UiT The Arctic University of Norway

Faculty of Health Sciences

Institute of Clinical Medicine

Wuthering heights

Outcomes from pancreatic surgery and trends in treatment of pancreatic ductal adenocarcinoma in Norway in a post-centralization era

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Linn Såve Nymo

A dissertation for the degree of Philosophiae Doctor - October 2021

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ACKNOWLEDGEMENTS

To do this PhD was from the sparse beginning in 2017 certainly more an outside demand from middle-aged men in senior positions than an internal desire on my own behalf. “Close your eyes and think of England, dear”, said Kim. Touching the finish line some four years later I have no choice but to admit that there was a core of truth in their promises of the reward of scientifical self-development, if not eternal glory. More important; some of these abovementioned middle-aged men I now proudly regard as my friends.

Dear Kristoffer, my scientifical druid; I am in your debt for the way you have introduced me to the sphere of academical surgery. Your enthusiasm is propulsive and has been necessary when I at times have been overwhelmed. To me you are a patient creature. I cherish our discussions covering life’s more essential topics ranging from the Oxford comma and passages from former century literature to the pitfalls of scientific methodology. Dear Stig, my spiritual druid, you are in more than one way the natural born leader of our herd. Thank you for providing me with some sense of a higher horizon in our work life domestics and for allowing me to escape from the daily duties to do this PhD. To my precious surgical druid and brother in arms, Kim, my eternal gratitude for the hours you have put in attempting to hand down your surgical capabilities to me, and even more for all the laughs. In memory of Jørn Kjæve, the one true rock-and-roll star of arctic surgery, and to all junior and senior colleagues in our department; Together towards the abyss!

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Linn Såve Nymo, Tromsø, June 2021

ORIGINAL PUBLICATIONS

Paper I

Nymo LS, Søreide K, Kleive D, Olsen F, Lassen K.

The effect of centralization on short-term outcomes of pancreatoduodenectomy in a universal health care system

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Paper II

Nymo LS, Kleive D, Waardal K, Bringeland EA, Søreide JA, Mortensen KE, Søreide K, Lassen K

Centralizing a national pancreatoduodenectomy service: Striking the right balance

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Paper III

Nymo LS, Myklebust T, Hamre H, Møller B, Lassen K

Progress for the few: Trends in treatment and survival after pancreatic ductal adenocarcinoma in a national 15-year cohort

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ABSTRACT

Aim: The main aim of this thesis was to explore the contemporary outcomes of pancreatic surgery and treatment of pancreatic ductal adenocarcinoma in Norway seen in light of the centralization process and the volume-outcome relationship.

Methods: We analysed three complete national patient cohorts using prospectively gathered data from national medical quality registries. The inclusion criteria were either a having a pancreatoduodenectomy (Paper I and II) or being diagnosed with pancreatic ductal adenocarcinoma (Paper III). The main studied outcomes were short-term morbidity and mortality, and for paper III provision of tumour-directed treatment and survival.

Results: In paper I we found that the national in-hospital mortality and 90-day mortality after pancreatoduodenectomy were 2% and 4%, respectively, and 14% of patients had a relaparotomy within 30 days. High age, male gender and relaparotomy were independent predictors of 90-day mortality, whereas Regional Health Authority where treated was not. In paper II we showed that patients who had a pancreatoduodenectomy at the medium/low-volume units had similar short-term outcomes to patients treated at the sole high-volume unit (>40 PDs a year). For patients diagnosed with pancreatic ductal adenocarcinoma between 2004-2018 (paper III), resection rates ($p<0.001$) and use of perioperative chemotherapy ($p<0.001$) increased over time, and survival after resection improved with a HR (95% CI) for death of 0.65 (0.57-0.76) between late and early study period. For non-resected patients, provision of palliative chemotherapy increased over time ($p<0.001$). Still, four in ten patients did not receive any tumour-directed treatment.

Conclusions: The postoperative outcomes after pancreatoduodenectomy in Norway are beneficial and the current level of centralization of surgery seems just. Although more patients with pancreatic ductal adenocarcinoma currently reach resection and the survival prospects for this subgroup are slightly improving, no sizeable improvement was seen for this patient group when viewed as a whole.

ABBREVIATIONS

PD	Pancreatoduodenectomy (Whipple procedure)
DP	Distal pancreatectomy
PDAC	Pancreatic ductal adenocarcinoma
POPF	Postoperative pancreatic fistula
PPH	Post-pancreatectomy haemorrhage
NPR	Norwegian Patient Registry
NoRGast	Norwegian Registry for Gastrointestinal and HPB surgery
CRN	Cancer Registry of Norway
FTR	Failure-to-rescue
ISGPS	International Study Group of Pancreatic Surgery
OS	Overall survival
ICU	Intensive care unit
MVR	Multi-visceral resection
VR	Vascular resection

1 INTRODUCTION

1.1 A century of pancreatic surgery and a century of despair

Already about 300 years B.C. a Greek anatomist named Eudemos stated on the pancreas: "From this gland a fluid similar to saliva runs into the intestine, intended for the improvement of digestion". The more renowned anatomist and surgeon for the roman gladiators, Galen (129 A.D. to 216 A.D.) some four hundred years later disregarded the pancreas as merely a "fatty cushion for the protection of the mesenteric vessels". Consequently, the organ did not receive attention from the medieval era anatomists and physiologists, and this misperception stood rather undisputed up until the 17th century. It was not until its endocrine and exocrine secretory functions were (re)discovered and further depicted that the pancreas became subject of much attention from physicians and surgeons, and recognized as a potential seat of disease. (1)

The close and complex anatomical relations between the pancreas and its neighbouring organs and vessels probably did not make it a tempting goal of major resections in the early eras of abdominal surgery. Still, the two-stage and later one-stage pancreatoduodenectomy was developed already early in 20th century by courageous surgical pioneers like Codivilla, Kausch and Whipple. (1-3) Both morbidity and perioperative mortality rates were initially discouraging, and one can only suspect some publication bias from early attempts. Nevertheless, perioperative survival was obtained for some patients who later died from cancer recurrence. When reading these early reports a century of years, but light-years in terms of medical knowledge and surgical progress later, one cannot help but conclude that nothing much has really changed. The battles accompanying pancreatic resections are still the same. Anastomoses to the pancreas, however sophisticatedly fashioned, still tend to leak. Even if all else is well, the postoperative delayed emptying of the stomach remains a common complaint. And, although the perioperative mortality has declined tremendously, the prospects of long-term survival from resected pancreatic ductal adenocarcinoma remain gloomy.

The present thesis will explore key elements pertaining to safety and quality of pancreatic surgery in a modern, high resource health care system in a country with a geography and demography seemingly unsuited for centralization of health care services.

1.2 Anatomy of the pancreas and its adjacent organs and vessels

The pancreatic gland is from an embryological point of view considered a “pseudo-retroperitoneal” organ. It is located behind the free abdominal cavity, but in front of the true retroperitoneal space. It is covered ventrally by the stomach, the transverse colon and the gastrocolic ligament. The head is attached to and covered laterally by the duodenum, and the tail extends to the hilum of the spleen. The head and body rests dorsally on the vena cava inferior and abdominal aorta, and the superior mesenteric artery and superior mesenteric vein, splenic vein and portal vein all run in close proximity. These above-mentioned organs and vessels must be either carefully mobilized, exposed or resected when obtaining surgical access to the pancreas.

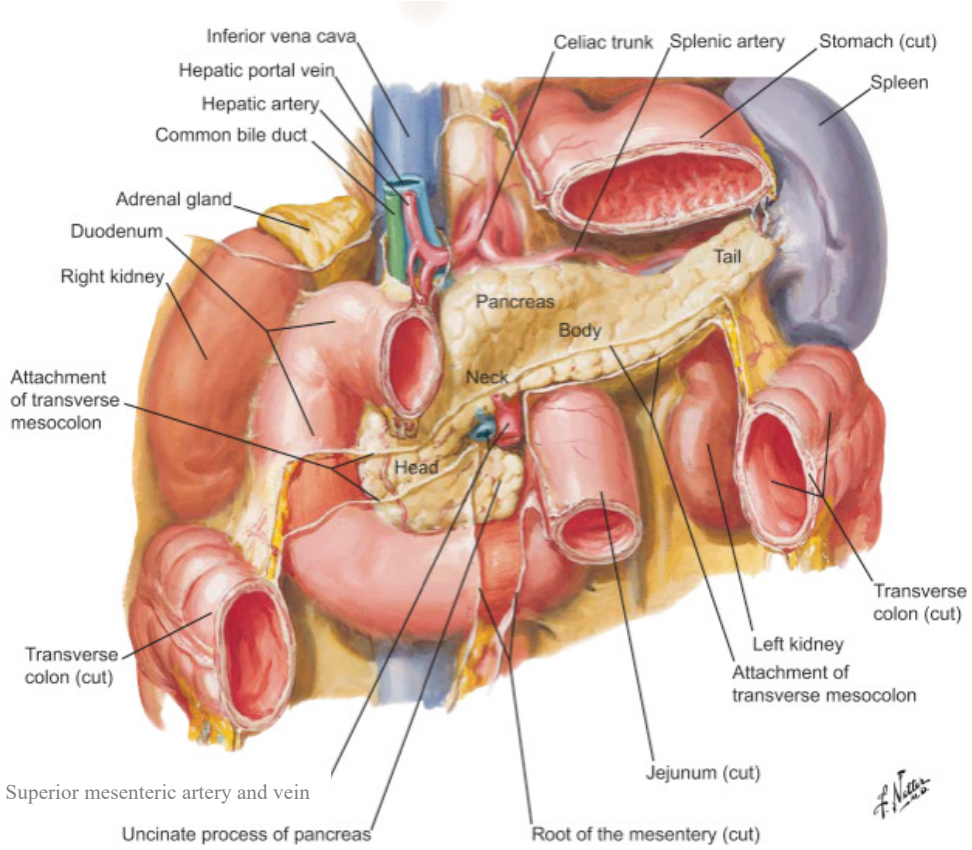


Figure 1: Anatomy of the pancreas and its adjacent organs and vessels. (From www.netterimages.com)

