PDAC patients with over ten-year survival. The study stated that local disease, T1 class, low lymph node ratio, negative margin status, adjuvant chemotherapy, tumour size <20 mm and educational level were associated with over ten-year survival. In our study only the tumour size persisted as prognostic factor for over four-year-survival. In a more detailed size analysis, we noticed that if the tumour size is over 25 mm, there is no significant difference between R0 and R1 groups in survival. This results agrees with the earlier published data from Tummala et al. [11]. Comparison with other studies is limited due to non-confirmed histopathology in other studies.

Interestingly, 38% of long-term survivors had R1 resections. The retrospective analysis of R status is known to be challenging. In this study, only one originally classified R0 resection could be confirmed in the pathological re-analysis due to the rarity of ink culture in Finland in 2000–2008. In addition, adjuvant chemotherapy did not seem to explain long-term survival in this study. Overall, under 50% of the patients received adjuvant therapy. It is possible that with better margin marking even more R1 resections would have been found [9] and more uniform treatment strategies would have emphasized the effect of the oncologic therapy.

Table 3
Logistic regression analysis of factors explaining four-year survival. The only significant factor was tumour size. Patients with neoadjuvant therapy were excluded from the analysis.

	p	ODDs-ratio	95% confidence interval
Age	0.718	0.993	0.955–1.032
ASA	0.525		
ASA 1		reference	
ASA 2	0.261	1.592	0.707–3.586
ASA 3-4	0.795	1.112	0.500–2.473
Operated in a high-volume centre	0.147	0.599	0.299–1.198
Nodal involvement	0.810		
N0		reference	
N+	0.809	0.915	0.445–1.883
NAS	0.591	1.575	0.301–8.244
R-status	0.491		
R0		reference	
R1	0.127	1.707	0.859–3.392
R2	0.998	0.000	0.000
NAS	0.921	0.896	0.103–7.774
Tumour size	0.019	0.709	0.533–0.944
Adjuvant therapy	0.576		
No adjuvant therapy		reference	
Adjuvant therapy	0.294	1.460	0.721–2.958
Adjuvant therapy NAS	0.999	0.000	0.000

In this study the diagnoses of only patients surviving for over four years were re-evaluated and the original diagnoses were used among the patients with shorter survival. This leads to a certain amount of inaccuracy in the overall survival estimation. However, it is more likely that patients with less aggressive neoplasms achieve long-term survival and that the number of other diagnoses is lower in the group of short-term survivors. All in all, an estimation of an overall minimum survival of over five years was at the level of 10.4% in HVCs and 5.8% in other centres. The better survival in HVCs may be explained by the low number of R2-resections. Also more nodes were detected in HVCs, but it is possible that it is mostly explained by differences in pathological evaluation. Earlier studies have reported over five-year survival rates of 11–24% [2,7]. In addition, a ten-year survival rate of 3.7% has recently been reported [10]. The lower five-year survival rates in the present study may be attributable to the careful review by an experienced pancreatic pathologist and uncentralized pancreatic surgery. Our previously published article [12] showed that survival is better in high volume centres at least up to three years post-operatively. Longer survival is achieved by low postoperative mortality rates and probably also low R2 resections rates. In this study 40% of the LTSs achieved minimum survival of eight years. Despite the poor prognosis of pancreatic adenocarcinoma some patients can clearly achieve long-term survival.

The surprisingly high number of stage IIB diseases and R1 resections may be explained by beneficial tumour biology in long-term survivors. Multiple gene defects have been associated with pancreatic cancer (KRAS2, CDKN2A, TP53; DCS4) [1] as well as differences in tumour angiogenesis (Hollander et al. [13]), tumour-DNA-patterns (Asting et al. [14]) and signaling pathways (Yang et al. [15]). Such studies will eventually lead to a better understanding of long-term survival.

The retrospective nature of this study imposes certain limitations on data collection. However, the study gives a reliable national picture of PDAC patients in Finland. All cancer patients are recorded in the Finnish Cancer Registry at the time of diagnosis and/or at the commencement of treatment and the data is updated post mortem. In addition, every hospital treatment period is communicated with procedures and diagnostic codes to the national register. With help of the two registers patients can be selected reliably. In light of the median 24–26 months [1,2] survival of PDAC patients, we set the minimum survival rate at four years to find patients with better survival than expected. With the help of this cut-off point we gained a better clinical overview of the characteristics of long-term survivors. A confounding factor in this study is the relatively high number of operating centres. This may have led to different treatment strategies and to variable operative and histopathological quality, which may bias the distribution of stages, R classification and the results of nodal assessment and eventually survival. However, the re-analysis by an experienced pancreatic pathologist balanced the differences among the patients included and importantly confirmed the diagnoses resulting in a more homogenous LTS group for analysis.

In conclusion, even patients with T3 and nodal involvement, in addition to patients with R1 resection, can achieve long-term survival. The five-year survival is, however, achievable only to 5.8–10.4% of the patients. Long-term survival after PDAC surgery may probably be explained by patient-specific tumour biology factors than conventional tumour characteristics. Precise histopathological evaluation is essential for reliable survival analysis and new ways to characterize PDAC to identify potential long-term survivors are needed.

Acknowledgements

This work was supported by the Competitive Research Funding of the Pirkanmaa Hospital District, Finland, the Sigrig Juselius Foundation, Finland and the Seppo Nieminen Foundation, Finland. Funding did not have involvements in the study design, data collection, data analysis, manuscript preparation or publication decisions.

Conflict of interest statement

None to declare.

References

[1] Hidalgo M. Pancettas cancer. N. Engl J Med 2010;362(July):1605.
[2] Ducreux M, Sa Cuhna A, Caramella C, Hollebecque A, Burtin P, Goéré D, et al. Cancer of the pancreas: ESMO clinical practice guidelines. Ann Oncol 2015;26(suppl 5)., v56. .
[3] Carpelan-Holmstrom M, Nordling S, Pukkala E, Sankila R, Luttges J, Kloppel G, et al. Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry. Gut 2005 Mar;54(3):385–7.
[4] Jorgensen MT, Fenger C, Kloppel G, Luttges J. Long-term survivors among Danish patients after resection for ductal adenocarcinoma of the pancreas. Scand J Gastroenterol 2008;43(5):581–3.
[5] Zijlstra M, Bernards N, de Hingh I, van de Wouw A, Goey S, Jacobs E, et al. Does long-term survival exist in pancreatic adenocarcinoma?. 1-6 Acta Oncol 2015 Nov 11;2015(11):1.
[6] Westgaard A, Clausen OP, Gladhaug IP. Survival estimates after pancreatoduodenectomy skewed by non-standardized histopathology reports. APMIS 2011 Oct;119(10):689–700.
[7] Weber CE, Bock EA, Hurtuk MG, Abood GJ, Pickleman J, Shoup M, et al. Clinical and pathologic features influencing survival in patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma. J Gastrointest Surg 2014 Feb;18(2):340–7.
[8] Raut CP, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg 2007 Jul;246(1):52–60.
[9] Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, et al. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol 2008 Jun;15(6):1651–60.
[10] Paniccia A, Hosokawa P, Henderson W, Schulick RD, Edil BH, McCarter MD, et al. Characteristics of 10-year survivors of pancreatic ductal adenocarcinoma. JAMA Surg 2015 Aug;150(8):701–10.
[11] Tummala P, Howard T, Agarwal B. Dramatic survival benefit related to R0 resection of pancreatic adenocarcinoma in patients with tumor </=25 mm in size and </=1 involved lymph nodes. Clin Transl Gastroenterol 2013 Mar 21;4:e33.
[12] Ahola R, Siiki A, Vasama K, Vornanen M, Sand J, Laukkarinen J. Effect of centralisation on long-term survival after resection of pancreatic ductal adenocarcinoma. Br J Surg 2017 May 18. http://dx.doi.org/10.1002/bjs.10560 [Epub ahead of print].
[13] Hollander LL, Guo X, Salem RR, Cha CH. The novel tumor angiogenic factor, adrenomedullin-2, predicts survival in pancreatic adenocarcinoma. J Surg Res 2015 Aug;197(2):219–24.
[14] Asting AG, Ljungman D, Caren H, Dambrauskas Z, Iresjo BM, Hyltander A, et al. Alterations in tumor dna are related to short postoperative survival in patients resected for pancreatic carcinoma aimed at cure. Pancreas 2015 Dec 17;00(00).
[15] Yang JY, Yang MW, Huo YM, Liu W, Liu DJ, Li J, et al. High expression of WISP-1 correlates with poor prognosis in pancreatic ductal adenocarcinoma. Am J Transl Res 2015 Sep 15;7(9):1621–8.

Original article

Effect of centralization on long-term survival after resection of pancreatic ductal adenocarcinoma

R. Ahola[1], A. Siiki[1], K. Vasama[2], M. Vornanen[2], J. Sand[1] and J. Laukkarinen[1]

[1]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, and [2]Department of Pathology, Fimlab Laboratories, Tampere University Hospital, Tampere, Finland

Correspondence to: Dr J. Laukkarinen, Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Teiskontie 35, 33521 Tampere, Finland (e-mail: johanna.laukkarinen@fimnet.fi)

Background: **Centralization of pancreatic surgery has resulted in improved short-term outcomes in a number of healthcare systems. The aim of this study was to see whether hospital volume influenced long-term prognosis, use of adjuvant therapy or histopathological evaluation of patients undergoing surgical resection for pancreatic ductal adenocarcinoma (PDAC).**

Methods: **Patients undergoing surgical resection of PDAC in Finland between 2002 and 2008 were identified from national registers. Demographic, histopathological, operative and oncological data were recorded, and the histopathological slides of patients who survived for more than 4 years were reviewed. Operative volume was defined according to the annual rate of pancreatoduodenectomy as: high-volume centres (HVCs; 20 or more resections per year), medium-volume centres (MVCs; 6–19 resection annually) and low-volume centres (LVCs; 5 or fewer resections annually).**

Results: **Some 467 patients who had undergone resectional surgery for PDAC at 22 centres were included. Patient demographics and resection types did not differ between centres. Thirty- and 90-day mortality rates were significantly lower in HVCs compared with LVCs: 0 *versus* 5·5 per cent ($P = 0·001$) and 2·5 *versus* 11·0 per cent ($P = 0·003$) respectively. Tumours in HVCs were generally at a more advanced stage than those in LVCs (stage IIB: 65·7 *versus* 40·6 per cent respectively; $P < 0·001$), but with no greater use of adjuvant therapy. Significantly more patients survived for 2 years (43·3 *versus* 29·7 per cent; $P = 0·034$) and 3 years (25·4 *versus* 14·1 per cent; $P = 0·045$) after surgery in HVCs than in LVCs. More information was missing in the histopathological reports from LVCs and MVCs than in those from HVCs ($P \leq 0·002$).**

Conclusion: **Both short- and long-term survival was significantly better for patients operated on in HVCs. Histopathological analysis appears to be more comprehensive in HVCs.**

Paper accepted 16 March 2017
Published online 18 May 2017 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10560

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a poor overall prognosis even after radical surgery, although a few patients may achieve 5- or even 10-year survival following radical resection[1]. High hospital mortality and morbidity rates associated with pancreatic surgery impose high demands on patient selection and postoperative care, and centralization of surgical services has been shown to decrease postoperative mortality and morbidity in a number of countries, including Finland[2–6]. In addition, there is a tendency for more R0 resections and more comprehensive radiology and histopathology reports to be attained in high-volume units[7,8]. The effect of centralization on long-term prognosis is unclear.

In sparsely populated Finland, the healthcare system includes several public hospitals with various levels of medical facility. Hospitals are required to report treatment periods and patients with cancer to national registers for analysis. Centralization of pancreatic surgery has proceeded gradually in Finland since the 1990s. The aim of this study was to see whether hospital volume had an effect on long-term prognosis, use of adjuvant therapy or quality of histopathological evaluation in patients undergoing resection for PDAC, regardless of the type of procedure.

Table 1 Demographic and resection details of patients in the three types of centre

	High-volume centre ($n = 201$)	Medium-volume centre ($n = 138$)	Low-volume centre ($n = 128$)	P‡
Age (years)*	66 (40–84)	69 (46–86)	66 (44–83)	0·371§
Sex ratio (F : M)	89 : 112	69 : 69	61 : 67	0·572
ASA fitness grade				0·596
I	100 (49·8)	62 (44·9)	67 (52·3)	
II	37 (18·4)	27 (19·6)	27 (21·1)	
III	64 (31·8)	49 (35·5)	34 (26·6)	
Pancreatic resections	201 (100)	138 (100)	128 (100)	0·783
PD	177 (88·1)	117 (84·8)	110 (85·9)	
Distal resection	11 (5·5)	11 (8·0)	11 (8·6)	
Other resection	13 (6·5)	10 (7·2)	7 (5·5)	
No. of hospitals	2	6	14†	
Mean number of PDAC operations per hospital per year	14·4	3·3	1·3	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). High-volume centres (20 or more resections of pancreatic ductal adenocarcinoma (PDAC) annually) were: Helsinki University Hospital (UH) and Tampere UH. Medium-volume centres (6–19 resections per year) were: Kuopio UH, Turku UH, Oulu UH, Kanta-Häme Central Hospital (CH), Keski-Suomi CH, Kymenlaakso CH. Low-volume centres (5 or fewer resections annually) were: Etelä-Karjala CH, Etelä-Pohjanmaan CH, Jorvi CH, Kainuu CH, Keski-Pohjanmaa CH, Lappi CH, Länsi-Pohja CH, Etelä-Savo CH, Peijas CH, Pohjois-Karjala CH, Päijät-Häme CH, Satakunta CH, Savonlinna CH, Vaasa CH; †as well as nine hospitals that performed pancreatoduodenectomies (PDs), five hospitals each performed one distal resection in the study interval. ‡Pearson's χ^2 test, except §Mann–Whitney U test.

Table 2 Stage, resection status and tumour size according to hospital volume

	High-volume centre ($n = 201$)	Medium-volume centre ($n = 138$)	Low-volume centre ($n = 128$)	P†
Tumour stage				< 0·001
IA	7 (3·5)	5 (3·6)	4 (3·1)	
IB	12 (6·0)	16 (11·6)	21 (16·4)	
IIA	29 (14·4)	26 (18·8)	26 (20·3)	
IIB	132 (65·7)	60 (43·5)	52 (40·6)	
III	12 (6·0)	10 (7·2)	8 (6·3)	
IV	8 (4·0)	5 (3·6)	3 (2·3)	
X	1 (0·5)	16 (11·6)	14 (10·9)	
Tumour size (mm)*	30 (8–120)	35 (10–100)	30 (10–70)	0·085‡
R status				0·001
R0	110 (54·7)	86 (62·3)	73 (57·0)	
R1	83 (41·3)	36 (26·1)	34 (26·6)	
R2	4 (2·0)	13 (9·4)	16 (12·5)	
Rx	4 (2·0)	3 (2·2)	5 (3·9)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Pearson's χ^2 test, except ‡Mann–Whitney U test.

Methods

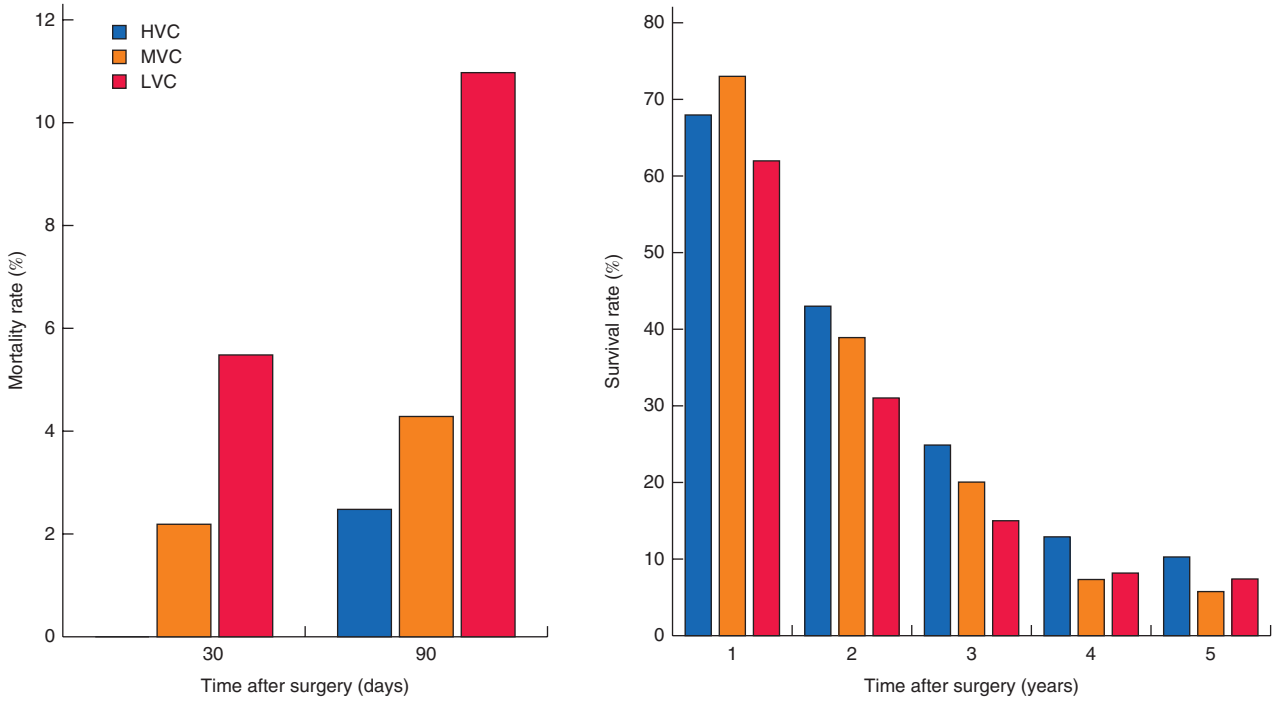
All patients diagnosed with pancreatic cancer between 2002 and 2008 were selected from the Finnish Cancer Register using the ICD-10 code C25. The treatment path was traced from the Finnish Operation and Treatment Register (HILMO) to detect the patients with a pancreatic resection using the Nordic Classification of Surgical Procedures. All patient files were collected and examined manually. Patients with a diagnosis other than PDAC were excluded, as were those who had a procedure other than resection for palliation according to patient archives. Patients with no available archival data were excluded. Incomplete archival data that led to exclusion consisted of missing histopathological or procedure reports, or unavailable medical case summaries.

The PDAC diagnoses of patients surviving for more than 4 years after operation were re-evaluated by two expert pancreatic pathologists. After the histopathological re-evaluation, patients whose diagnoses were not confirmed or those with missing slides that prevented confirmation were also excluded.

The original pathological reports of all patients were analysed and missing data on TNM stage, nodal analysis and tumour size were recorded. There was no national protocol for processing the excised pancreas or reporting the histopathological findings.

Data on medical history, the resected tumour (TNM, grade, R status (R0, microscopic resection margins 1 mm or more; R1, microscopic resection margins less than 1 mm; R2, macroscopic tumour at margins or known to have been left at surgery), tumour size, number of total and positive lymph nodes, including reanalysis whenever histological slides permitted), neoadjuvant/adjuvant therapy and survival were recorded. Although treatment paths were preplanned regionally, these were scrutinized to identify exceptions. The adjuvant therapy path was followed until receipt of an oncologist's statement up to 6 months after the operation. The censored date for survival was 31 December 2013.

Operating centres were categorized as high-volume (HVC; 20 or more resections per year), medium-volume



a Postoperative mortality rates according to operation volume

b Long-term survival rates according to operation volume

Fig. 1 a Postoperative mortality rates according to operation volume. **b** Long-term survival rates in relation to operation volume, excluding patients who died within 30 days of operation. HVC, high-volume centre (20 or more pancreatoduodenectomies (PDs) per year); MVC, medium-volume centre (6–19 PDs annually); LVC, low-volume centre (5 or fewer PDs per year)

(MVC; 6–19 resections annually) and low-volume (LVC; 5 or fewer resections annually) centres according to the mean yearly number of pancreatoduodenectomies (PDs) performed for any diagnosis (also diagnoses other than PDAC) during the period 2002–2008.

The study was approved by the Regional Ethics Committee of Pirkanmaa, Finland (code R12241).

Statistical analysis

Data are presented as median (range) or mean values. Fisher's exact test, χ^2 test and Mann–Whitney *U* test were used to calculate statistical significance, as appropriate. Survival analysis was done using Kaplan–Meier analysis, and curves were compared with the log rank test. Statistical analysis was performed with IBM SPSS® Statistics version 23 software (IBM, Armonk, New York, USA). $P < 0{\cdot}050$ was considered statistically significant.

Results

The search identified 743 potential patients with pancreatic cancer who underwent resection in Finland between 2002 and 2008. According to the original pathological reports, 218 patients had diagnoses other than PDAC and were excluded. Survival analysis found 80 patients with greater than 4-year survival; two expert pancreatic pathologists reviewed 69 slide sets from these long-term survivors. The diagnosis was confirmed in 46, and 23 patients were excluded as not having PDAC after pathological reanalysis. In addition, 11 long-term survivors with unavailable slides, 11 other patients with incomplete records and 13 patients who had undergone palliative surgery only were excluded. The final study population consisted of 467 patients who had undergone resection for PDAC.

In 2002 and 2008 there were 5·2 and 5·3 million inhabitants of Finland respectively. During that time, patients with PDAC underwent resectional surgery in 22 hospitals. By the end of 2008, the number of surgical units had decreased to 17. There were two HVCs, six MVCs and nine LVCs. In addition, five hospitals that had each performed only one distal resection during the study period were included in the LVC group for purposes of analysis. The mean numbers of operations per year for PDAC

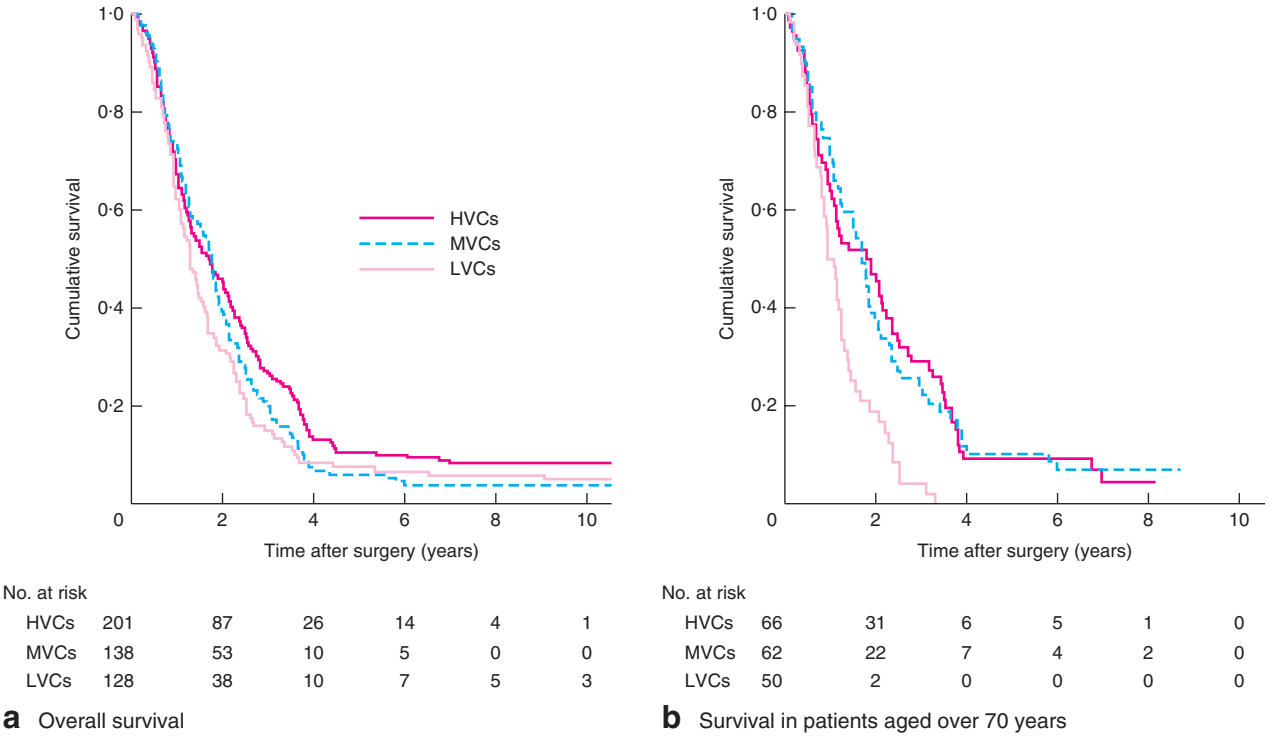


Fig. 2 Kaplan–Meier analysis of **a** overall survival and **b** survival in patients aged over 70 years who had surgery in high-volume centres (HVCs), medium-volume centres (MVCs) and low-volume centres (LVCs). **a** $P = 0{\cdot}040$, **b** $P < 0{\cdot}001$ (log rank test)

only were 14·4, 3·3 and 1·3 in the HVCs, MVCs and LVCs respectively (*Table 1*). Some 43·0 per cent of patients had resection in a HVC, 29·6 per cent in a MVC and 27·4 per cent in a LVC. Between 2002 and 2008 the annual number of PDAC procedures increased from 59 to 78, and the proportion of operations performed in a HVC increased from 36·5 to 52·5 per cent.

The demographics of patients did not differ between HVCs, MVCs and LVCs. The proportions of PDs, distal resections, total pancreatectomies and other resections were similar across the volume categories (*Table 1*). Stage distribution differed with regard to hospital volume ($P < 0{\cdot}001$). More advanced stages were more frequent in HVCs than in LVCs (stage IB: 6·0 per cent *versus* 11·6 and 16·4 per cent in MVCs and LVCs; stage IIB: 65·7, 43·5 and 40·6 per cent respectively). Despite this, more R2 resections were performed in LVCs and MVCs than in HVCs (12·5, 9·4 and 2·0 per cent respectively; $P = 0{\cdot}001$). Median tumour size was similar in HVCs, MVCs and LVCs (*Table 2*).

Both 30- and 90-day mortality rates were significantly better for patients treated in HVCs than for those having surgery in LVCs ($P = 0{\cdot}001$ and $P = 0{\cdot}003$ respectively) (*Fig. 1a*).

Median survival (excluding patients who died within 30 days of operation) was 20, 22 and 16 months in HVCs, MVCs and LVCs respectively ($P = 0{\cdot}780$, HVCs *versus* MVCs; $P = 0{\cdot}048$, HVCs *versus* LVCs). The Kaplan–Meier curve showed a statistically significant difference between types of centre ($P = 0{\cdot}040$) (*Fig. 2a*). The difference in survival rates between LVCs and HVCs was significant at 2 years ($P = 0{\cdot}034$) and 3 years ($P = 0{\cdot}045$) after resection, whereas that between MVCs and HVCs was not ($P = 0{\cdot}397$) (*Fig. 1*; *Table S1*, supporting information). Survival among patients older than 70 years was better in HVCs ($P < 0{\cdot}001$) (*Fig. 2b*).

Original pathological reports were less comprehensive regarding information on detected nodes, positive nodes, tumour size or TNM classification in MVCs and LVCs than in HVCs (all $P \leq 0{\cdot}002$). R status was rarely reported. Following histopathological reanalysis of 46 long-term survivors, TN status was upgraded in seven patients (15 per cent), with no significant difference between the centres in the rate of confirmed diagnosis ($P = 0{\cdot}236$) (*Table 3*).