Surgical resection of the pancreas is largely dominated by two entities: Resection of the pancreatic head and neck (pancreatoduodenectomy, aka Whipple procedure) constituting about 70% of procedures, and resection of pancreatic body and tail (distal or subtotal pancreatectomy) which represents about 20-25%. In addition, but in a far lower scale, total

pancreatectomies (or total pancreatoduodenectomies), central pancreatectomies and enucleations are also performed.

1.2.1 Pancreatoduodenectomy (Whipple procedure)

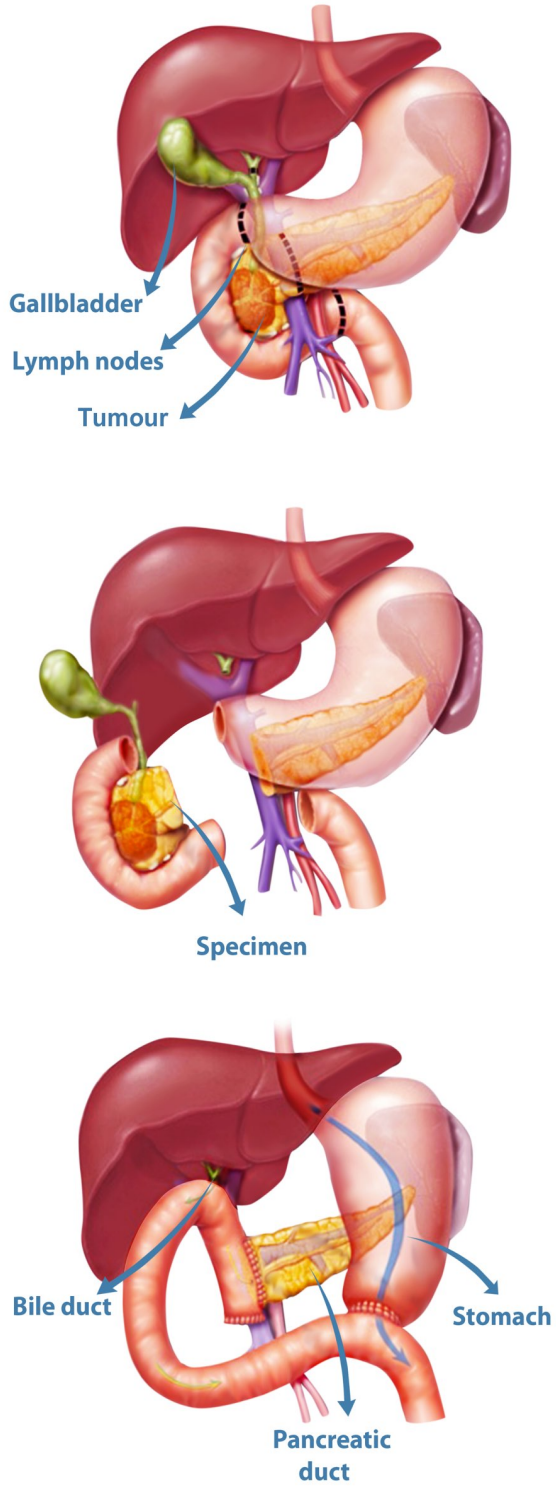


Figure 2: Pancreatoduodenectomy, classic Whipple procedure (From www.thesurgeonscollective.com.au)

In a classic Whipple procedure (see figure 2), the pancreatic head and neck are removed together with the duodenum, the common bile duct (ductus choledochus) and the most distal part of the stomach. The reconstruction is most commonly comprised of three anastomoses, a pancreatico-jejunostomy, a hepatico-jejunostomy and a gastro-jejunostomy. Variants of the reconstruction exist, including the pylorus-preserving procedure where the gastro-jejunostomy is replaced by a duodeno-jejunostomy, and the Roux-en-Y variant where the end-to-side gastro-jejunostomy is replaced by an end-to-end gastrojejunostomy and a distal small bowel anastomosis.

In all forms, a pancreatoduodenectomy is considered a technically challenging procedure. Mini-invasive access pancreatoduodenectomy, either by standard laparoscopy or robot-assisted, is increasingly reported. So far, studies have failed to prove superior outcomes compared to open access surgery besides a slightly shorter length-of-stay. (4) A recent national Dutch RCT set out to compare short-term outcomes after mini-invasive and open pancreatoduodenectomy but was pre-emptively haltered due to higher mortality in the mini-invasive access group. (5) As with all other minimally invasive

procedures, we will probably see further implementation despite lack of randomized data to support it.

1.2.2 Distal pancreatectomy

In a distal (or subtotal) pancreatectomy, the tail (and body) of the pancreas is removed (see figure 3). The cut-end of the pancreatic gland and duct (head and neck) is left closed, usually by surgical staplers or sutures. No anastomosis is fashioned. Depending on which type of neoplasia that is suspected, a lymph node toilette and splenectomy may be warranted. A distal pancreatectomy is regarded as a far less complicated procedure than a pancreatoduodenectomy, and mini-invasive techniques has gained worldwide acceptance, partly also for pancreatic adenocarcinoma. Beneficial short-term outcomes are documented (6-8), but studies on long-term oncological outcomes are awaited.

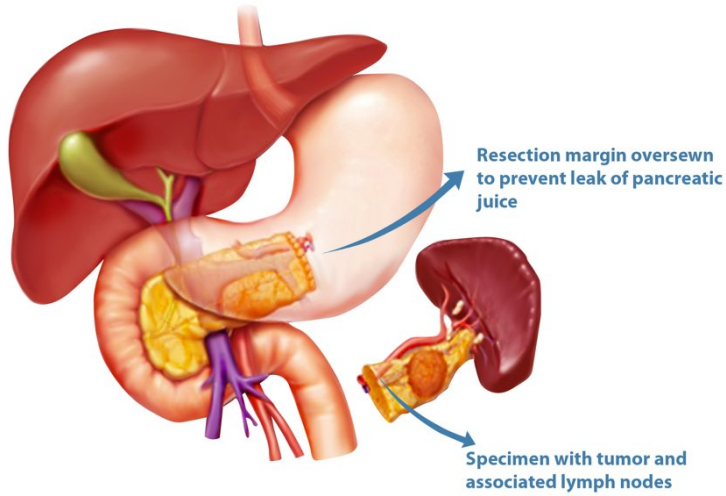


Figure 3: Distal pancreatectomy (From www.thesurgeonscollective.com.au)

1.2.3 Concomitant vascular and multi-visceral resection

Supported by the improved postoperative outcomes from major pancreatic resection during the last decades, and in the pursuit of expanding resectability criteria (and subsequently survival), concomitant resection and reconstruction of major mesenteric vessels are increasingly performed. The relative safety and efficacy of venous reconstruction techniques have been demonstrated (9, 10) while reconstruction of the mesenteric arteries is more prone to grave complications and are also of more debatable oncological value. (11)

Resection of neighbouring organs (multi-visceral resection) due to either direct tumour involvement in organs or essential vessels necessitating organ resection is most commonly comprised of partial resection of either the transverse colon, small bowel or stomach. An associated increase of both morbidity and mortality is reported in the literature (12, 13) but it may be feasible for selected, fit patients to enable pancreatic resection at all. (13)

1.3 Indications for pancreatic resection

Formal pancreatic resections are almost exclusively performed for confirmed or suspected malignant or premalignant disease.

Specimens	n	(%)
Any malignancy	**324**	**(82)**
PDAC	161	(41)
CBD cancer	58	(15)
Duodenal cancer	36	(9)
Ampulla cancer	30	(8)
Other malignancies	39	(10)
Benign disease	**69**	**(18)**
IPMN	25	(6)
Pancreatitis	11	(3)
Other	33	(8)

Table 1: Histopathology distribution in pancreatoduodenectomy specimens in Norway 2015-2016 (n=393). PDAC: Pancreatic ductal adenocarcinoma. CBD: Common bile duct. IPMN: Intraductal papillary mucinous dysplasia. Data extracted from supplementary analyses in paper II (see chapter 4.2.1)

A national population-based study from Sweden (14) and a recent single centre series from Norway covering a larger time cohort (15) confirmed similar distributions. Notably, pancreatic ductal adenocarcinoma (i.e., "true" pancreatic cancer) constitutes less than half of the specimens. A national cohort study from Norway covering all distal pancreatic resections between 2012 and 2016 (Figure 4) showed that more than 90% were performed on suspicion of either malignant or premalignant disease. (16)

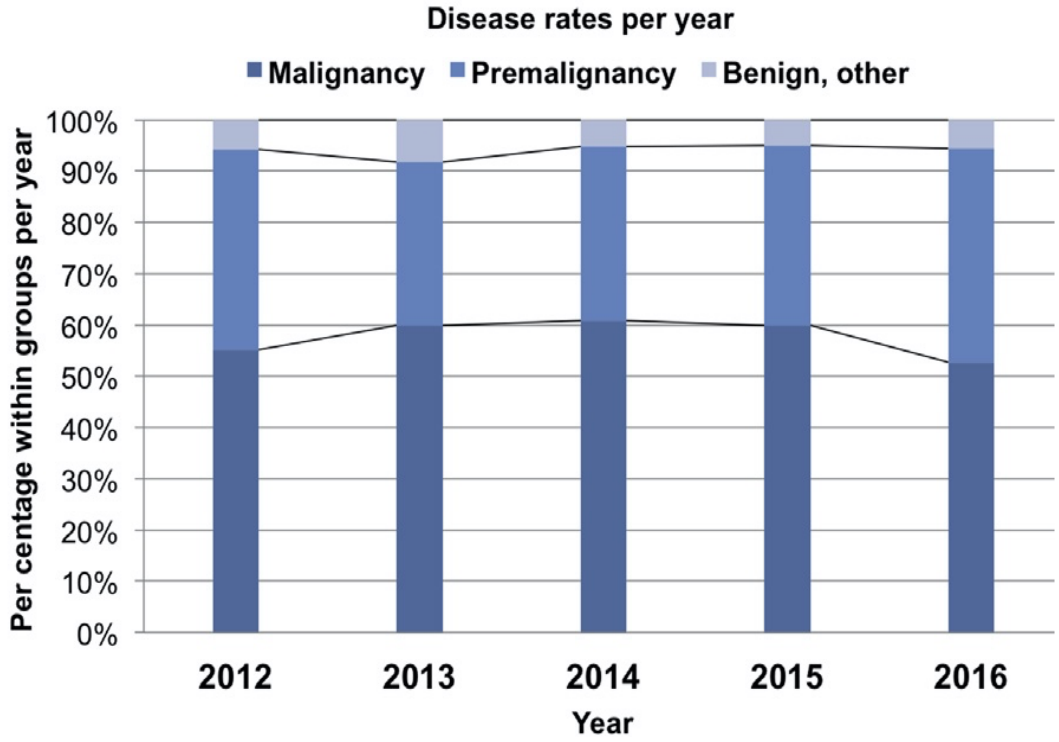
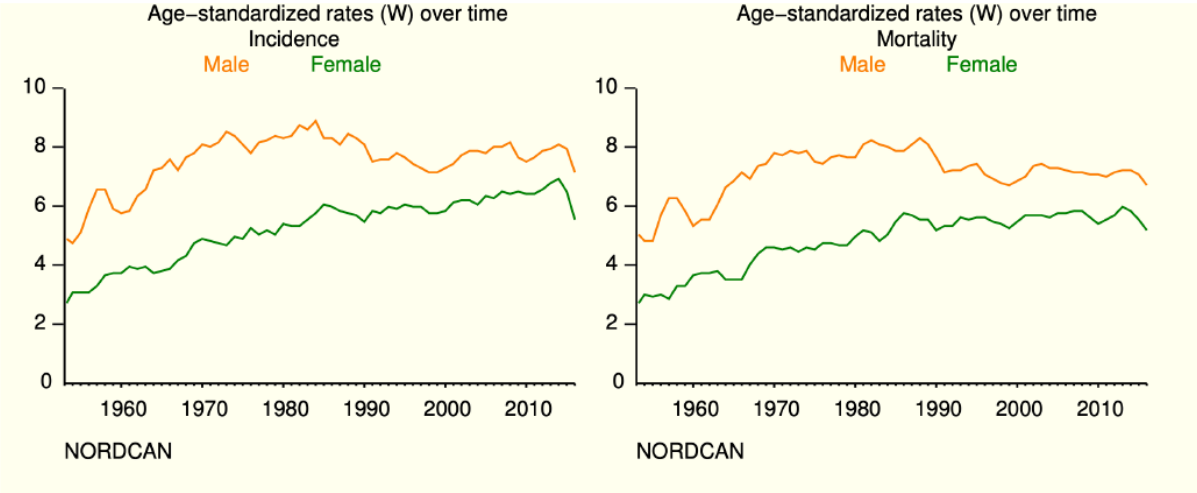


Figure 4: Distribution in indication for distal pancreatic resections in Norway 2012-2016 (From "A nationwide cohort study of resection rates and short-term outcomes in open and laparoscopic distal pancreatectomy", Søreide, Olsen, Nymo et al, HPB 2018)

1.3.1 Pancreatic ductal adenocarcinoma

Pancreatic cancer, or pancreatic ductal adenocarcinoma (PDAC), is the most common indication for pancreatic resection. This malignancy is renowned for a dismal long-term prognosis even in patients with early-stage disease. It is now the fourth leading cancer-related cause of death in Norway with a relative 5-year survival (all stages) for males of 9 % (95% CI 8-11) and for females 11% (95% CI 10-13) (17) As illustrated in the two lowermost panels in figure 5, it is predominantly a disease of the elderly with a sharp increase in incidence from the fifth and sixth decades of life.



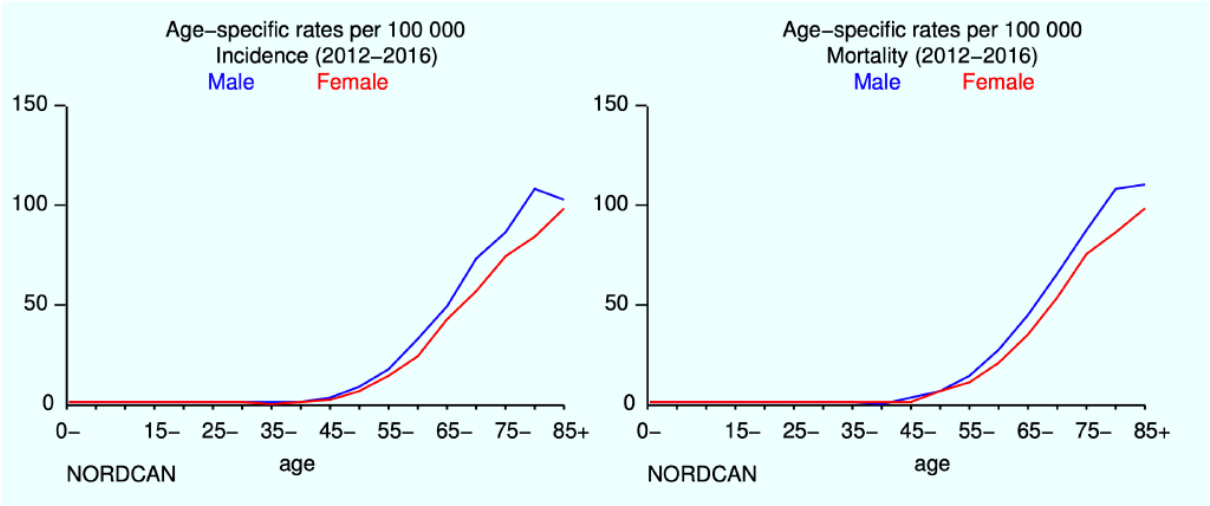


Figure 5: Age-standardized incidence (upper left) and mortality rates (upper right) over time and age-specific incidence (lower left) and mortality rates (lower right) per 100 000 inhabitants (Norway). Source: NORDCAN, https://www-dep.iarc.fr/NORDCAN/english/frame.asp)

Surgical removal of the pancreatic tumour is considered the keystone in treatment with curative intent, but more than two thirds of patients present with either locally unresectable or metastatic disease, or with other frailty barring them from full treatment. Given the distribution in age at time of diagnosis (see figure 5) and extent of surgery, only a subset of patients with early-stage disease actually reach resection.

In addition to radiological screening for metastatic disease, technical resectability of PDAC is commonly categorized as *primary resectable, borderline resectable* or *locally advanced* based on tumour relation to, and involvement of, the portal and superior mesenteric veins and root and branches from the coeliac arterial trunk and the superior mesenteric artery. (18) Surgery is offered to otherwise fit patients with primary resectable disease, borderline

resectable tumours without radiological progression on neoadjuvant CTx and for selected patients with locally advanced disease with radiological tumour regression after neoadjuvant CTx (down-staging).