Adjuvant oncological therapy was used more frequently in MVCs (61·9 (range 51·4–80·0 in different hospitals) per cent) than in HVCs (43·4 (36·9–63·3) per cent) or LVCs (42·5 (0–75·0) per cent), excluding patients who died

Table 3 Differences in histopathological reporting in the three types of centre

	High-volume centre ($n = 201$)	Medium-volume centre ($n = 138$)	Low-volume centre ($n = 128$)	P†
Total no. of long-term survivors according to original pathological analysis	37 (18·4)	18 (13·0)	14 (10·9)	
Rate of confirmed PDAC in long-term survivors following reanalysis	26 of 37 (70)	10 of 18 (56)	10 of 14 (71)	0·507
Upgraded TN status in long-term survivors after reanalysis	2 of 26 (8)	2 of 10 (20)	3 of 10 (30)	0·236
No. of nodes detected in original pathological report*	20 (2–70)	8 (0–27)	6·5 (0–26)	< 0·001‡
Information missing from original pathological report				
On tumour size	2 (1·0)	11 (8·0)	16 (12·5)	0·002
On total no. of nodes detected	16 (8·0)	55 (39·9)	68 (53·1)	< 0·001
On no. of positive nodes	5 (2·5)	28 (20·3)	27 (21·1)	< 0·001
On TNM stage	57 (28·4)	67 (48·6)	58 (45·3)	< 0·001

Values in parentheses are percentages unless indicated otherwise; *values are median (range). PDAC, pancreatic ductal adenocarcinoma. †Pearson's χ^2 test, except ‡Mann–Whitney U test.

within 30 days of operation ($P = 0·001$). The use of adjuvant therapy was more common in MVCs for different R status groups (R0: 64·2 per cent in MVCs *versus* 43·2 and 40·6 per cent in HVCs and LVCs respectively; $P < 0·001$) and for different stages ($P = 0·005$). The median initiation of adjuvant therapy was 8 weeks in all three groups. Neoadjuvant therapy was used in HVCs for only eight patients.

Discussion

This study aimed to assess the effect of centralization on both short- and long-term survival, and also to analyse the background data on histopathological analysis and the effect of adjuvant therapy. Short- and long-term prognoses were significantly better for the patients with PDAC who had resection in an HVC.

Mortality rates and complication risks characterize pancreatic resections as high-risk surgery. This requires sufficient resources in the surgical unit both before and after operation. Postoperative mortality rates of 2–15 per cent have been reported after pancreatic resections[4,9,10]. In the present study, the 30-day mortality rate was zero for patients with PDAC resected in HVCs and 5·5 per cent in LVCs. Other studies[2,4,5,11] have identified this volume–outcome effect and commented on factors likely to be involved, including surgeon volume and facilities to handle complications such as the greater availability of ICU beds.

In the present study, the significant difference in mortality between HVCs and LVCs persisted for 90 days after surgery. Mortality was over four times higher in LVCs than in HVCs. At 1 year after surgery the number of survivors became more even, but the survival gap began to widen again more than 2 years after surgery in favour of HVCs. A study of the impact of centralization in the Netherlands[3] also found a significant difference between 1 and 2 years after surgery, although not in 30- or 90-day mortality rates. The impact of survival at 90 days is most likely more dependent on hospital facilities, complications and preoperative diagnostics, after which survival has more to do with the resection success, postoperative follow-up and possible treatments. Patient-specific tumour factors play a role in all phases, but beneficial tumour biology probably dominates in long-term survivors.

Five-year survival rates in the present study (5·9–10·0 per cent) were slightly lower than those in other studies[12–14]. This may reflect the confirmation of the diagnosis undertaken here as part of the histopathological review, which found 33 per cent (23 of 69) of the original diagnoses of long-term survivors to be imprecise. Original reports from MVCs and LVCs were more likely to be deficient in information than reports from HVCs. Nodal analyses in particular were inadequate, potentially affecting perceived stage and the likelihood of offering adjuvant therapy. In HVCs, more resected stage IIB tumours were reported than in LVCs (65·7 *versus* 40·6 per cent respectively), which can at least partly be explained by a more comprehensive nodal analysis. Despite the apparently higher proportion of better stage disease in the LVCs, this did not result in better survival in LVCs.

Earlier studies[15–17] suggested that only 30 per cent of procedures result in a true R0 resection, with the area near the vessels most likely to remain only macroscopically clear. In this study, there was no significant difference between the centres in the proportion of R0 resections, but the true number of R0 resections is debatable. There were more R2 and fewer R1 resections in the LVCs than in the HVCs. Differentiation between R0 and R1 resections, in particular, is dependent on the pathological assessment, which showed shortcomings in the LVCs in the present

study. It is possible that the actual rate of R1 resection was higher in all units. The availability of expertise with vascular resections may also have influenced the number of R2 resections, as this addition was not standard in the study period.

Adjuvant chemotherapy is now widely recommended after resection of PDAC, subject to fitness and the patient's wishes[13]. Adjuvant therapy was not standardized in Finland during the study interval and there were also regional differences in its use. The proportion of patients who had no adjuvant therapy varied from 36·9 to 63·3 per cent between the two HVCs, and this cannot be explained by stage or R distributions. Despite these differences in adjuvant therapy, the survival of patients undergoing resection in HVCs tended to be better, which may demonstrate the crucial effect of a proper resection. Taking into consideration adjuvant therapy aspects and histopathological analysis, the treatment of PDAC was far from uniform in Finland during the study period.

The actual yearly PD volume is debatable. Although HVCs are described as centres performing over 20–25 PDs per year[2,3,5], recent reports suggest even better results in centres with a yearly volume of more than 40 PDs[18]. In Finland, the organization of surgical treatment faces challenges attributable to low population density (18 inhabitants/km^2) and uneven population distribution. During the study period, an annual PD rate above 40 was achievable in the south-west of the country, although this volume was not reached by any centre. Organizational and geographical challenges have to be addressed in Finland. In the north of Finland, the population density drops to fewer than five inhabitants/km^2, and the distance to the nearest high-volume unit can easily be over 500 km. Despite these practical problems, the superior short- and long-term results in HVCs reported here, and internationally, justify rationalization, so that two to three centres could attain more than 40 PDs per year and guarantee patients proper access to treatment.

A strength of this study is that it includes all resections for PDAC in a single country. The national registers in Finland allow a comprehensive analysis. The results give a more reliable view of the effect of hospital volume on survival than is possible with results from only one unit. The bias of incorrect histopathological diagnosis among long-term survivors was minimized via the reconfirmation of the diagnosis, as well as the effect of 30-day mortality in long-term survival analysis. Despite its retrospective nature, few patients had to be excluded owing to unavailable records. On the other hand, TNM and R classifications were dependent on information in the patient records, and the quality of these varied across regions. The diagnosis of patients who had survived for more than 4 years was reviewed, balancing out possible differences in pathological analysis and allowing correction of the overall survival estimates. A histopathological review of the whole study population would have yielded even more precise results, but it seems reasonable to assume that less aggressive tumours dominate the group of long-term survivors and that the influence of incorrect diagnoses would have been small among the short-term survivors. The distal resections and total pancreatectomies in the present study complicate generalization of the results to all pancreatic cancer resections, but, like all national series, the proportion of patients having a procedure other than PD was small.

In common with other Western countries, better short- and long-term survival following surgical resection for PDAC in HVCs supports the centralization of pancreatic cancer surgery in Finland.

Acknowledgements

The authors thank statistician M. Helminen (University of Tampere) for comments on statistical analysis and research assistant S. Järvinen (Tampere University Hospital) for archive management.

This work was supported by the State Research Funding (VTR) and the Sigrid Juselius Foundation. Neither of these was involved in the study design, data collection, data analysis, manuscript preparation or publication decisions.

Disclosure: The authors declare no conflict of interest.

References

1 Paniccia A, Hosokawa P, Henderson W, Schulick RD, Edil BH, McCarter MD *et al*. Characteristics of 10-year survivors of pancreatic ductal adenocarcinoma. *JAMA Surg* 2015; **150**: 701–710.

2 Ansari D, Williamsson C, Tingstedt B, Andersson B, Lindell G, Andersson R. Pancreaticoduodenectomy – the transition from a low- to a high-volume center. *Scand J Gastroenterol* 2014; **49**: 481–484.

3 Gooiker GA, Lemmens VE, Besselink MG, Busch OR, Bonsing BA, Molenaar IQ *et al*. Impact of centralization of pancreatic cancer surgery on resection rates and survival. *Br J Surg* 2014; **101**: 1000–1005.

4 Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery. *Med Care* 2011; **49**: 1076–1081.

5 Lemmens VE, Bosscha K, van der Schelling G, Brenninkmeijer S, Coebergh JW, de Hingh IH. Improving outcome for patients with pancreatic cancer through centralization. *Br J Surg* 2011; **98**: 1455–1462.

6 Nordback L, Parviainen M, Raty S, Kuivanen H, Sand J. Resection of the head of the pancreas in Finland: effects of hospital and surgeon on short-term and long-term results. *Scand J Gastroenterol* 2002; **37**: 1454–1460.
7 Westgaard A, Clausen OP, Gladhaug IP. Survival estimates after pancreatoduodenectomy skewed by non-standardized histopathology reports. *APMIS* 2011; **119**: 689–700.
8 Walters DM, Lapar DJ, de Lange EE, Sarti M, Stokes JB, Adams RB *et al*. Pancreas-protocol imaging at a high-volume center leads to improved preoperative staging of pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 2011; **18**: 2764–2771.
9 Reames BN, Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and operative mortality in the modern era. *Ann Surg* 2014; **260**: 244–251.
10 Elberm H, Ravikumar R, Sabin C, Abu Hilal M, Al-Hilli A, Aroori S *et al*. Outcome after pancreaticoduodenectomy for T3 adenocarcinoma: a multivariable analysis from the UK Vascular Resection for Pancreatic Cancer Study Group. *Eur J Surg Oncol* 2015; **41**: 1500–1507.
11 Mamidanna R, Ni Z, Anderson O, Spiegelhalter SD, Bottle A, Aylin P *et al*. Surgeon volume and cancer esophagectomy, gastrectomy, and pancreatectomy: a population-based study in England. *Ann Surg* 2016; **263**: 727–732.
12 Carpelan-Holmström M, Nordling S, Pukkala E, Sankila R, Lüttges J, Klöppel G *et al*. Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry. *Gut* 2005; **54**: 385–387.
13 Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D *et al*.; ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26**(Suppl 5): v56–v68.
14 Jorgensen MT, Fenger C, Kloppel G, Luttges J. Long-term survivors among Danish patients after resection for ductal adenocarcinoma of the pancreas. *Scand J Gastroenterol* 2008; **43**: 581–583.
15 Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H *et al*. Most pancreatic cancer resections are R1 resections. *Ann Surg Oncol* 2008; **15**: 1651–1660.
16 Raut CP, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH *et al*. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg* 2007; **246**: 52–60.
17 Konstantinidis IT, Warshaw AL, Allen JN, Blaszkowsky LS, Castillo CF, Deshpande V *et al*. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections *versus* locally advanced unresectable tumors? What is a 'true' R0 resection? *Ann Surg* 2013; **257**: 731–736.
18 van der Geest LG, van Rijssen LB, Molenaar IQ, de Hingh IH, Groot Koerkamp B, Busch OR *et al*. Volume–outcome relationships in pancreatoduodenectomy for cancer. *HPB (Oxford)* 2016; **18**: 317–324.

Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Pairwise analysis of survival and mortality (Word document)

Access to radical resections of pancreatic cancer is region-dependent despite the public healthcare system in Finland

Reea Ahola,[1] Heini Hölsä,[2] Samuli Kiskola,[2] Pirkka Ojala,[2] Aino Pirttilä,[2] Juhani Sand,[1] Johanna Laukkarinen[1,2]

[1]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland
[2]Medicine, University of Tampere, Tampere, Finland

Correspondence to
Professor Johanna Laukkarinen, Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere 33521, Finland; johanna.laukkarinen@fimnet.fi

Received 30 October 2017
Revised 23 March 2018
Accepted 16 April 2018
Published Online First 2 May 2018

ABSTRACT

Background Surgical resection is the best treatment option to improve the prognosis of pancreatic cancer (PC). Our aim was to analyse whether PC treatment strategies show regional variation in Finland, a country with a nationwide public healthcare system.

Methods All patients diagnosed with PC in 2003 and 2008 were identified from the Finnish Cancer Registry. The data regarding tumour, treatment, demographics and timespans to treatment were recorded from the patient archives. Patients were included in the healthcare district where the diagnosis was made. The healthcare districts were classified according to experience in pancreatic surgery into three groups (high level of experience region (HLER), n=2; medium level of experience region (MLER), n=6, and low level of experience region (LLER), n=13).

Results Patients included numbered 1546 (median age 72 years (range 34–97), 45% men). Demographics and the ratio of stage IV disease (53%) were similar between the regional groups. Despite this, the proportion of radical surgery was greater in HLERs than in the MLERs and LLERs (18% vs 8%–11%; p<0.01). Logistic regression analysis including age, American Society of Anesthesiologists classification, stage and level of experience showed that more radical resections were performed in the HLERs. Preoperative bile drainage showed no regional differences (p=0.137). Palliative chemotherapy only was used more frequently in MLER and LLER than in HLERs (24% vs 33%–30%; p<0.01).

Conclusion Access to PC curative treatment was more likely for patients in healthcare districts including a hospital with high level of experience in pancreatic surgery. This highlights the importance of centralized treatment guidance.

INTRODUCTION

Radical surgery is the only option to achieve longer survival after a diagnosis of pancreatic cancer. However, only 10%–20% of patients have a resectable tumour at the time of diagnosis.[1] Pancreas surgery is high-risk surgery with postoperative mortality up to 5%–15%, thereby decreasing the number of patients suitable for surgery. Earlier studies have demonstrated that more radical resections are attempted in high-volume centres and short-term prognosis after the operation is better.[2–4]

Finland is a sparsely populated country with a comprehensive public healthcare system which aims to offer access to evidence-based treatments for all residents. However, the population density ranges from 170 to under 5/km^2, which challenges the organising of healthcare, especially now when the population pyramid is narrowing and economic pressure is increasing. Earlier we have shown that long-term survival (>4 years) after radical surgery is possible especially in high-volume centres, where the mortality is the lowest up to 90 days postoperatively compared with medium-volume or low-volume centres.[5 6]

Finland maintains comprehensive national registers on treatment periods. However, no studies have so far attempted to demonstrate the accessibility of pancreatic cancer treatment in Finland. The aim of this study was to evaluate whether patients from different areas end up in uniform treatment strategies and to analyse whether experience in pancreatic surgery has an effect on the treatment strategies adopted.