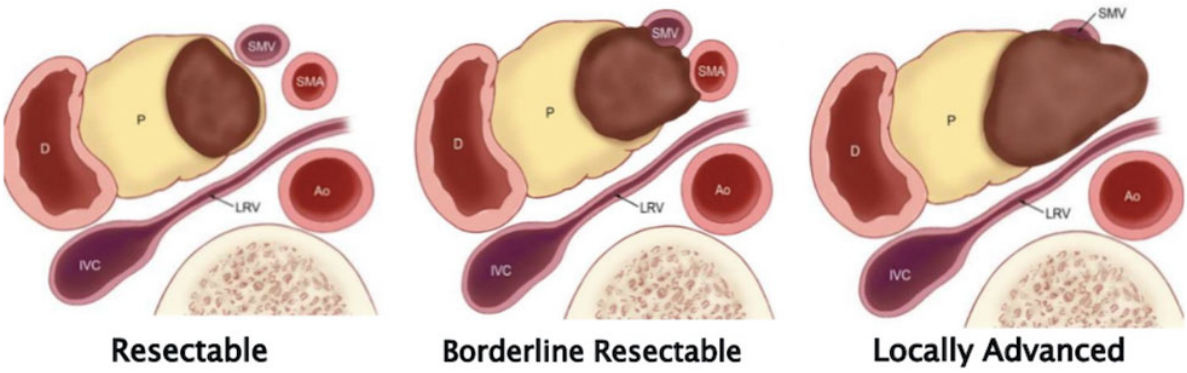


Figure 6: D: duodenum. IVC: inferior vena cava, P: pancreas, SMV: superior mesenteric vein, SMA: superior mesenteric artery, LRV: left renal vein. Source: https://drcesarramirez.com/cirug

Chemotherapy is increasingly provided in both neoadjuvant and adjuvant settings. The Norwegian guidelines recommend adjuvant chemotherapy for resected patients, and neoadjuvant treatment is given for borderline tumours and in attempts to downsize locally advanced tumours in selected patients. An adjunctive neoadjuvant regimen for primarily resectable disease is currently explored within a pan-Scandinavian randomized controlled trial (NorPACT-1). (19)

A Finnish national cohort study re-examined the surgical specimens from long-term survivors after resection for PDAC, excluded almost one in two as non-PDACs, and reported a “true” 5-year overall survival of 7.2%. (20) A more recent national cohort from the Netherlands reported a 5-year overall survival after resection of 16.7%. (21) At the other end of the scale, single centre series from tertiary referral units in other countries report 5-year overall survival after resected PDAC of up to 30-40%. (22, 23) This discrepancy is probably multifactorial. Patient selection most likely differs between expert centre series and population-based studies; use of chemotherapy plays an increasingly important role and is unevenly implemented. Regardless, there is so far little evidence to suggest that modern treatment including radical surgery and extensive chemotherapy in fact results in a substantially higher long-term (five-year) survival for resected patients. Time from primary treatment to documented recurrence of disease and median overall survival may increase, but “true” curation in terms of long-term disease-free survival is still anecdotal to the extent that it is haunted by scepticism towards the original histopathological diagnosis. (20)

Patients with primary metastatic or recurrent disease in Norway are currently considered for palliative treatment in terms of chemotherapy. Palliative radiotherapy is occasionally used for localized unresectable disease or for pain relief.

1.3.2 Cystic lesions of the pancreas

Asymptomatic cystic lesions of the pancreas are increasingly detected in radiological examinations of the abdomen performed for unrelated or vague indications, and often in elderly patients. (24) Although originally benign, some of these cystic lesions (mainly intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs)) hold an inherent potential of malignant transformation to adenocarcinoma. A timely identification and resection of a premalignant pancreatic lesion represents a golden opportunity to prevent the development of a next to incurable malignancy. Importantly, the uncertain individual benefit from such a prophylactic pancreatic resection must be viewed against the fact that many of these patients are elderly or otherwise frail and may have other more impending threats influencing on their life expectancy.

1.4 The nature and incidence of postoperative complications after pancreatic surgery

1.4.1 Overall complication burden

Pancreatic resections carry a heavy complication burden, even in the era of modern surgery and modern perioperative management. For pancreatoduodenectomies, about one in three patients experience at least one major complication, and 10-15% need a relaparotomy within 30 days from the index procedure. (25-27) However, the short-term mortality is decreasing, with both expert centre series and recent population-based cohorts reporting a short-term mortality after pancreatoduodenectomy below 5%. (25, 28, 29) Both morbidity and mortality rates following distal resections are far lower, but the development of a postoperative pancreatic fistula from the remnant gland is frequent. Occurrence of complications and nutritional issues are the most common causes to a prolonged length-of-stay, especially after a pancreatoduodenectomy. The median *aggregated length-of-stay* (see Methods, 3.3.1) after a distal pancreatic resection and a pancreatoduodenectomy in Norway is currently 7 and 14 days, including transfer stays and readmissions within 30 days. (30)

Even in the absence of postoperative surgical complications, a pancreatic resection holds the potential of substantial unavoidable long-term nutritional side effects. Of note, more than one

in two patients undergoing a scheduled pancreatic resection meet the GLIM (Global Leadership Initiative in Malnutrition (31)) criteria of malnutrition already prior to surgery, as shown by Skeie, Tangvik, Nymo et al in a nationwide analysis of data from the Norwegian Registry for Gastrointestinal and HPB surgery (NoRGast). (32) After pancreatoduodenectomy, a significant permanent weight loss and up to 3-6 months recovery-time for restored quality of life are expected. (33) Following any formal pancreatic resection, both endocrine (34) and exocrine (35) post-resection dysfunction of the pancreas frequently occur, necessitating life-long substitution.

Considering the poor prognosis for resected ductal adenocarcinomas, the uncertain individual survival gain from resection of premalignant cysts and the inescapable long-term aftermath after resection, keeping short-term complications to a minimum is crucial to be able to justify surgery at all. A pancreatic resection is a major undertaking, and the decision to embark on surgery must be taken with caution, in particular for the elderly or otherwise frail. The risk of doing more harm than good is indeed present. In the words of Donald J. Trump: "Sometimes your best investments are the ones you don´t make".

1.4.2 Postoperative pancreatic fistula (POPF)

A postoperative pancreatic fistula is a persistent leak of pancreatic juice from either the pancreatico-jejunal anastomosis (after a pancreatoduodenectomy) or the suture line from the pancreatic remnant (after a distal pancreatectomy). It is (obviously) a complication unique to pancreatic surgery and also the main determinator of short-term outcome. The international study group of pancreatic surgery (ISGPS) holds an internationally accepted definition of a POPF that is based on the clinical consequences following development of a fistula. (36) The phenomenon is divided into three clinical entities. Group B and C fistulas are often conjointly named *clinically relevant fistulas* (CR POPF). The detrimental potential of a pancreatic fistula after a pancreatoduodenectomy is larger than one occurring after a distal resection, as the fistula can prohibit the healing of all three anastomoses and is more likely to cause late haemorrhage due to erosion of the dissected vessels. The most broadly accepted risk factors for fistula development are small

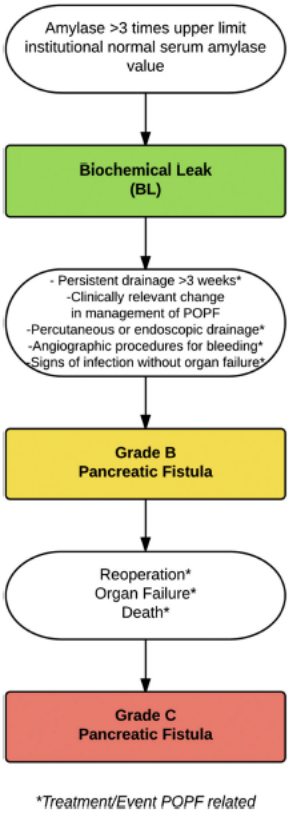


Figure 7: ISGPS definition and grading of POPF. Bassi et al, Surgery 2016

pancreatic duct size and soft gland texture, as well as having a high body mass index. (37, 38) The reported contemporary incidences of a clinically relevant fistula lie about 12-15% for pancreatoduodenectomies (25, 39, 40), and for distal resections 19-30%. (6, 7) The invasive treatment options for fistulas include percutaneous drainage of fluid collections and relaparotomy for either drainage alone, externalization of anastomotic leakage by drains or completion pancreatectomy. A timely handling of a fistula is key to prevent sepsis and organ failure. In-hospital mortality following a clinically relevant fistula after pancreatoduodenectomy has been reported to be about 18%. (39)

1.4.3 Post-pancreatectomy haemorrhage (PPH)

A significant post-pancreatectomy haemorrhage is probably the most feared and lethal complication following pancreatic surgery. Similar to the fistulas, ISGPS has graded PPH into three entities: grade A is an early (within 24 hours after index surgery) mild bleeding with no clinical consequences, grade B is either an early, severe bleeding or a late, mild bleeding and grade C is a late, severe bleeding. (6) Bleedings may origin from either the anastomoses or from significant vessels that are divided, dissected or reconstructed during the resection and occur more frequently in the presence of a pancreatic fistula. Interventional radiographical procedures (angiographic coiling or stenting), endoscopic intervention and relaparotomy are the invasive treatment options for a PPH. The reported incidence of PPH grade B or C ranges from 6.8% to 7.3% (40-42) after a standard pancreatoduodenectomy but may occur as frequent as in 14.2% of procedures if a concomitant venous resection is performed. (42) Mortality following a late PPH can be as high as 21%. (43)

1.4.4 Failure-to-rescue (FTR)

FTR is a quality metric used to measure the ability to prevent mortality after complications following medical treatment and is expressed as a ratio of fatalities divided by the number of patients with complications. It is gaining popularity worldwide and is considered the "new kid on the block" in evaluating and comparing quality of care between units. (44, 45) Up to date, no consensus definition of *complication* exists (severity, excluding/including non-surgical complications etc.), and this precludes comparison of FTR-rates across published series. Complex surgical procedures with a high complication load, like pancreatic resections, are especially suited for this quality metric. A timely and correctly chosen re-intervention for either a fistula or haemorrhage demands competent surgical personnel including ward staff, interventional radiology service and advanced ICU support available around the clock. Divergence in this ability to rescue patients from deteriorating from complications has been

proposed as a key reason as to why high-volume specialized HPB units in numerous publications are able to obtain lower mortality rates than low volume units, and a more important factor than the occurrence of complications in itself. (46, 47) A recent international multicentre benchmarking of acceptable outcomes after pancreatoduodenectomy included all complications with Clavien-Dindo grade >2 and recommended a cut-off for an acceptable rate of FTR of < 9%. (48)

1.5 Centralization of pancreatic surgery and the volume-outcome effect

An inverse correlation between hospital surgical caseload and short-term mortality after pancreatic surgery has repeatedly been demonstrated in the literature, and this volume-outcome effect is now a broadly accepted paradigm worldwide. (49, 50) For malignant disease, the diagnostic work-up and surgical and oncological treatment options available are also of increasing complexity and demand a multi-disciplinary approach. (51) An optimal handling of postoperative complications illustrated by low FTR rates contribute significantly to the superior short-term mortality rates documented in units with a higher case load (46), and the hospital academic status is possibly also a part of the picture. (52, 53) Together, this has led to a call for centralization of all pancreatic surgery to dedicated high-volume HPB units. (54) This process has been gradually implemented in the UK, the Netherlands and Scandinavia throughout the last 10-20 years (55), while other large western countries such as France, Germany and the US are lagging behind.

Importantly, there is no clear consensus definition of the respective unit volume categories. While some use a cut-off in minimum case load for high volume units at 40 PDs a year (27), others advocate a lower threshold with 40 *pancreatic* resections (PD and DP) a year (56) or 20 PDs a year. (50) One must take cation to this inconsistency when assessing literature on the topic.

Registry data for unselected population-based cohorts naturally constitute the optimal background to study the overall quality of care and the concept of centralization, and in particular the optimal *level* of centralization.

1.6 The Norwegian medical registries

1.6.1 Cancer Registry of Norway (CRN)

The CRN was established in 1951 and has since collected data for all new confirmed malignancies in the Norwegian population. It is one of the world's oldest existing national cancer registries. Direct reporting from pathology departments, clinicians and death certificates to CRN is compulsory, and hence coverage rates for diagnoses are considered complete. (57) Epidemiological data on incidence and survival is published annually, and numerous national and international cancer research projects have sprung out from the CRN database. A dedicated sub-registry for pancreatic cancer has recently been established and is expected to publish the first annual report by 2021.

1.6.2 The Norwegian Patient Registry (NPR)

The NPR has gathered patient level data for all admissions and procedure- and diagnosis codes registered in Norwegian hospitals since 2008. The Norwegian hospitals are reimbursed based on this coding, and data is considered to be complete from 2010. The accuracy in cancer diagnosis codes is in relatively high accordance with data from the CRN (58), but the quality of surgical procedure codes, especially for major resections, is considered to be very high due to the reimbursement practice.

1.6.3 The Norwegian Registry for Gastrointestinal and HPB surgery (NoRGast)

NoRGast was funded in 2014 as a nationwide complication registry for major abdominal resections and granted status as a national medical quality registry in 2015. (59) Core data on patient case mix, procedures and complications within 30 days from index surgery is gathered prospectively. An automatic coupling with the National Registry allows for long-term data on survival. The overall coverage rate on patient level for 2019 was 70%, but for hepatobiliary resections the coverage rate has been high since 2016 and was 94% for pancreatic resections in 2019. (60)

1.7 Pancreatic surgery in Norway

Bakkevold et al published in 1993 a national cohort study of results after radical and palliative surgery for pancreatic cancer in Norway. (61) At this time point, altogether 23 separate units (university, county and district hospitals) performed surgery for pancreatic cancer. The 30-day mortality after radical surgery was 11%. During the next decades, a gradual

regionalization of pancreatic resections took place. It was initiated not by strict legislations from central health governments, but by an understanding and agreement (or so) within the clinical societies in the respective regions. In an international perspective, Norway was an early adopter of the volume-outcome doctrine in spite of a demography and geography unsuited for centralization. During the last decade, formal pancreatic resections in Norway have been performed solely in five university hospital units throughout the four autonomous Regional Health Authorities (OUS Rikshospitalet, Stavanger University Hospital, Haukeland University Hospital, St Olav University Hospital and the University Hospital of North Norway, Tromsø). A formal clinical and scientific multi-disciplinary cooperation with representation from all five units has been established (Norwegian Gastrointestinal Cancer Group, HPB chapter) in collaboration with the Cancer Registry of Norway. Despite the completion of this centralization, or regionalization, the inter-unit variation in annual case volume for pancreatic resections vary extensively due to large discrepancies in the uptake population in the respective regions.

K. Søreide et al. / Pancreatology 19 (2019) 880–887

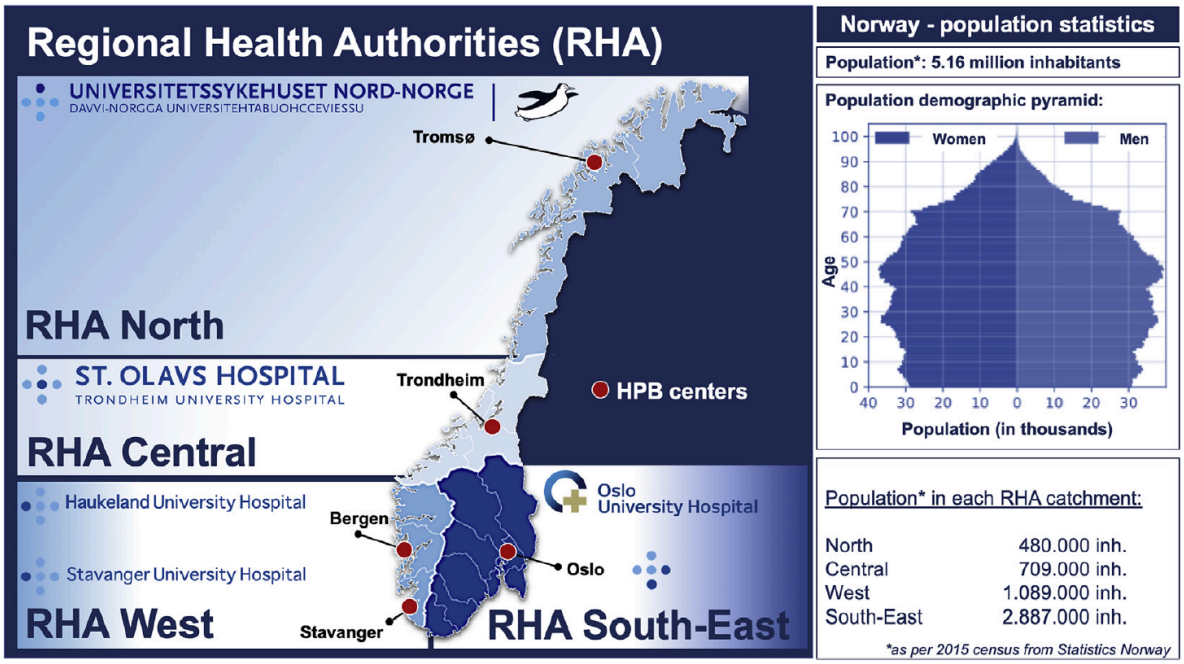


Figure 8: Demographic overview of the regional catchment populations in the Norwegian health regions (Variation in use of open and laparoscopic distal pancreatectomy and associated outcome metrics in a universal health care system", Søreide, Nymo, Kleive et al, Pancreatology 2019)

Some single-centre series (15, 62, 63) have been published since the paper by Bakkevold et al in 1993. (61) NoRGast data have documented that laparoscopy is an established method for distal pancreatectomy in all five operating units, and nationally more than one in two DPs are currently done laparoscopically. (60) Mini-invasive PD however has not yet been established in either of the units. The annual volume of pancreatic resections in Norway is presently increasing, and for 2019 altogether 371 formal pancreatic resections were reported to Norwegian Patient Registry.