PATIENTS AND METHODS

All patients diagnosed with pancreatic cancer in 2003 and 2008 were selected from the Finnish Cancer Registry using the International Classification of Diseases code, Tenth Revision C25. Hospitals are obligated to send information on the patients with cancer they have treated to the Finnish Cancer Registry. The data are confirmed with a 2-year delay. The years were selected to include 5-year survival results at the time of data retrieval in 2014. During our earlier studies, we had noticed challenges in obtaining patient records from 2000 to 2002, so the analysis was started from the year 2003. Patients' treatment paths were traced from the Finnish Operation and Treatment Register (hoitoilmoitusjärjestelmä (HILMO)) and patient files concerning pancreatic cancer were examined manually. Patients with diagnoses other than primary pancreatic cancer, with diagnoses set outside the study years (2003 and 2008) or with unavailable or incomplete data were excluded.

Data on medical history, cancer stage and treatment strategy (radical surgery, palliative surgery, biliary drainage, oncological therapy, other palliative therapy, no therapy) were recorded from the patient records. Information on medical history is reported as ASA (American Society of Anesthesiologists classification) classes. Missing data are reported and not included in the calculations. In addition, information on the time elapsing from diagnosis to the initiation of each treatment was recorded.

To cite: Ahola R, Hölsä H, Kiskola S, *et al*. *J Epidemiol Community Health* 2018;**72**:803–808.

At the time of the study, there were 21 healthcare districts in Finland. For the purposes of the study, these were categorised into three groups based on the yearly number of pancreatoduodenectomies (PD) performed in the respective districts between 2002 and 2008: high level of experience region (HLER; >20 PD/year), medium level of experience region (MLER; 6–19 PD/year) and low level of experience region (LLER; <6 PD/year or only distal resections or no pancreas resections).

In the study database, the patients were included in the healthcare district in which they were resident at the time of the pancreatic cancer diagnosis.

Data are shown as median (range). Fisher's exact test, χ^2 test and Kruskall-Wallis test were used to calculate statistical significance. Survival analysis was performed using Kaplan-Meier analysis. Multivariate analysis was performed with logistic regression. A p value of ≤0.05 was considered statistically significant.

The study was approved by the National Institute for Health and Welfare in Finland (decision code: THL/1681/5.05.00/2013) and the Regional Ethics Committee of Pirkanmaa, Finland (code R12241).

RESULTS

Patients with pancreatic cancer

The search in the Finnish Cancer Registry identified 1936 patients with pancreatic cancer diagnosed in 2003 and 2008. Ninety per cent of the patients' files were available for further analysis. A further 153 patients were excluded after reviewing the information in the patient archives and 43 because the diagnosis had been set postmortem. The final data comprised 1546 patients figure 1. Each patient with pancreatic cancer was included with any subtype. The subtype of pancreas cancer was reported in 59% of cases.

Healthcare districts

During the study period, there were 21 healthcare districts in Finland: 2 HLERs, 6 MLERs and 13 LLERs, with PDs in the latter performed occasionally or not at all. Neither PD or distal pancreatectomies were performed in one district only. The number of operating centres did not change between 2003 and 2008. The median yearly incidence of pancreatic cancer was 15.5/100 000 pop (range 23.7–12.9/100 000 pop, p=0.458, Kruskall-Wallis test, degree of freedom 20).

Demographic and tumour data

Median age at the time of diagnosis was 72 years (33.9–97.0 years) and 45% of the patients were men. ASA classes 1, 2 and 3–4 comprised 33.9%, 30.3% and 35.8% of the patients, respectively. Median age at diagnosis and ASA classes were at their lowest in HLERs (0.014, Kruskall-Wallis test, degree of freedom 2 and 0.031 Pearson's χ^2 test, degree of freedom 4, for ASA). The age group-based analysis (<60, 60–75 and >75 years at the diagnosis) revealed no significant differences between HLERs, MLERs and LLERs (p=0.062, Pearson's χ^2 test, degree of freedom 4). The proportion of stage IV tumours at diagnosis varied between the 21 healthcare districts (p=0.013, Pearson's χ^2 test, degree of freedom 4), but no correlation to pancreatic surgery experience (HLER/MLER/LLER) was found (p=0.060, Pearson's χ^2 test, degree of freedom 2) (table 1).

Treatment strategies

Radical resection was more likely if the patient was living in an HLER (17.9% of the patients were radically resected in HLERs vs 11.0% in MLERs and 7.7% in LLERs, p<0.001, Pearson's χ^2 test, degree of freedom 10). The difference persisted when analysing only patients with non-metastatic disease (49% in HLERs, 29% in MLERs and 22% in LLERs; p=0.002, Pearson's χ^2 test, degree of freedom 2). In the logistic regression analysis also concerning ASA class, age groups and stage (groups I–III, IV, NAS), level of experience in pancreatic surgery persisted as a significant factor for selection for radical surgery. The OR for patients with undefinable stage class was low, demonstrating that their treatment strategies were more likely to be of a palliative nature (tables 2 and 3 and figure 2).

The median incidence of radical surgery was almost twice as high among patients resident in HLERs than in LLERs: 4.9 operations/100 000 vs 2.5 operations/100 000, but the difference was not statistically significant (p=0.144, Kruskal-Wallis test, degree of freedom 2). Among patients without a defined pancreas cancer subtype, 1.1% had undergone surgery and the rest palliative treatment strategy (figure 2).

Between 2003 and 2008, the proportions of radical surgery did not significantly increase in the districts (p=0.245 for HLER, p=0.321 for MLER and p=1.000 for LLER, Fisher's exact test). There was no significant difference in bile drainage preoperatively (52% in HLERs, 30% in MLERs and 49% in

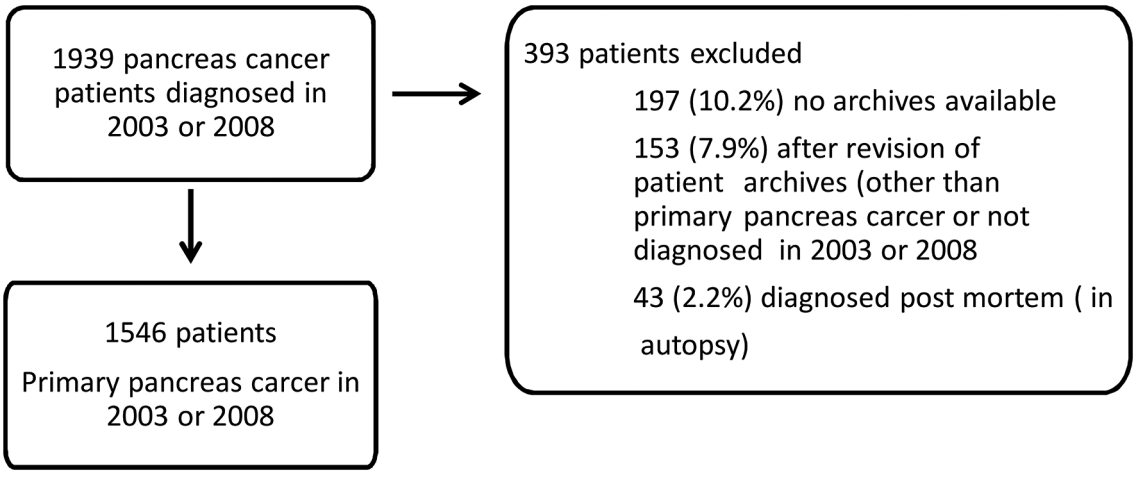


Figure 1 The search from the Finnish operation and treatment register (HILMO) identified 1939 patients with pancreatic cancer of whom 1546 were included in the study.

Table 1 Demographics

	HLER	MLER	LLER	P values
Total	504	508	534	
Male/Female (%)	220/284 (43.7/56.3)	228/280 (44.9/55.1)	254/280 (47.6/52.4)	0.430*
Median age, years (range)	69.9 (34.1–95.8)	72.4 (37.3–97.0)	72.9 (33.9–94.9)	
Categorised ages (years)				0.062†
<60 (%)	102 (20.2)	84 (16.5)	85 (15.9)	
60–75 (%)	229 (45.1)	222 (43.7)	221 (41.4)	
>75 (%)	173 (34.3)	202 (39.8)	228 (42.7)	
ASA				0.031* without NAS
1 (%)	186 (36.9)	137 (27.0)	170 (31.8)	
2 (%)	169 (33.5)	140 (27.6)	168 (31.5)	
3–4 (%)	133 (26.5)	159 (31.3)	177 (33.1)	
NAS (%)	16 (3.2)	72 (14.2)	19 (3.6)	
Stage				0.060* without NAS
I–III	148 (29.4)	112 (22.0)	114 (21.3)	
IV	270 (53.6)	282 (55.5)	277 (51.9)	
NAS	86 (17.1)	114 (22.4)	143 (26.8)	

The age groups showed no significant differences.
ASA and stage distribution showed varied between the groups. ASA and stage groups were analysed without the unknown data.
*Pearson's χ^2 test.
† Kruskal-Wallis test.
ASA, Amercian Society of Anesthesiologists classification; HLER, high level of experience region; LLER, low level of experience region; MLER, medium level of experience region; NAS, non aliter specificatus (unknown).

LLERs (p=0.137, Pearson's χ^2 test, degree of freedom 2). The proportion of palliative chemotherapy was lowest in HLERs (24.2% vs 32.9%–30.0%, p=0.033, Pearson's χ^2 test, degree of freedom 2). The significant difference persisted among patients with stage I–III disease (p<0.001, Pearson's χ^2 test, degree of freedom 2) (table 3).

Table 2 Logistic regression analysis taking into consideration age, ASA, metastatatic/non-metastatic stage and the level of experience in pancreatic surgery

	P values	Degree of freedom	OR	95% CI
Age, years, general	<0.001	2		
<60			Reference	
60–75	0.131	1	0.690	0.426 to 1.117
>75	<0.001	1	0.171	0.093 to 0.314
Stage	<0.001	2		
I–III			Reference	
NAS	<0.001	1	0.092	0.051 to 0.167
IV	<0.001	1	0.016	0.008 to 0.031
ASA	0.266	2		
1			Reference	
2	0.480	1	0.847	0.534 to 1.344
3–4	0.104	1	0.652	0.390 to 1.091
Level of experience in pancreas surgery	<0.001	2		
High level			Reference	
Medium level	0.026	1	0.585	0.365 to 0.938
Low level	<0.001	1	0.387	0.239 to 0.627

Experience in pancreatic surgery remains a significant factor explaining the differences.
ASA, Amercian Society of Anesthesiologists classification, NAS, non aliter specificatus (unknown).

Time elapsing from diagnosis to initiation of treatment

The median time elapsing from diagnosis to radical surgery was 28, 18 and 27 days in HLERs, MLERs and LLERs, respectively. This timespan varied between the districts in favour of MLERs (p=0.001, Kruskal-Wallis test, degree of freedom 2) and the difference persisted if the timespan analysed was cut to 8–60 days (medians 28.0, 20.0 and 27.5 days in HLER, MLER and LLER, respectively, p<0.001, Kruskal-Wallis test, degree of freedom 2). The timespan information was not available in 7.5% of cases (14 patients). The time elapsing to the initiation of palliative oncological therapy was statistically equally long (49 to 45.5 days;

Table 3 Treatment strategies. Radical surgery was significantly more common in HLER than in MLER or LLER, where palliative oncological therapy was more frequent among non-metastatic disease (stages I–III)

	HLER	MLER	LLER	P values*
Total	504	508	534	
Radical surgery (%)	90 (17.9)	56 (11.0)	41 (7.7)	<0.001
Only biliary drainage	140 (27.8)	110 (21.8)	130 (24.3)	0.076
Palliative oncological therapy	122 (24.2)	158 (32.9)	160 (30.0)	0.033
Palliative surgery	24 (4.8)	36 (7.1)	50 (9.4)	0.016
Other palliative approaches	128 (25.4)	148 (29.1)	153 (28.7)	0.351
Total, stage I–III	148	112	114	
Radical surgery among stage I-III (%)	79 (49.1)	46 (28.6)	36 (22.4)	0.002
Palliative oncological therapy among stage I–III (%)	20 (13.7)	38 (34.2)	39 (34.2)	<0.001

*Pearson's χ^2 test.
HLER, high level of experience; LLER, low level of experience; MLER, medium level of experience.

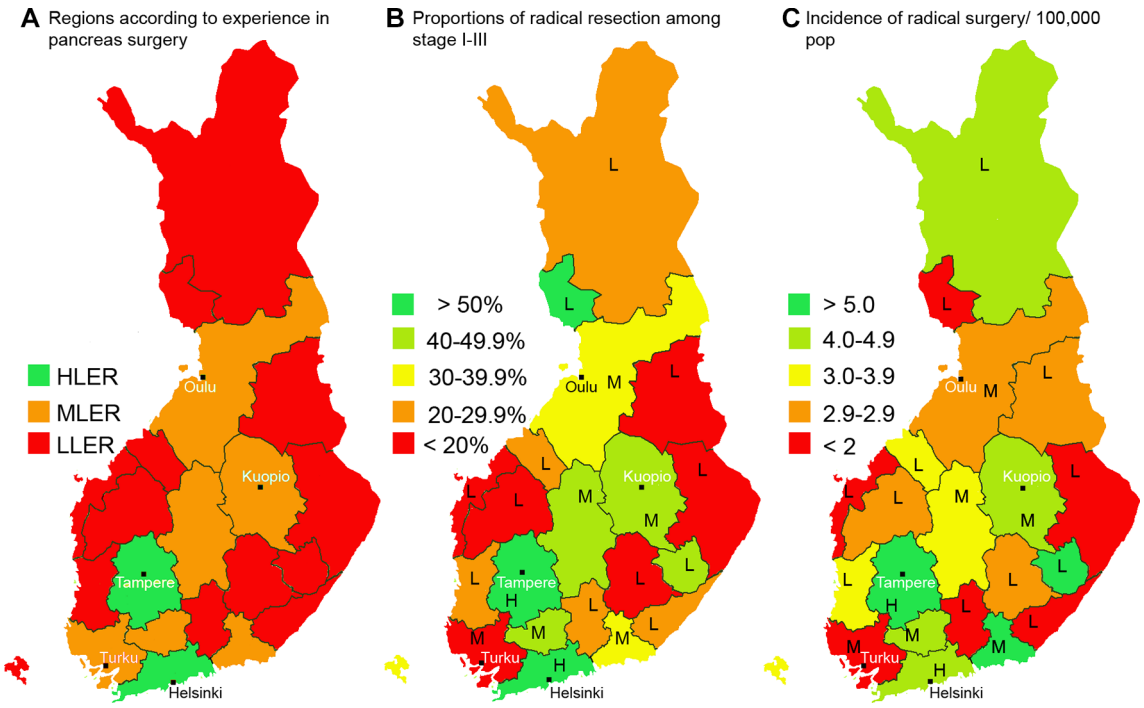


Figure 2 (A) Healthcare districts according to level of experience in pancreatic surgery. (B) Proportions of radical resections among patients under 75 years with stage I–III disease showed regional differences attributable to the experience in pancreatic surgery (p=0.002, Pearson's χ^2 test). (C) Incidence of radical resections/100 000 pop varied, but no statistical difference was found in correlation to experience in pancreatic surgery (p=0.144, Kruskal-Wallis test). H, high level of experience region; M, medium level of experience region; L, low level of experience region; university hospital cities mentioned in the figure.

p=0.290, Kruskal-Wallis test, degree of freedom 2), but 33.5% of the timespan information about the palliative chemotherapy was incomplete (figure 3).