In association to this PhD project, we published two papers covering a national 5-year cohort (2012-2016) of distal pancreatic resections using administrative data from the NPR. (16, 64) The population-based procedure incidence of DP (any indication) increased during the study period, especially for laparoscopic DP. The 90-day mortality was low (1.9%) and *aggregated length of stay* (for further description see Methods, 3.3.1 and (30)) was lower following laparoscopic procedures. (16)

1.8 Summarized rationale behind the thesis

While excellent outcomes have been reported in trials and patient series from large centres, most patients do not participate in trials, nor do they have surgery at expert centres. Even large registry cohorts will present selected series if not all (e.g., private sector hospitals) participate, and this is presently the reality in most countries. It is highly likely that many of the hallmark publications that currently dominate the "knowledge base" on which physicians base their clinical practice regarding pancreatic resection on, underestimate the real-life burden of complications and that the reported length-of-stays (LoS) do not correctly capture transfer stays at local hospital facilities or readmissions in other units. Likewise, intervention trials on novel chemotherapy regimens for pancreatic cancer have strict inclusion criteria, which limits its relevance to an unselected PDAC population where many patients, even most, are too frail for any regimen.

Population-based, high-quality medical registry data from countries with government-funded public health care systems without private sector alternatives are especially suitable sources to survey the true image of the complication burden and recovery after surgery. These unselected and complete data represent a valuable complement to data derived from

intervention studies or expert centre cohorts as the latter show what under optimal conditions might be obtained for the few, while the former depicts the real-life prospects for the many.

To our knowledge, from the publication by Bakkevold in 1993 and up to present date, no national Norwegian cohort analysis covering short-term outcomes after pancreatic surgery or treatment practice and long-term survival after PDAC in the post-centralization era has been published. The large inter-regional unit volume discrepancy also raises the question of whether the current degree of centralization is sufficient, or if it should be intensified.

2 Aims

2.1 Main aim of the thesis

We aimed to explore national and regional practice patterns and short-term complication burden after pancreatic resection in Norway in the post-centralization era. For pancreatic ductal adenocarcinoma, the most common diagnosis leading to a pancreatic resection, we investigated patterns in resection rates and provision of chemotherapy, and long-term survival.

2.1.1 Paper I

To assess the contemporary national and regional population-based procedure incidences, patient journeys and short-term complication burden following pancreatoduodenectomy after long-standing centralization in Norway.

2.1.2 Paper II

To compare short-term results including procedure-specific complications after pancreatoduodenectomy in one high-volume centre with four medium/low volume centres (combined). Would a further centralization lead to improved results across the nation, or is the current degree of centralization well-balanced?

2.1.3 Paper III

To examine diagnosis-specific resection rates, use of chemotherapy and long-term survival for pancreatic ductal adenocarcinoma in Norway in a fifteen-year cohort (2004-2018). Are the improved survival data that lately have been reported from expert centre resection series and chemotherapy trials, mirrored in an unselected population-based cohort?

3 METHODS

3.1 Ethical considerations

From a patient' perspective, both on individual and group level, the risk of negative effects from the conducted data gathering, alignment and analyses seems low. Regarding data security and protection, only patient data already available within the Norwegian medical registries or electronic patient files were used. No new information on patients was gathered. Patient information regarded as backwards identifiable was kept to a minimum. All data were gathered, transferred and stored in line with the regulations given by the Regional Research Committee, the local and national data protection offices and the Norwegian Health Directory.

A possible positive effect from the results derived from the studies may be a better evidence base and raised awareness for the regional and national clinical societies and administrative decision makers. From the provision of evidence for practice patterns and both occurrence and handling of complications arises a possibility to pinpoint areas for further quality improvement. Contemporary, representative data on expected patient journeys can also aid directly in shared decision-making between patient and surgeon on whether to embark on surgery or not. For pancreatic ductal adenocarcinoma, with an inherent dismal prognosis, and cystic lesions with an unknown potential for development of malignant disease, this weighing of risk against potential benefits for each individual patient is crucial.

3.2 Data sources and formal approvals

Paper 1 was conducted in cooperation with the Centre for Clinical Documentation and Analyses (SKDE) in Tromsø. SKDE holds a licence from the National Data Protection office for use and analyses of data from the National Patient Registry (NPR), and no additional application to the Regional Research Committee was required.

Paper II used data from the Norwegian Registry for Gastrointestinal and HPB surgery (NoRGast). All patients entered into the registry have given a written informed consent form also allowing for the use of data in research. The Norwegian Health directory granted access to local electronic patient files for completing data, and approval for alignment of data across centres was given by the National Data Protection Authority. (Reference 17/33320-2).

Combining data from the Cancer Registry of Norway and the Norwegian Patient Registry formed the data set for paper III. This was approved by separate applications to the Regional Research Committee (reference 81594), the Norwegian Health Directory (reference 20/12868-5), the data protection office at the Arctic University of Norway (reference 611888) and Cancer Norway.

3.3 Methodology and study designs

All three studies were cohort studies of complete national patient cohorts strictly defined by either a specific procedure performed (Paper I and II) or a specific diagnosis given (Paper III) in a set time period (five-, two- and fifteen-year cohorts). The inclusion criteria and the definitions of outcomes were well defined prior to patient-data entry thus minimizing the risk of bias. While analyses were performed at a later time point, all datasets were true cohort series (i.e., patients were included by a common exposure and analysed by a later occurring outcome). STROBE guidelines for reporting observational studies were adhered to where applicable. (65)

3.3.1 Paper I

Each individual patient journey in a five-year cohort (2012-2016) of all patients who underwent a PD was tracked within the NPR to benchmark the contemporary outcomes after longstanding centralization of surgery.

National and regional population-based procedure incidence rates of PD (of any indication) was calculated and adjusted for age- and gender composition over time and between the regional populations. Concomitant vascular resection was defined by the presence of procedure code(s) for any major venous or arterial reconstruction at the same day of the index procedure. Code sets signifying vascular suture, ligature or simple angioplasty were not included in the definition. No attempt was made to separate venous from arterial procedures due to concerns of a low precision level in coding practice. Multi-visceral resections were identified in a similar manner using code sets for simultaneous formal resection (more than a wedge resection) of either the colon, small bowel or stomach.

Relaparotomies were identified by a defined set of NCSP procedure codes denoting *any surgical access to the abdominal cavity* from postoperative day one up to 30 days from index

surgery. Any relaparotomy in any Norwegian hospital during the set time interval (including transfer stays and readmissions in any unit) was included.

Length-of-stay was assessed by *aggregated length of stay* (a-LoS) within 30 days, defined by the total aggregated number of days the patients were admitted to any hospital unit in Norway, including index stay, transfer stay and readmissions. The complete patient journeys for the first 30 days after resection were tracked within the NPR. The novel a-LoS concept and benchmark data for all major gastrointestinal resections was published by our group in 2018. (30)

All fatalities within 180 days after resection and admission status by demise were registered, which allowed for calculation of both 30-, 90- and 180-day as well as in-house and index-stay mortality rates.

The search algorithms for relaparotomy, vascular resection and multi-visceral resection were validated against EPJ data for all study patients treated at one unit (UNN Tromsø) and found to have a complete (100%) accuracy (data not reported).

3.3.2 Paper II

Based on the volume-outcome relationship, we hypothesized that patients who had surgery at the one very-high volume unit would fare better in terms of short-term morbidity and mortality compared to patients treated at the four lower volume units. A two-year complete national cohort of PDs (2015-2016) with more granular data on patients, procedures, complications and histopathology was assessed. This dataset was based on NoRGast data. Due to an incomplete coverage rate in the registry, a search on procedure codes for PD was done within the EPJs at the local units by an HPB surgeon to identify any missing patients. The dataset was completed on a patient level and extended with granular information on vascular reconstruction, POPF and PPH scored according to the ISGPS definitions for all patients. (36, 66, 67) Details on histopathology and the patient journeys of patients who died within 90 days were also gathered.

3.3.3 Paper III

A complete 15-year cohort (2004-2018) of all patients diagnosed with PDAC was assessed for trends in treatment and survival. The dataset was drawn from the Cancer Registry of Norway, also utilizing their automatic coupling with the National Patient Registry (NPR).

A set of procedure codes and/or diagnostic codes within the NPR was used to identify the provision of chemotherapy. For non-resected patients, all chemotherapy between date of diagnosis and demise was categorized as palliative treatment. For resected patients, the relation in time between the dates of codes denoting provision of chemotherapy and the pancreatic resection was used to classify in which setting (neoadjuvant, adjuvant or palliative) the chemotherapy was provided. As the NPR does not register pharmaceutical data, the specific chemotherapy regimens administered were not possible to identify, nor was the method deemed to be of necessary accuracy to describe number of or completeness of chemotherapy cycles as codes may be registered for follow-up consultations where no therapy was administered.

To assure data quality on both 1) PDAC diagnosis against other related malignancies in non-resected patients and 2) provision and setting of chemotherapy, a subgroup of 160 patients was randomly drawn from the CRN dataset and cross-checked against electronic patient files. This revealed a perfect accuracy (100%) for chemotherapy data and only minor adjustments were necessary for the identification of non-resected patients with PDAC. (Data not reported) Results from this data validation is planned used as part of a future separate scientific publication on the use of combined CRN and NPR data.

3.4 Statistics

For crude description, categorical outcome measures were reported as rates in absolute figures with percentages, and incidences as cases per population size per year. Further, continuous variables were reported as medians with 95% confidence intervals (CI) or means with standard deviation, as fit. Univariate analyses of categorical variables were done by chi-square or Fisher exact tests and continuous variables were compared by student t-test or Kruskal-Wallis test. Comparisons of incidences and rates between regions or over time were adjusted for age- and gender composition in the populations.

Models for binary, logistic multivariable regression analyses were built in a stepwise backwards selection manner, and models were tested for significant interactions and adjusted for multiple testing by the Bonferroni method (the latter for Paper I, only). Effect measures from univariate and multivariate regression analyses were reported in odds ratios with 95% CI. Level of significance for all analyses was set to $p < 0.050$. Survival curves for paper III

were drawn by the Kaplan Meyer method and multivariable Cox proportional hazard regression models were estimated to present age-adjusted hazard ratios (95% CI) of death (all causes) across time periods. Provision of chemotherapy and surgery was treated as time-varying covariates in all survival analyses in order to avoid immortal time bias.

For paper I, the study analyses description including variable definitions and algorithms was developed by the first (Nymo) and last author (Lassen), while co-author Frank Olsen at the Centre for Clinical Documentation and Evaluation (SKDE) performed the actual statistical analyses as he was the only one with permission to access the complete NPR dataset. Similarly, for paper III the study analyses were described by the first (Nymo) and last author (Lassen), but all statistical analyses were conducted by the second author Tor-Åge Myklebust at the Cancer Registry of Norway. All statistical analyses in paper II were done by the first author (Nymo).

4 SUMMARIZED RESULTS

4.1 Paper I

The effect of centralization on short term outcomes of pancreatoduodenectomy in a universal health care system

HPB 2019, 21 (319-327)

Paper I was an analysis of a five-year national cohort of PDs for all indications, using administrative data (NPR) only.

Altogether 930 procedures were performed between 2012-2016. The incidence of the procedure per population increased during the study period (p=0.006). The national rates of concomitant vascular resection and multi-visceral resection were 139 (15%) and 44 (5%), respectively. After adjusting for age, gender and patients being operated outside their residing RHA there was no difference in use of the procedure between the regional populations, with a procedure incidence ranging from 3.4-3.8 PDs per 10^5 inhabitants per year (p=0.929). There was, however, a significant difference in the use of concomitant vascular resection ranging from 19% in RHA South-East to 8% in RHA West (p for comparison between all four regions =0.021).

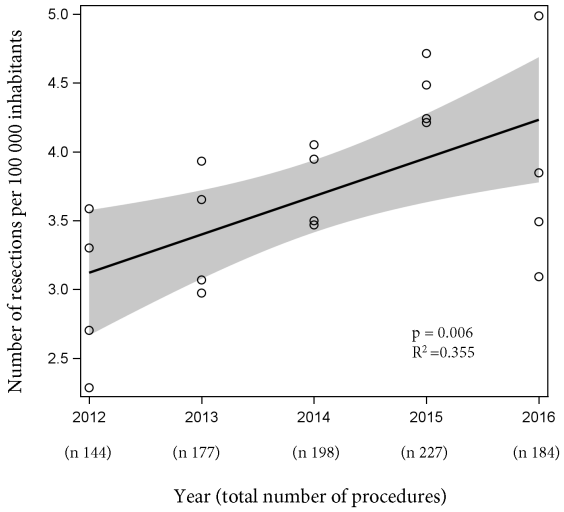


Figure 9: Trend for incidence of pancreatoduodenectomy performed each year in Norway (black line with 95% CI in grey) Age-and gender-adjusted incidences for the separate Regional Health Authority (RHA) regions shown in circles.

Some 131 patients (14%) underwent a relaparotomy within 30 days, and 34 patients (3.7%) died within 90 days (Figure 3). Of these, one in five relaparotomies and two in five deaths occurred outside the index unit. In multivariable analyses, being aged 75 years or more (OR 13.8, CI 4.2-63.0), male gender (OR 3.4, CI 1.5-9.0) and undergoing a relaparotomy within 30 days (OR 5.9, CI 2.7-12.8) were independent predictors of mortality within 90 days, whereas treating RHA or having a concomitant vascular resection were not.

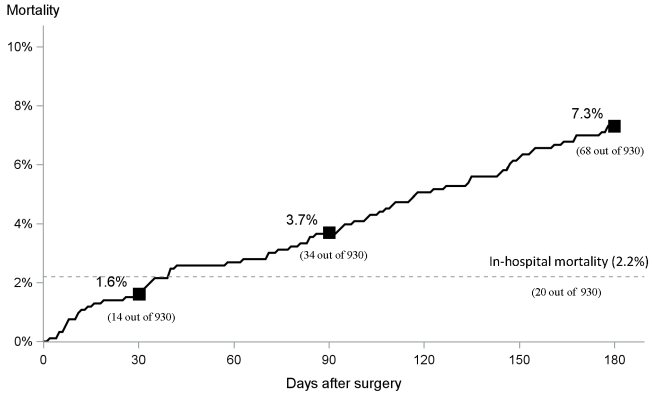


Figure 10:Over-all postoperative mortality for 2012-2016. Rates at 30, 90 and 180 days after surgery are marked with black boxes and in-hospital mortality in dotted grey line.

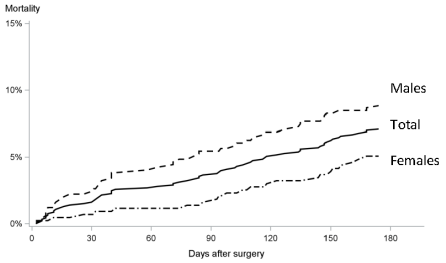


Figure 2a: Mortality stratified by gender

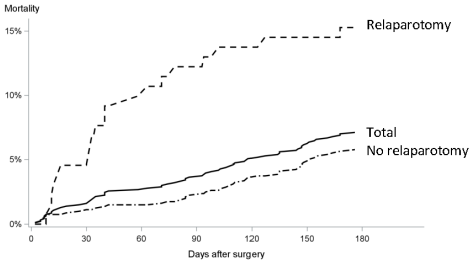


Figure 2b: Mortality stratified by relaparotomy

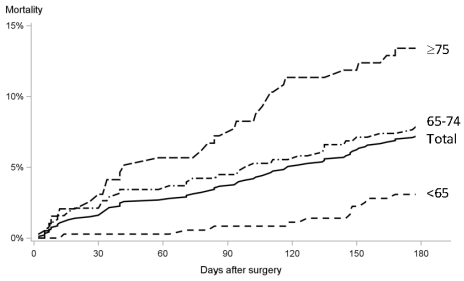


Figure 2c: Mortality stratified by age group

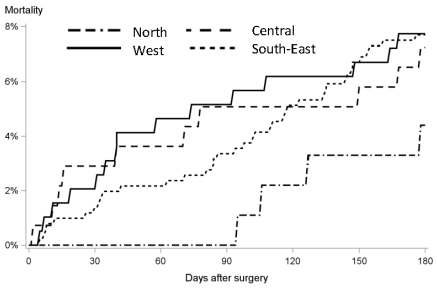


Figure 2d: Mortality stratified by regional health authority

Figure 11: Mortality rates stratified by gender (2a), relaparotomy (2b), age group (2c) and treating RHA (2d).