Survival

The overall 5-year survival rate was 1.2%. Median overall survival was 19 weeks (range 15.0–23.6) in HLERs, 16.4 weeks (14.3–18.6) in MLERs and 14.4 weeks (12.0–16.8) in LLERs. Kaplan-Meier analysis showed significantly better overall survival (p<0.001, log rank, degree of freedom 2) in HLERs (figure 4). However, 5-year survival after radical resections did not differ significantly (7.7% for HLERs, 5.4% for MLERs and 7.3% for LLERs, p=0.869, Fisher's exact test).

DISCUSSION

Earlier studies have demonstrated improved quality of pancreatic tumour diagnostics, number of pancreas resections and survival after radical resection if the patient is treated in a high-volume centre.[4 7–11] However, no analyses have been reported concerning nationwide access to radical surgery. This study aimed to assess the effect of experience in pancreatic surgery in place of residence on overall access to radical surgery in Finland during the 2000s. Our study showed better access to a potentially curative treatment of pancreatic cancer if the patient was resident in a healthcare district with a centre with high level of experience in pancreatic surgery.

At the time of diagnosis, 50%–60% of patients with pancreatic cancer worldwide had a metastatic disease, whereas 10%–20% had a resectable tumour.[1 12] In the present study, the overall proportion of stage IV disease was at the level reported internationally, but significant differences were revealed in the analysis of healthcare districts. The proportion of metastatic disease at diagnosis varied from 91% to 57%, but the difference was not explained by level of experience in pancreatic surgery. The challenges in the diagnostics of pancreatic cancer include mild or asymptomatic onset of the disease, which may cause patients to hesitate before seeking medical advice. On the other hand, without CT/MRI scans diagnosis of stage I–II pancreatic cancer is usually impossible. In addition, regional difficulties in recruiting doctors and arranging public healthcare may have played a role if a diagnosis was made too late. In Finland, where the national healthcare system is public, organising healthcare plays a key role in access to evidence-based treatment.

In this study, the proportion of radical resections only reached an internationally acceptable level of ca. 20% in the two healthcare districts with a highly experienced centre. A recent Danish study reported an overall resection rate of 16%, which is comparable with our results from highly experienced centres.[13] In our study resection rates of non-metastatic disease were even higher, reaching a level of 50% among patients in HLERs and 20%–30% in MLERs and LLERs. These results did not lose their significance in the multivariate analysis. Van der Geest *et al* demonstrated that elderly patients in particular benefit from an operation in a tertiary hospital.[14] Onete *et al* reported increased number of R0 resections in high-volume centres and stated that advanced stage diseases were also more likely to be operated on in high-volume centres.[15] Our study demonstrated that palliative oncological therapy was more common if a patient was not resident in an HLER, which corroborates the results of Onete. The overall experience in elderly patients, more complex medical history and advanced stage diseases may also affect the primary decisions on treatment strategies in the districts and increased experience may lead to an increased number of candidates for surgery. This can be explained by more refined treatment paths

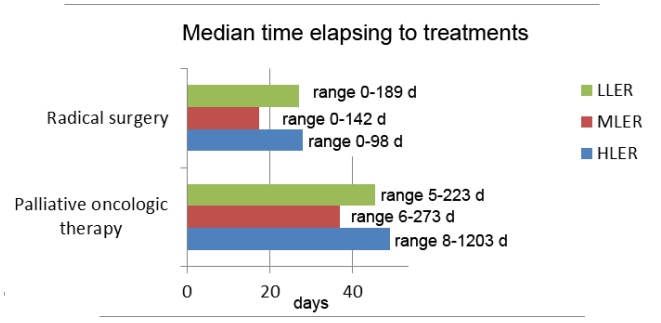


Figure 3 Median time elapsing from diagnosis to radical surgery showed a significant difference of 10 days in favour of MLERs (p=0.001, Kruskal-Wallis test). Among palliative oncological therapy median time elapsing did not differ significantly. HLER, high level of experience; LLER, low level of experience; MLER, medium level of experience.

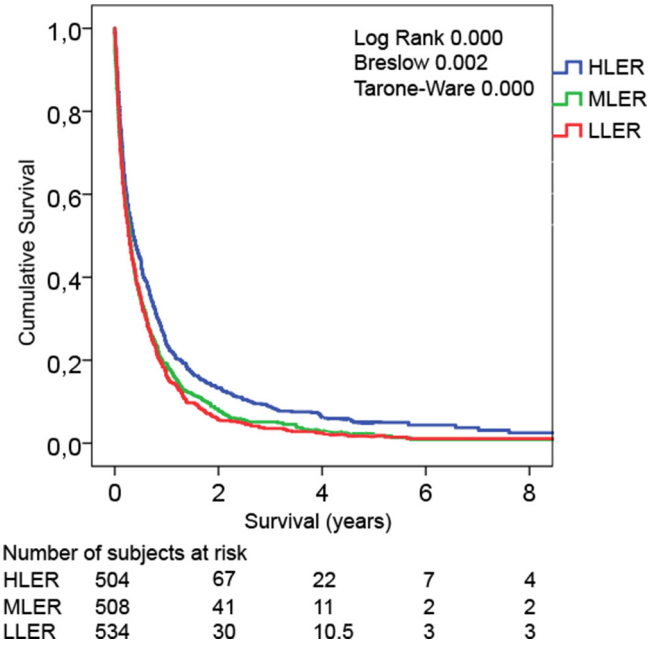


Figure 4 Kaplan-Meier curve demonstrating longer overall survival of patients with pancreatic cancer in HLER. HLER, high level of experience region; LLER, low level of experience region; MLER, medium level of experience region.

in highly experienced healthcare districts, more comprehensive postoperative follow-up facilities and also by the more experienced analysis of the patient's stage and status.

In the Danish register study, an acceptable timespan for a diagnostic pathway, waiting time for surgery as well as for oncological therapy was 14 days.[13] Our results of approximately 17–28 days elapsing from diagnosis to radical resections are comparable, but the time elapsing to the initiation of oncological therapy was far from the Danish goal. In our study, it seemed that the waiting time for surgery was about 1 week shorter if the patient was diagnosed in healthcare districts with a medium level of experience. This can be a reflection of more crowded high-volume centres. One week may not be clinically relevant otherwise, but it may increase the risk of biliary drainage before the operation. In this study, 44% of the patients diagnosed in healthcare districts with high level of experience underwent biliary drainage (endoscopic retrograde cholangiopancreatography/percutaneous transhepatic drainage) before the surgery, whereas the proportion was 30% in the healthcare districts with medium level of experience (not significant (NS)). After the period scrutinised in this study, 2003 and 2008, poorer survival and increased postoperative morbidity have been reported among patients with routine preoperative biliary drainage, which emphasises the need for rapid access to radical resection.[16] We can find no reason why in the HLERSs, the waiting time could not be reduced to at least at the same level as in MLERs, but our data cannot give exact answers as to how such improvements could be achieved.

Overall 5-year survival with pancreatic cancer is usually estimated to be as low as under 5%.[1 17] However, survival is stage and treatment dependent and 20% 5-year survival has been reported after radical surgery.[16] In Finland, 5-year survival after histologically verified pancreatic ductal adenocarcinoma has been reported to be 0.2%,[18] but recent data on overall survival from pancreatic cancer in Finland have not been available. In this study, overall 5-year survival was 1.2% and 5-year survival after radical surgery was 7%. The Danish[13] study reported a 3-year survival of 6% for ductal pancreatic adenocarcinoma, which was surpassed in our study. However, comparison of survival rates is challenging because of the lack of histological specimens from patients not undergoing surgery. In addition, our study reported overall survival, because patient archives and the Finnish Cancer Registry do not automatically contain information about the cause of death. However, the overall poor prognosis of pancreatic cancer being poor, we consider the overall survival a reasonable result in this study. In our study, in the healthcare districts with greater experience in pancreas surgery, the overall survival curve was, however, significantly better than in the healthcare districts with less experience. This is partly explained by larger proportions of radical surgery in the more experienced regions. The radiological facilities are probably also more comprehensive in these healthcare districts, which may enable earlier diagnosis.

The strength of this study is the nationwide approach to analysing the treatment paths. This is crucial in a public healthcare system aiming at equality. At the time of writing, the Finnish healthcare system is under major reorganisation and information on the pros and cons of the earlier system is needed to achieve improvements. National registers are obligatory for public healthcare and enabled comprehensive data gathering for this study. Despite the registers, no earlier study has tried to describe the challenges in achieving equality of treatment among patients with pancreatic cancer in Finland. The patient archives themselves, however, showed regional and occasional differences in the data recorded, which resulted in incomplete information in some parts of the analysis. This incompleteness may have biased the results. Our study evaluated the functioning of the healthcare districts. In addition to the healthcare structures, patient-related factors, such as socioeconomic status and patient's perceptions of the local healthcare may also play a role in how the healthcare system is or can be used. However, despite some incompleteness and the challenges of retrospective data, Strengthening the Reporting of Observational Studies in Epidemiology guidelines can have been followed. We consider the study generalisable both to other countries with public healthcare and also to those with private healthcare: hospitals have different treatment strategies.

The costs of pancreas resections have been reported to be lower in high-volume centres.[19] The evaluation of total costs from diagnosis to initiation of treatment is more challenging. In Finland, where population density varies across healthcare districts, from 170 to 2/km^2, organising effective treatment paths is crucial. Our study revealed that organising pancreatic surgery in 20 healthcare districts did not result in equal availability of pancreas surgery throughout the country. Despite the public healthcare, patients

What is already known on this subject

- Resection is the only possible curative treatment for pancreatic cancer, but only 20% of patients are candidates for surgery.
- Patient selection requires an experienced multidisciplinary team.
- Hospitals with high resection volumes have been associated to better prognosis and longer.

What this study adds

- More patients are selected for radically aimed surgery in healthcare districts with a high resection volume centre.
- This emphasises the need for centralised guidance of the whole treatment path.

may be referred or they can request treatment in another healthcare district, but these alternatives did not seem to be common during the time of this study. As the differences in stage distribution at diagnosis are already present, thorough regional organising of the education and radiological services could increase the proportion of patients with early stage disease at diagnosis. Routine consultancy facilities in the highly experienced regions may even out the treatment strategies, increase resection rates and result in lower costs. In addition, our earlier study showed longer survival of the patients with pancreatic cancer if they are operated on in high-volume centres.[5] Cancer treatment is undergoing reorganisation in Finland. Future Finnish cancer centres have emulated the Danish model in limitations on waiting time to diagnosis and treatments which will challenge the treatment path even more. This highlights the importance of centralisation and education regarding the whole treatment path.

Acknowledgements The authors thank Satu Järvinen for archive management, statistician Mika Helminen for comments and Virginia Mattila for proofreading.

Contributors RA: planning, acquisition of data, analysis,interpretation of data, writing, refining and revision of the manuscript. HH, AP, SK and PO: acquisition of data, analysis,reporting and revision of the manuscript. JS and JL: planning, conducting, interpretation of data, writing and revising of manuscript.

Funding This work was supported by the State Research Funding (VTR), Finland, and the Sigrid Jusélius Foundation, Finland, which have no involvement in the study design, data collection, data analysis, manuscript preparation or publication decisions.

Competing interests None declared.

Patient consent Not required.

Ethics approval Ethical committee of Pirkanmaa district.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Ducreux M, Cuhna AS, Caramella C, *et al*. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26(suppl 5):v56–v68.
2 Gooiker GA, Lemmens VEPP, Besselink MG, *et al*. Impact of centralization of pancreatic cancer surgery on resection rates and survival. *Br J Surg* 2014;101:1000–5.
3 Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery. *Med Care* 2011;49:1076–81.
4 Søreide JA, Sandvik OM, Søreide K. Improving pancreas surgery over time: Performance factors related to transition of care and patient volume. *Int J Surg* 2016;32:116–22.
5 Ahola R, Siiki A, Vasama K, *et al*. Effect of centralization on long-term survival after resection of pancreatic ductal adenocarcinoma. *Br J Surg* 2017;104:1532–8.
6 Ahola R, Siiki A, Vasama K, *et al*. Patients with resected, histologically re-confirmed pancreatic ductal adenocarcinoma (PDAC) can achieve long-term survival despite T3 tumour or nodal involvement. The Finnish Register Study 2000-2013. *Pancreatology* 2017:17:822–6.
7 Westgaard A, Clausen OP, Gladhaug IP. Survival estimates after pancreatoduodenectomy skewed by non-standardized histopathology reports. *APMIS* 2011;119:689–700.
8 Walters DM, LaPar DJ, de Lange EE, *et al*. Pancreas-protocol imaging at a high-volume center leads to improved preoperative staging of pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 2011;18:2764–71.
9 Lemmens VE, Bosscha K, van der Schelling G, *et al*. Improving outcome for patients with pancreatic cancer through centralization. *Br J Surg* 2011;98:1455–62.
10 Nordback L, Parviainen M, Räty S, *et al*. Resection of the head of the pancreas in Finland: effects of hospital and surgeon on short-term and long-term results. *Scand J Gastroenterol* 2002;37:1454–60.
11 Reames BN, Ghaferi AA, Birkmeyer JD, *et al*. Hospital volume and operative mortality in the modern era. *Ann Surg* 2014;260:244–51.
12 Weledji EP, Enoworock G, Mokake M, *et al*. How grim is pancreatic cancer? *Oncol Rev* 2016;10:294.
13 Fristrup C, Detlefsen S, Hansen CP, *et al*. Danish pancreatic cancer database. *Clin Epidemiol* 2016;8:645–8.
14 van der Geest LG, Besselink MG, Busch OR, *et al*. Elderly patients strongly benefit from centralization of pancreatic cancer surgery: a population-based study. *Ann Surg Oncol* 2016;23:2002–9.
15 Onete VG, Besselink MG, Salsbach CM, *et al*. Impact of centralization of pancreatoduodenectomy on reported radical resections rates in a nationwide pathology database. *HPB* 2015;17:736–42.
16 Dusch N, Weiss C, Ströbel P, *et al*. Factors predicting long-term survival following pancreatic resection for ductal adenocarcinoma of the pancreas: 40 years of experience. *J Gastrointest Surg* 2014;18:674–81.
17 Hidalgo M. Pancreatic cancer. *N Engl J Med* 2010;362:1605–17.
18 Carpelan-Holmström M, Nordling S, Pukkala E, *et al*. Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry. *Gut* 2005;54:385–7.
19 Tran TB, Dua MM, Worhunsky DJ, *et al*. An economic analysis of pancreaticoduodenectomy: should costs drive consumer decisions? *Am J Surg* 2016;211:991–7.

Pancreatic resections are not only safest but also most cost-effective when performed in a high-volume centre: A Finnish Register Study

Reea Ahola MD[1], Juhani Sand [1,2], Johanna Laukkarinen, Ass. Prof.[1, 3]

[1]Dept of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Finland and [2] Päijät-Häme Central Hospital, Medical School, University of Tampere, Finland

Correspondence and reprints:

Johanna Laukkarinen, MD, PhD

Associate professor in surgery

Head, Dept. of Gastroenterology and Alimentary Tract Surgery

Tampere University Hospital

Teiskontie 35, 33521 Tampere, Finland

Tel. (office) +358 3 311 64314

Tel. (cell) + 358 50 358 6556

Email johanna.laukkarinen@fimnet.fi

Fax +358 3 311 64358

Funding

This work was supported by State Research Funding (VTR), Finland; the Sigrid Juselius Foundation, Finland and Toivo Eklund Fund, Finland. They have no involvements in the study design, data collection, data analysis, manuscript preparation or publication decisions.

ABBREVIATIONS

ASA	American Society of Anesthesiologists classification
C-D	Clavien-Dindo classification
HVC	high volume centre
LVC	low volume centre
MVC	medium volume centre
PD	pancreatoduodenectomy
TP	total pancreatectomy

ABSTRACT

Background. It is not known whether the treatment costs of pancreatic surgery can be reduced by centralisation. The aim of this study was to analyse the impact of hospital volume on the short-term prognosis and costs in a nationwide study.

Methods. National registry was searched for Patients undergoing pancreatoduodenectomy (PD) or total pancreatectomy (TP) in Finland between 2012 and 2014. Patient data was recorded up to ninety days postoperatively. Complications were classified according to Clavien-Dindo. The hospitals were categorized by yearly resection rate: high (≥20, HVC), medium (6-19, MVC) and low (≤5, LVC). Costs were calculated according to the 2012 billing list. The costs of different levels of treatments were related to the costs of one post-operative day on a surgical ward.

Results. The study comprised 501 patients. Demographics were similar in the HVC, MVC and LVC groups. Mortality was lower in the HVCs than in MVCs and LVCs at 30 days (0.7% vs. 8.8-12.1%; $p<0.01$) and at 90 days (1.8% vs. 10.4-15.2%; $p<0.01$). Hospital volume and age were significant factors for mortality in multivariate analysis. Median costs among all patients were lower in the HVC group than in the MVC/LVC groups ($p=0.014$), among Clavien-Dindo class III (0.015), among patients over 75 years ($p=0.002$) and among patients who survived over five days ($p=0.010$).

Conclusions. 30- and 90-day mortality is 10 times lower when the patient is operated on in an HVC. The study shows that overall costs of surgical treatment are 0.87-0.89 times lower in HVCs.

INTRODUCTION

Pancreatic surgery is known for its high post-operative morbidity and mortality. A centre performing pancreatic surgery needs to have expertise available 24h/7 to ensure a safe post-operative period. Centralisation of pancreatic surgery to high-volume centres has been reported to improve the short- and long-term prognosis. Postoperative mortality in particular has been reported to be lower in high-volume centres [1-5]. It has been suggested that larger centres have a better capability to recognize post-operative problems before they accumulate and result in the patient's death[6]. However, the effect of centralisation on the costs of treatment has been unclear. Various reports have been published, but variation in the methods and health care structures makes comparison between the reports challenging[7]. In Finland the centralisation of pancreatic surgery has proceeded gradually since the 90s. Pancreatic surgery is performed only in public hospitals. It is not known whether the costs of treatment can also be reduced by centralisation.

The aim of this study was to analyse the effect of hospital operation volume on the number of complications, post-operative mortality and costs of pancreatic resections up to 90 days post-operatively.

PATIENTS AND METHODS

All patients undergoing pancreatic surgery (JLC*; Nordic Classification of Surgical Procedures) between 2012 and 2014 nationwide in Finland were selected from the Finnish Operation and Treatment Register (HILMO) in November 2016 and re-checked in March 2017. PDs (code JLC20, JLC30) and TPs (code JLC40) were included in the study. Children and trauma patients were excluded. The HILMO register records all treatment episodes nationwide in Finland (involving any Finnish hospital). For this study, all treatment episodes of the patients included were selected up to 90 days postoperatively from the HILMO register. Patient files were collected from the associated hospitals according to the treatment episode dates retrieved from the HILMO register. Patient files were examined manually. From the patient files, data on medical history, resected tumour (diagnosis,

TNM, gradus, R-status, size, number of total and positive lymph nodes), complications, procedures performed and the length of hospital stay and stay in intensive care were recorded. Patient data was examined for up to 90 days postoperatively at the operating hospital and also at possible other hospitals. The cut-point of survival was 1 February 2017.

Complications were classified according to the Clavien-Dindo classification[8] (C-D) according to the patient records. Delayed gastric emptying (DGE), pancreatic fistulas (POPF) and postpancreatectomy haemorrhage (PPH) were classified according to the most recent international guidelines, clinically significant being grades B and C[9-11]. The grading was based on the data in the patient records. Data on other possible complications was also retrieved from the patient records. Unspecified infection was defined as a situation were antibiotics were initiated for a CRP reaction without specific target detected (findings in X-ray, CT, cultures, for example).

Cost evaluation was performed according to the 2012 pricelist of Tampere University Hospital and one local health care centre (Pirkkala in southern Finland) to be able to compare the actual cost differences, unaffected by possible billing differences between hospitals. The cost evaluation was the sum of costs of ward days, intensive care days, endoscopies performed, interventional radiology and re-operations as well as ward days in primary health care facilities totalling up to 90 days postoperatively. Because the pricelist was not comprehensive for all procedures, the mean price of the procedures was used. For intensive care and stays on the ward, the mean price of a normal care day and of an extra demanding care day was used because it was not possible to distinguish between these retrospectively. The primary operation costs were not included in the calculations, as this was considered similar across centres.

In the cost analysis, the costs of different levels of treatment were related to the cost of one post-operative day on a surgical ward (DHos=day at a hospital=784 USD) and changed to factors accordingly: factor 1 DHos for a day at any hospital, 5.5 DHos (4,312 USD) for an intensive care day, 1.1 DHos (862 USD) for endoscopies or interventional radiology, 4.0 (3,136 USD) DHos for re-

operations and radiologic angiographic procedures and 0.3 DHos (235 USD) for a day in primary health care.

To analyse the effect of hospital volume on patient data, operating centres were categorized as high (HVC; ≥ 20), medium (MVC; 6-19) and low (LVC; <6) volume pancreatic centres according to the mean yearly number of PDs and TPs performed for any diagnosis during the period 2012-2014.

Data is shown as median (range). Fisher's exact test, Chi-Square test and Kruskall-Wallis test were used to calculate statistical significance. Logistic regression analysis was performed in multivariate analysis. A p-value of ≤0.05 was considered statistically significant.

The study was approved by the Regional Ethics Committee of Pirkanmaa (code R12241).

RESULTS

Operations. The search identified 523 patients who had possibly undergone PD or TP in Finland between 2012 and 2014. After studying patient records, twenty-two patients were excluded. The final study population consisted of 501 patients, of whom 466 were PD and 35 TP patients. Figure 1.

Operating centres. There were two high (≥20 PD or TP operations/year), 5 medium (6-19 PD or TP/year) and 6 low (≤5 PD or TP /year) volume centres. The median numbers of PDs and TPs per year were 47.3 (range 31 -63), 13.7 (range 10.7-16.7) and 1.8 (range 0.3- 3.3) in HVC, MVC and LVC respectively). Of the patients 284 (56.7%) were operated on in HVC, 184 (36.7%) in MVC and 33 (6.6%) in LVC respectively.

Demographic and surgical data. The demographics of the patients were similar in the HVC, MVC and LVC groups. The proportions of PDs (93-94%) and TPs (6-7%) were similar in HVCs, MVCs and LVCs (p=0.915, Pearson Chi-squared test). The majority of patients had a malign disease and the proportions (82, 86, 82%) were similar in HVCs, MVCs and LVCs (p=0.542, Pearson Chi-Squared test). More vascular resections were performed in HVCs (16% vs. 4.0% and 3.0% in MVC and LVC; p<0.001; Pearson Chi-Squared test). Table 1.

Complications. Overall complications classified according to C-D did not differ between volume groups except in mortality (C-D V: 1.1% in HVCs, 8.7% in MVCs and 12% in LVCs; p<0.01, Pearson Chi-squared test). Figure 2. The absolute number of PD-related complications was higher in lower volume centres than in high volume centres, but this did not reach statistical significance; DGE gr B-C (6.6-6.5-15%), POPF gr B-C (5.6-9.2-9.1%) and PPH gr B-C (5.3-6.0-9.1%) in HVC, MVC and LVC respectively. More unspecified infections were present in the MVC group (20% vs. 12% in HVC and 6.1% in LVC, p=0.034, Pearson's Chi-squared test). More leakages in gastro-

enterostomies/enteroenterostomies were present in the MVC group, but the total number was low (5, 2.7%, p=0.013, Pearson Chi-squared test). Table 2.

Postoperative short-term survival. Both 30-day and 90-day mortality were significantly lower in the HVC group: the 30-day mortality rates were 0.7% in the HVC-group vs. 8.8% in the MVC-group and 12% in the LVC-group (p<0.001, Pearson Chi-squared test) and the 90-day mortality rates were 1.8% in the HVC group vs. 10% in the MVC group and 15% in the LVC group (p=0.000; Pearson Chi-squared test). In a logistic regression analysis considering sex, ASA, malignant/benign, age and operation volume, age and operation volume were statistically significant variates in 30- and 90-day mortality rates. The nature (benign/malignant) of the disease was slightly significant in the 90-day mortality analysis (p=0.049), when metastasis surgery was excluded. In a logistic regression analysis performed inside each volume subgroup (HVC, MVC, LVC), a single operating hospital was not a significant factor for 30-day and 90-day mortality (considering sex, ASA, malignant/benign, age and hospital). No deaths occurred during the first 20 days postoperatively in HVCs. Among critically ill patients (C-D 4 and 5) signs of failure to rescue were apparent as more patients were lost in the lower volume groups than in the HVC group (p<0.001 for MVC vs. HVC and p=0.009 for LVC vs. HVC, Pearson's Chi-squared test). Table 3 and Figures 3a and 3b.

When patients over 75 years old were analysed, there were more critical complications (C-D 4-5) in the MVC group than in the HVC group (9.3% in HVCs and 34% in MVCs; p=0.003, Pearson's Chi squared test) and more patients were lost (0% in HVCs vs. 20% in MVCs; p=0.000, Pearson's Chi squared test). The LVC group comprised only four patients over 75 years old and was not analysed in this subset.

Use of health care resources for 90 days postoperatively. The median numbers of days spent in hospitals or in primary health care centres were 14, 16 and 15 days in the HVC, MVC and LVC groups respectively (range 1-90 days) without differences between the operating hospital volumes.

Comparing different C-D groups there was a trend towards lower number of days spent in hospital in the HVC group. The difference was significant in C-D class 3 (p=0.018, Kruskall-Wallis). The number of reoperations, endoscopies or radiological drainage procedures was the same in the different volume groups. Radiological procedures for vascular complications were only performed in high volume centres. From these patients 6/7 had a haemorrhage complication, 1/7 died and none of them required re-operation. Table 4.

Cost-analysis. Median costs were at lowest in the HVC group (14 (10,976 USD) DHos vs. 16 (12,544 USD) DHos in MVC and 16 DHos in LVC; p=0.019, Kruskall-Wallis) both analysing the data as a whole and considering only patients who survived longer than five days (p=0.010, Kruskall-Wallis). The median costs in C-D grades 0, I, II and IV seemed higher in the LVC group, but the differences were not significant between the volume groups (p=0.139, p=0.129, p=0.353, p=0.761 respectively, Kruskall-Wallis). However, the median costs patients with grade III complications were the lowest in the HVC group (p=0.015, Kruskall-Wallis). Table 5.

The difference was also significant when median costs per survival were calculated (up to 2 years) among cancer patients in C-D classes 0-II (7.0/8.5/10 Dhos in HVCs/MVCs/LVCs; p=0.002, Kruskall-Wallis). Among C-D classes III-IV differences were insignificant (20/28/26 Dhos in HVCs/MVCs/LVCs; p=0.535, Kruskall-Wallis). Among patients over 75 years, median costs were lowest in the HVC group (14 DHos in the HVC group and 25 DHos in the MVC group, p=0.002, Kruskall-Wallis). There were only four patients over 75 years in the LVC group so the LVC group could not been analysed in this subset.

Factors associated with costs in different cost quartiles were analysed with logistic regression analysis considering sex, age, operation volume and ASA class. In the highest cost quartile (>24 DHos) only ASA-class was a significant factor. Significant factors associated with higher than median costs

(>15 DHos) comprised operation volume and ASA class. The only factor associated with costs in the lowest cost quartile (<11 DHos) was ASA class. Table 6.

DISCUSSION

Low post-operative mortality has been widely presented as an advantage after pancreas resection in a HVC[1,3,5,12,13]. This has been related to the failure to rescue concept as well as hospital characteristics[6,14]. This nation-wide study aimed to assess the effect of operation volume on complications, mortality and cost accumulation of pancreas resections in Finland. In our study 30-day and 90-day mortality were heavily dependent on operation volume. Although the distribution of other complications showed no significant differences, overall cost accumulation was decidedly lowest in the HVC group, resulting in safe and cost-effective management of patients undergoing pancreatic surgery.

Pancreatic surgery has traditionally been deemed high-risk surgery. Even recently 90 –day post-operative mortality rates of 8-10% have been reported [12,15]. Our study showed 90-day mortality of only 1.8% in the HVC group. This is extremely low, but is close to the internationally reported rate of 0-4% in HVCs and in accordance with our previous results from the period 2002-2008[1,3,16]. It is interesting that in the HVC group no deaths occurred during the first 20 days after operation, although in lower volume centres patients were lost from the first day onwards. As the complication distribution did not differ, this suggests more successful treatment in the HVC group, and failure to rescue the patients from complications in the MVC and LVC groups. The shortage of means in the surgical, anaesthesiological and interventional radiological treatment of complications may present as increased mortality shortly after the operation.

The concept of failure to rescue has been set as a new benchmark of surgical quality. In our study failure to rescue was defined as death of critically ill patients (C-D IV-V). Analysis of the volume groups showed that not only was mortality lowest in the HVC group, but also that more critically ill patients were saved. Operation volume was also linked to failure to rescue patterns in a study by Ghaferi et al[6]. In that study patient death was 3.2 times more frequent after a major complication in lower volume centres. In addition, the benefit seemed to be the greater the older the patients are[4],

which was also confirmed in our study. A recent study by van Rijssen et al.[16] confirmed an association between failure to rescue and mortality differences.

The background of failure to rescue is complex. Sheetz et al.[14] reported that hospital size, occupancy, intensive care availability, teaching status and technology offer a survival advantage for patients undergoing major surgery. The high-volume group in our study comprised the two biggest teaching hospitals in Finland, which treat most of the critically ill patients in Finland overall. This may give a benefit of experience, which contributes to low post-operative mortality. Wakeam et al.[17] studied secondary complications after surgery and observed wide hospital-level variation in their analysis. It emerged that it is crucial to understand the effect of both structures; the effect of operation volume in general, and the circumstances in individual hospitals. Our study found no significant variation within the volume groups, and it is noteworthy that pancreatic resections were performed in both university and smaller central hospitals.

Although there was a clear survival advantage in the HVC group, the C-D distribution in classes 0-IV did not differ significantly. Closer inspection of specific complications revealed more undefined infections in the MVC group. The antibiotic usage may be a reflection of different approaches to post-operative care in hospitals or a reflection of circumstances where availability of specialized experience varies across weekdays and working hours.

A recent review of improvements in pancreatic surgery emphasized the availability of multimodal treatment strategies and high operation volumes[18]. Radiological drainage, re-operations and other interventional radiology are crucial in the modern treatment of complications after pancreatic resections. In Finland the availability of interventional radiology is at its best in university hospitals. Despite the supposed availability of vascular procedures, the use of these seemed to be more common in the HVC group than in MVC group.

Although it has been suggested that sufficient volume would result in lower costs in pancreatic surgery[19], the relationship has not been simple to describe[20]. Nathan et al. stated, however, that the better prognosis in HVCs has not been reached with higher costs. In our study the median costs were

lowest in the HVC group in all data and in the subgroups. When the costs were adjusted for survival among cancer patients, the costs were interestingly the lowest in C-D grades 0-II in the HVC group. This can be explained by the refined post-operative protocols in HVCs and, of course, potentially longer survival in the HVCs. The volume advantage was not so very obvious in the multivariate analysis, which may have suffered from low statistical power. However, costs lower than the median cost were associated with high operation volume. ASA class was the only factor unequivocally associated with costs in all-cost quadrilles.

The actual rate of yearly pancreatic resection volume is still debatable. The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland published Guidance on minimum surgeon volumes in 2010[21] and suggested that the yearly volume of pancreatic resections should be 80-100 resections per year and 12-16 per surgeon per year. Studies concerning surgical performance have also suggested that a sufficient volume per surgeon is related to better outcomes[22,23]. Van der Geest et al.[24] demonstrated in a Dutch study that mortality is lower when the yearly number of PDs is over 40. In our study the hospital volumes ranged from <1 per year to over 60 procedures, so the cut-offs of 20 for high-volume and 6 for low volume were appropriate for our data.

The strength of this study is that it succeeded in covering data on patients' treatment paths up to 90 days postoperatively and all procedures and ward days are included in the cost analysis. In addition, the study covers all PDs and TPs performed nationwide in Finland between 2012 and 2014, affording a good insight into national surgical quality after pancreatic resections. The Finnish registries are considered trustworthy because information on treatment episodes is sent routinely to the national registries at the end of an episode, but the process may naturally be affected by human error. Even though the retrospective nature of our study inevitably leaves some uncertainty in the treatment processes, no patient had to be excluded from the study because of unavailable or missing patient records. The relative costs used in this study are based on the billing list of one hospital, which facilitated the comparison between different volume groups. However, the effect of fixed costs of a hospital was not evaluated in this study. Whether the lower costs achieved for pancreas resections in

HVCs would also result in lower overall hospital costs is also debatable: the possible savings might just balance the budget among other medical specialities.

In conclusion, short-term prognosis after pancreatic surgery is better when the operation is performed in an HVC. Experience refers not only to surgical experience, but also to the ability of a hospital to avoid failure to rescue. The lower mortality rates are explained by the beneficial rescue protocols after complications in the HVC group. Cost analysis showed significantly lower median costs in the HVC group. Thus pancreatic resections are not only the safest but also the most cost-effective when performed in a high volume centre, thus favouring the centralisation of this demanding type of surgery. We consider the cost-evaluation generalizable especially to other public health care systems.

ACKNOWLEDGEMENTS

We thank statistician Mika Helminen (University of Tampere) for comments on the statistical analysis, research assistant Satu Järvinen (Tampere University Hospital) for archive management and Virginia Mattila for proof reading.

REFERENCES

1. Ahola R, Siiki A, Vasama K, Vornanen M, Sand J, Laukkarinen J. Effect of centralization on long-term survival after resection of pancreatic ductal adenocarcinoma. Br J Surg 2017;104:1532-1538.

2. Ahola R, Siiki A, Vasama K, Vornanen M, Sand J, Laukkarinen J. Patients with resected, histologically re-confirmed pancreatic ductal adenocarcinoma (PDAC) can achieve long-term survival despite T3 tumour or nodal involvement. the finnish register study 2000-2013. Pancreatology. 2017;17:822-826.

3. Gooiker GA, Lemmens VE, Besselink MG, Busch OR, Bonsing BA, Molenaar IQ et al. Impact of centralization of pancreatic cancer surgery on resection rates and survival. Br J Surg 2014;101:1000-1005.

4. van der Geest, LG, Besselink MG, Busch OR, de Hingh IH, van Eijck CH, Dejong CH et al. Elderly patients strongly benefit from centralization of pancreatic cancer surgery: A population-based study. Ann Surg Oncol 2016;23:2002.

5. Ansari D, Williamsson C, Tingstedt B, Andersson B, Lindell G, Andersson R. Pancreaticoduodenectomy-the transition from a low- to a high-volume center. Scand J Gastroenterol 2014;49:481-484.

6. Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery. Med Care 2011;49:1076-1081.

7. Ke KM, Hollingworth W, Ness AR. The costs of centralisation: A systematic review of the economic impact of the centralisation of cancer services. Eur J Cancer Care 2012;21:158-168.

8. Dindo D, Demartines N and Clavien PA, 2004. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of Surgery 2004; 240: 205-213.

9. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Allen P et al. The 2016 update of the international study group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery 2017;161:584-591.

10. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR et al. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the international study group of pancreatic surgery (ISGPS). Surgery 2007;142:761-768.

11. Wente MN, Veit JA, Bassi C, Dervenes C, Fingerhut A, Gouma DJ et al. Postpancreatectomy hemorrhage (PPH): An international study group of pancreatic surgery (ISGPS) definition. Surgery 2007;142:20-25.

12. Farges O, Bendersky N, Truant S, Delpero JR, Pruvot FR, Sauvanet A. The theory and practice of pancreatic surgery in France. Ann Surg. 2017;266:797-804.

13. Reames BN, Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and operative mortality in the modern era. Ann Surg 2014;260:244-251.

14. Sheetz KH, Dimick JB, Ghaferi AA. Impact of hospital characteristics on failure to rescue following major surgery. Ann Surg 2016;263:692-697.

15. Nimptsch U, Krautz C, Weber GF, Mansky T, Grutzmann R. Nationwide in-hospital mortality following pancreatic surgery in Germany is higher than anticipated. Ann Surg 2016;264:1082-1090.

16.van Rijssen LB, Zwart MJ, van Dieren S, de Rooij T, Bonsing BA, Bosscha K, van Dam RM, van Eijck CH, Gerhards MF, Gerritsen JJ, van der Harst E, de Hingh IH, de Jong KP, Kazemier G, Klaase J, van der Kolk BM, van Laarhoven CJ, Luyer MD, Molenaar IQ, Patijn GA, Rupert CG, Scheepers JJ, van der Schelling GP, Vahrmeijer AL, Busch ORC, van Santvoort HC, Groot Koerkamp B, Besselink MG; Dutch Pancreatic Cancer Group. Variation in hospital mortality after pancreatoduodenectomy is related to failure to rescue rather than major complications: a nationwide audit. HPB 2018;20:759-767.

17. Wakeam E, Hyder JA, Lipsitz SR, Cohen ME, Orgill DP, Zinner MJ et al. Hospital-level variation in secondary complications after surgery. Ann Surg 2016;263:493-501.

18. Hartwig W, Werner J, Jager D, Debus J, Buchler MW. Improvement of surgical results for pancreatic cancer. Lancet Oncol. 2013;14:e476-85.

19. Tran TB, Dua MM, Worhunsky DJ, Poultsides GA, Norton JA, Visser BC. An economic analysis of pancreaticoduodenectomy: Should costs drive consumer decisions? Am J Surg. 2016;211:991-997.

20. Nathan H, Atoria CL, Bach PB, Elkin EB. Hospital volume, complications, and cost of cancer surgery in the elderly. J Clin Oncol 2015;33:107-114.

21. Clinical Service Committee AUGIS. Guidance on minimum surgeon volumes 2010. . ;http://www.augis.org/wp-content/uploads/2014/ 05/AUGIS_recommendations_on_Minimum,Accessed November 27, 2017.

22. Mamidanna R, Ni Z, Anderson O, Spiegelhalter D, Bottle A, Aylin P et al. Surgeon volume and cancer esophagectomy, gastrectomy, and pancreatectomy: A population-based study in England. Ann Surg 2016;263:727-732.

23. Maruthappu M, Gilbert BJ, El-Harasis MA, Nagendran M, McCulloch P, Duclor A et al. The influence of volume and experience on individual surgical performance: A systematic review. Ann Surg 2015;261:642-647.

24. van der Geest LG, van Rijssen LB, Molenaar IQ, de Hich IH, Koerkamp BG, Busch OR et al. Volume-outcome relationships in pancreatoduodenectomy for cancer. HPB (Oxford) 2016;18:317-324.

Table 1.Demographics of the patients did not differ between the volume groups.

	HVC	**MVC**	**LVC**	p
Total,No	284	184	33	
Median age, years (range)	67 (22-86)	67 (30-85)	64 (47-85)	0.475*
Number of patients over 75 year, (%)	54 (19)	41 (22)	4 (12)	0.358†
M/F (%)	56/44	52/48	49/51	0.295†
ASA				0.725†
ASA 1	97 (34)	54 (30)	12 (36)	
ASA 2	85 (30)	69 (38)	12 (36)	
ASA 3-4	102 (36)	60 (33)	9 (27)	
ASA (patients over 75 years)				0.890†
Number of pancreatoduodenectomies (%)	263 (93)	172 (94)	31 (94)	0.678†
Number of vascular resections, (%)	46 (16)	7 (3.8)	1 (3.0)	0.000†
Number of patients operated after neoadjuvant therapy, (%)	19 (6,7)	0	0	0.001†
Number of resections with a malign diagnosis, (%)	233 (82)	158 (86)	27 (82)	0.542†
*HVC= high volume centre, MVC= medium volume centre, LVC= low volume centre, *Pearson's Chi squared test, †Kruskall-Wallis*				

Table 2. Distribution of complications. There were more unspesific infection complications in MVC.

Complication,no (%)	**HVC (n=284)**	**MVC (n=184)**	**LVC (n=33)**	p*
Leakages				-
Pancreato-jejunostomy, gradus B-C	16 (5.6)	17 (9.2)	3 (9.1)	0.306
Hepatico-jejunostomy, Clavien-Dindo III-V	11 (3.9)	8 (4.3)	1	0.927
Gastro/enteroenterostomy, Clavien-Dindo III-V	0	5 (2.7)	0	0.013
Hemorrhage	15 (5.3)	11 (6.0)	3 (9.1)	0.668
Delayed gastric emptying , gradus B-C	17 (6.6)	12 (6.5)	5 (15)	0.140
Infectious complications				
Infection NAS†	35 (12)	36 (19)	2 (6.1)	0.034
Pneumonia	26 (9.2)	19 (10.3)	3 (9.1)	0.911
Collection or abscess	23 (8.1)	9 (4.9)	0	0.115
Bacteremia or candidemia	8 (2.8)	10 (5.4)	0	0.172
Thromboembolic complications	10 (3.5)	9 (4.9)	1 (3.0)	0.729
Wound problems				
Rupture of fascia	0	4	0	-
Wound infection	9 (3.2)	11 (6.0)	1 (3.0)	0.315
Resuscitation	0	2	0	-

** Pearson's Chi squared, †Infection NAS: use of antiobiotics, but aetiology not unrevealed*
HVC=high volume centre, MVC=medium volume centre, LVC= low volume centre

Table 3. Logistic regression analysis of short-term mortality. Both operation volume and age of the patient were risk factors for poor prognosis.

Variate		**30-day mortality, p**	**OR (95% COI)**	**90-day mortality, p**	**OR (95% COI)**
Sex	male	reference		reference	
	female	0.235	1.762 (0.692-1.098)	0.775	1.124 (0.505-2.498)
Age		0.010	1.080 (1.019-1.144)	0.041	1.052 (1.002-1.104)
ASA		0.608		0.198	
	ASA1	reference		reference	
	ASA 2	0.742	0.810 (0.231-2.837)	0.686	1.273 (0.395-4.102)
	ASA 3-4	0.594	1.395 (0.410-4.742)	0.120	2.447 (0.791-7.567)
Operation volume		0.001		0.000	
	HVC	reference		reference	
	MVC	0.001	14.329 (3.180-64.567)	0.000	7.028 (2.508-19.693)
	LVC	0.001	20.954 (3.527-124.486)	0.000	11.250 (2.941-43.043)
Benign/Malignant	benign	reference		reference	
	malignant	0.074	0.378 (0.130-1.098)	0.101	0.449 (0.173-1.168)

HVC= high volume centre, MVC=medium volume centre, LVH=low volume centre, OR= odds ratio, COI=confidence interval

Table 4. Use of different resources did not show statistical significance.

Resource	**HVC**	**MVC**	**LVC**	**p**
Number of patients	284	184	33	
Median number of days spent in different health care units	14 (6-90)	15 (1-90)	16 (2-90)	0.213*
Clavien-Dindo 0	11.0 (6-36)	13.0 (7-37)	15 (6-49)	0.173*
Clavien-Dindo 1	12.0 (7-80)	13.0 (9-27)	20.5 (13-28)	0.264*
Clavien-Dindo 2	15 (7-61)	17 (7-72)	18.5 (9-36)	0.686*
Clavien-Dindo 3	20.0 (8-90)	29.0 (10-90)	43.0 (42-48)	0.018*
Clavien-Dindo 4	34.0 (11-90)	35.5 (13-90)	31.0 (29-33)	0.981*
Median number of days in operating hospital (range)	14.0 (6-90)	16.0 (1-90)	15.0 (2-49)	0.213*
Median number of days in intensive care unit (range)	5.5 (0-31)	4.0 (0-37)	2.5 (1-12)	0.262*
Median number of days in other hospitals (range)	0 (0-56)	0 (0-45)	0 (0-33)	0.213*
Median number of days in primary health care facilities (range)	0 (0-63)	0 (0-48)	0 (0-10)	0.240*
Number of patients needing additional operations (%)	21.0 (7.4)	25.0 (14)	3.0 (9.4)	0.088†
Number of patients needing endoscopies	16.0 (5.6)	10.0 (5.4)	1.0 (3.0)	0.821†
Number of patients in radiological drainage	21 (7.4)	14 (7.6)	2 (6.1)	0.952†

*HVC=high volume centre, MVC=medium volume centre, LVC=low volume centre,*Kruskall-Wallis, †Pearson Chi-squared test*

Table 5. Median costs (DHos) after the operation were the lowest in the HVC-group among all patients and in complication grade III.

		HVC	MVC	LVC	p*
Total, DHos (range)		14 (6.0-203)	16 (5.5-285)	16 (6-92)	0.019
Complication grade					
	0	10 (6.0-24)	13 (7.0-37)	13 (6.0-49)	0.158
	1	11 (7.0-59)	13 (9.0-27)	21 (13-28)	0.129
	2	15 (7.0-43)	17 (7.0-57)	17.8 (9.0-33)	0.498
	3	21 (9.1-89)	30 (11-100)	46 (40-51)	0.015
	4	57 (19-203)	66.6 (17-285)	80.6 (6.0-92)	0.777
**Kruskall-Wallis, HVC=high volume centre, MVC=median volume centre, LVC=low volume centre*					

Table 6. Logistic regression analysis of factors associated with costs. ASA class was associated with costs in the lowest quadrille (< 11DHos). In addition to ASA class, operation volume was associated with costs higher than median level (15 DHos). ASA class was the only associated factor in the highest cost quadrille (>24 DHos).

		Costs <25%		**Costs >50%**		**Costs >75%**	
Variable		p	OR (95% COI)	p	OR (95% COI)	p	OR (95% COI)
Sex	male	reference		reference		reference	
	female	0.603	0.893 (0.584-1.367)	0.209	0.793 (0.551-1.139)	0.143	0.728 (0.476-1.113)
Age		0.990	1.000 (0.980-1.021)	0.528	0.994 (0.977-1.012)	0.813	0.997 (0.977-1.019)
ASA		0.000		0.004		0.015	
	ASA1	reference		reference		reference	
	ASA 2	0.027	0.574 (0.346-0.937)	0.203	1.344 (0.852-2.120)	0.172	1.475 (0.844-2.575)
	ASA 3-4	0.000	0.316 (0.180-0.553)	0.001	2.178 (1.365-3.476)	0.004	2.242 (1.290-3.897)
Operation volume		0.164		0.019		0.135	
	HVC	reference		reference		reference	
	MVC	0.080	0.6561 (0.416-1.050)	0.007	1.690 (1.153-2.477)	0.081	1.479 (0.953-2.295)
	LVC	0.712	1.164 (0.520-2.605)	0.168	1.677 (0.804-3.499)	0.169	1.765 (0.785-3.969)

HVC=high volume centre, MVC=median volume centre, LVC=low volume centre, OR=odds ratio, COI=confidence interval

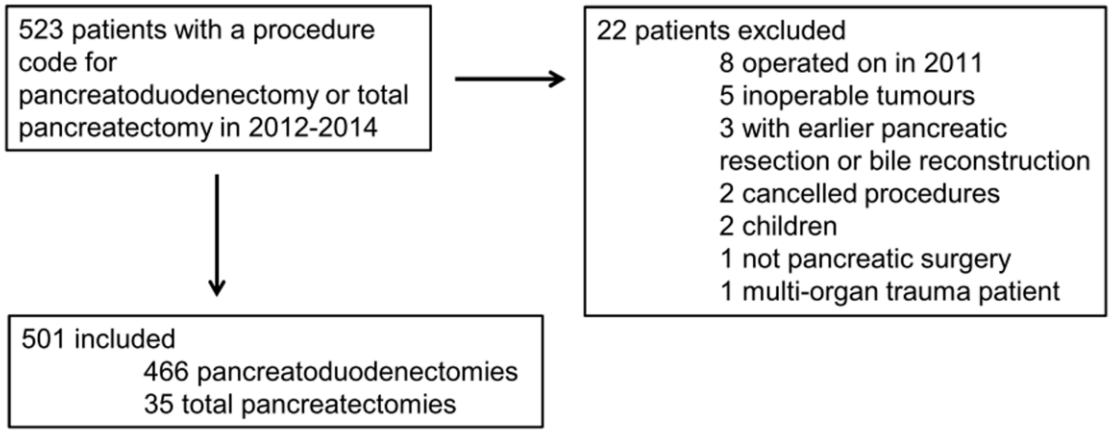


Figure 1. Flowchart. The Finnish Operation and Treatment Register (HILMO) was searched for procedures codes of PD (JLC20/30) or TP (JLC40). Twenty-two patients were excluded after studying patient archives. Finally, the study comprised 501 patients.

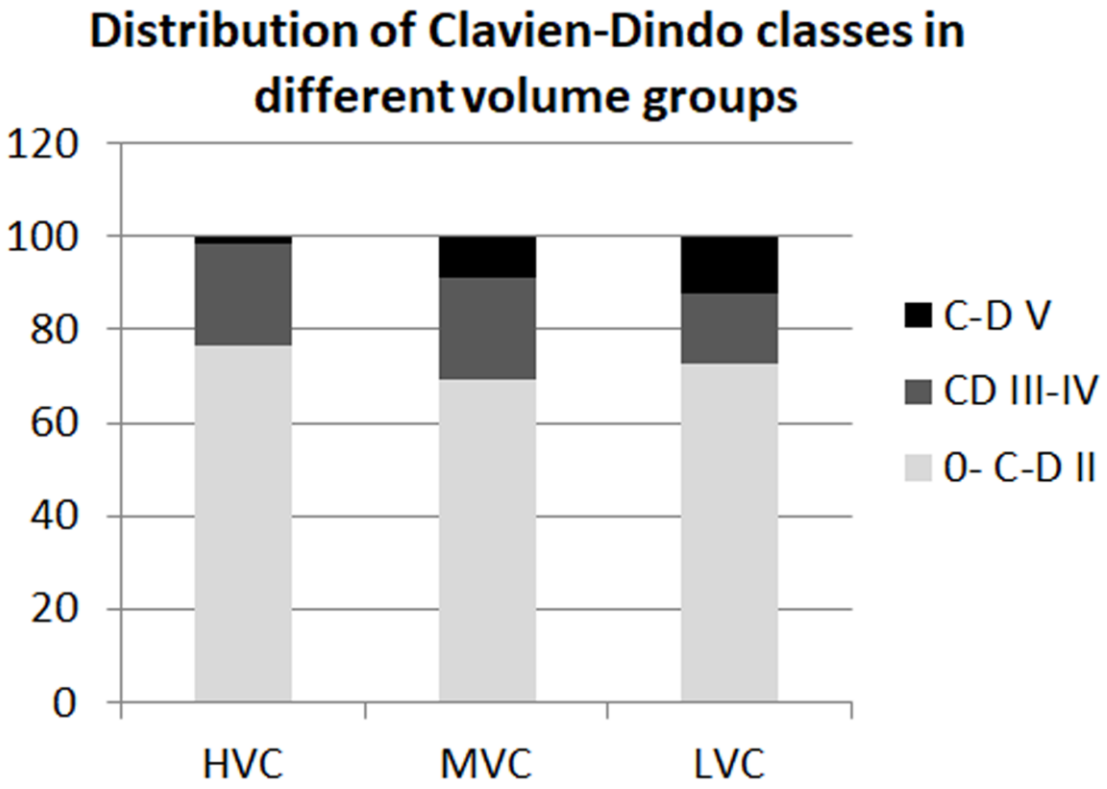


Figure 2. Complication were cathegorized according to Clavien-Dindo- classification. Less patients were lost in the high-volume centre group. ($p<0.001$, Pearson Chi-squared test)

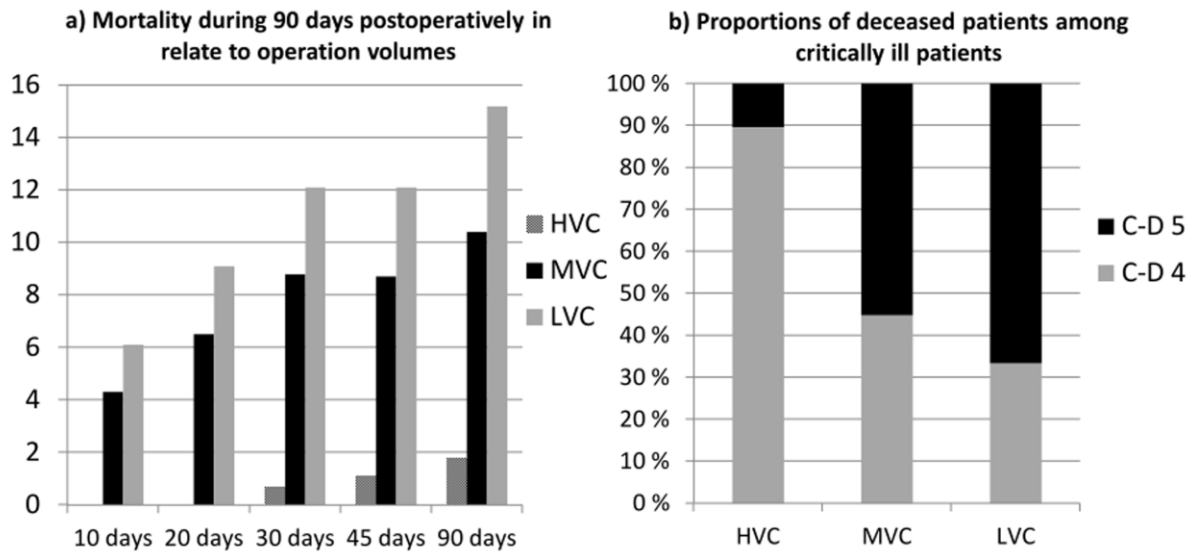


Figure 3a. Mortality rates were at lowest in the HVC group and patients were lost later ($p<0.001$ for 30-day mortality and $p<0.001$ for 90-day mortality; Pearson Chi-squared- test)

Figure 3b. Among critically ill patients death occurred more often in lower volume centre groups ($p=0.000$ for MVC vs. HVC and $p=0.009$ for LVC vs. HVC, Pearson's Chi-squared test).

Figure 3. Median costs increased as the Clavien-Dindo grade increased. There was significant difference in grade III (p=0.015, Kruskall-Wallis) in favour of the HVC-group. *Costs were approximated to the cost of one day at surgical ward; DHos= costs of a day at a hospital. HVC=high-volume centre, MVC=medium-volume centre, LVC= low-volume centre