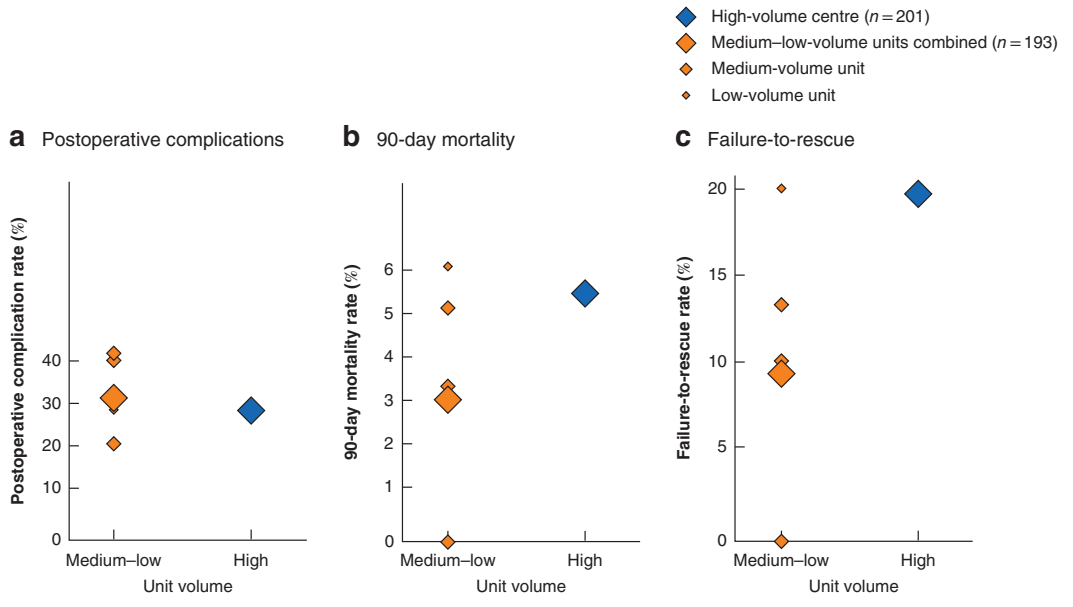
4.2 Paper II

Centralizing a national pancreatoduodenectomy service: Striking the right balance

BJS Open 2020

In paper II, a two-year cohort of PDs was analysed for procedure-specific and general postoperative complications including failure-to-rescue rates. Results from the one high-volume centre (n procedures = 201) alone serving more than half of the national population was compared to outcomes from the other four medium/low-volume units combined (n procedures = 193). The high-volume centre had results in line with internationally established benchmarked cut-offs for outcome metrics, but of note, so had the medium volume centres. In multivariate regression analyses, the 90- day mortality was lower in the medium/low volume group (p=0.023) and although not statistically significant, their failure-to-rescue rate was 6 out of 68 (8.8%) compared to 11 out of 57 (19.2%) in the high-volume unit.

Fig. 1 Comparison of any major complication, 90-day mortality and failure-to rescue in medium–low-volume and high-volume units



a Postoperative complications (Accordion grade 3–6); **b** 90-day mortality; **c** failure-to-rescue. Multivariable analysis with high volume as reference (odds ratio (OR) 1·00): **a** OR 1·28 (95 per cent c.i. 0·82 to 1·98), *P* = 0·274; **b** OR 0·24 (0·07 to 0·82), *P* = 0·023; **c** OR 0·49 (0·26 to 1·63), *P* = 0·243.

Figure 12: Accordion grade 3 or higher, 90-day mortality and failure-to-rescue after pancreatoduodenectomy 2015-2016, stratified for high-volume vs medium/low volume units.

4.2.1 Supplementary results not included in paper II

Vascular resection

There were significantly more vascular resections performed in the high-volume patient population with an OR of 3.1 (CI 1.7-3.5) compared to patients treated at medium-low volume units. There were no differences in postoperative outcomes after vascular resection between the two volume categories.

	Total n=394	**High-volume unit n= 201**	**Medium/low volume units combined n=193**	**Age- and gender adjusted comparison high vs medium/low volume units[1]**
Procedures				***OR (95% CI), p-value***
Any vascular resection (patients)	70 (18%)	50 (25%)	20 (10%)	**OR 3.1 (1.7-5.3) p<0.001**
Postoperative outcomes for patients with concomitant vascular resection (n=70)				
Accordion 3-6	25 (36%)	19 (38%)	6 (30%)	OR 1.5 (0.5-4.5) p=0.492
Relaparotomy	18 (26%)	15 (30%)	3 (15%)	OR 2.8 (0.7-11-4) p=0.153
Post-pancreatectomy haemorrhage grade B/C	19 (27%)	14 (28%)	5 (25%)	OR 1.2 (0.4-3.8) p=0.808
Postoperative pancreatic fistula grade B/C	7 (10%)	4 (8%)	3 (15%)	OR 0.5 (0.1-2.4) p=0.352
90-day mortality	4 (6%)	3 (6%)	1 (5%)	OR 1.2 (0.1-12.2) p=0.888

[1] Logistic regression analyses (adjusted for age and gender) of high volume as predictor of procedures and outcomes, with medium/low volume as reference

Table 2: Postoperative outcomes after PD with concomitant vascular resection, stratified for unit volume category

Failure-to-rescue

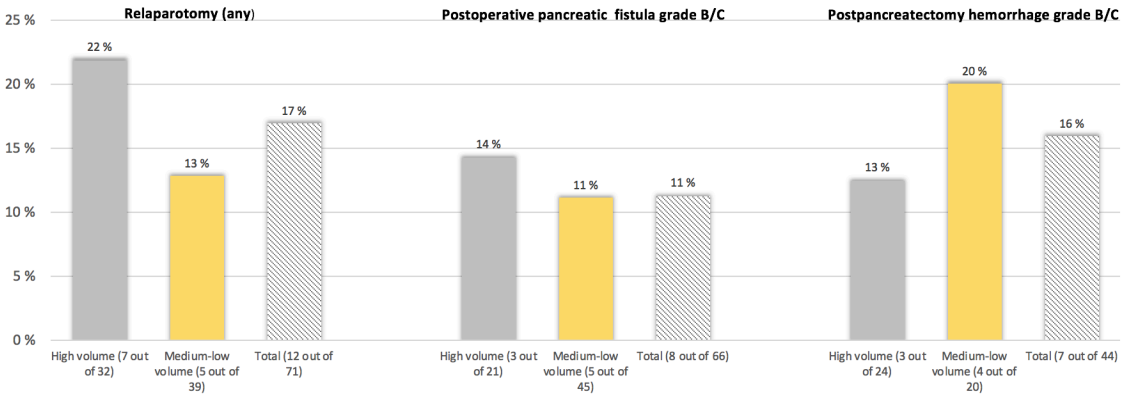


Figure 13: 90-day mortality (Failure-to-rescue) following relaparotomy, POPF grade B/C and PPH grade B/C, stratified for unit volume category

The national failure-to-rescue rates following relaparotomy (any), POPF grade B/C and PPH grade B/C were 17%, 11% and 16%, respectively. 15 out of 17 patients who died within 90 days experienced at least one of these three complications. Conversely, the national 90-day mortality rate among patients who did not experience neither of these was 2 out of 269 (0.7%).

Histopathological distribution of resected specimens

Specimens	n	(%)
Any malignancy	**324**	**(82)**
PDAC	161	(41)
CBD cancer	58	(15)
Duodenal cancer	36	(9)
Ampulla cancer	30	(8)
Other malignancies	39	(10)
Benign disease	**69**	**(18)**
IPMN	25	(6)
Pancreatitis	11	(3)
Other	33	(8)

Table 3: Histopathology distribution in pancreatoduodenectomy specimens in Norway 2015-2016 (n=393). PDAC: Pancreatic ductal adenocarcinoma. CBD: Common bile duct. IPMN: Intraductal papillary mucinous dysplasia.

(Note: Table 3 is also displayed under 1.3, there numbered as Table 1)

Outcomes stratified by histopathology

	PDAC (n=161)	All malignancies except PDAC (n=163)	*Any malignancy (n=324)*	*Any benign disease (n=69)*
Outcomes n (%)				
Relaparotomy	30(18.6)	30(18.4)	*60(18.5)*	***11(15.9)***
POPF grade B/C	15(9.3)	31(19.0)	*46(14.2)*	***20(29.0)***
PPH grade B/C	19(11.8)	18(11.0)	*37(11.4)*	***7(10.1)***
90 d-Mortality	4(2.5)	11(6.7)	*15(4.6)*	***1(1.4)***
Non-R0	105(66.5)	77(47.2)	*182(56.9)*	**-**

Table 3: Postoperative outcomes stratified by histopathology. POPF: Postoperative pancreatic fistula, PPH: Post-pancreatectomy haemorrhage.

The rates of non-R0 in PDAC-specimens with and without concomitant vascular resection were 43 out of 52 (83%) and 62 out of 106 (58%), respectively.

4.3 Paper III

Progress for the few: Treatment and survival after pancreatic ductal adenocarcinoma in a 15-year national cohort

(Submitted for review, May 2021)

A total of 10630 patients were diagnosed with PDAC between 2004 and 2018. The fraction of patients who *did not* receive any tumour-directed treatment (resection or chemotherapy) decreased over time from 52.9% in 2010 to 37.9% in 2018, p for trend <0.001.

During the studied period a rising proportion of patients underwent formal tumour resection with a peak of 18.9% for 2018, and the median age of those resected increased by four years. The largest increase in resection rate was for patients aged 75+, with an OR for resection of 2.11 (CI 1.59 – 2.79) when diagnosed 2014-2018 compared to 2004-2008.

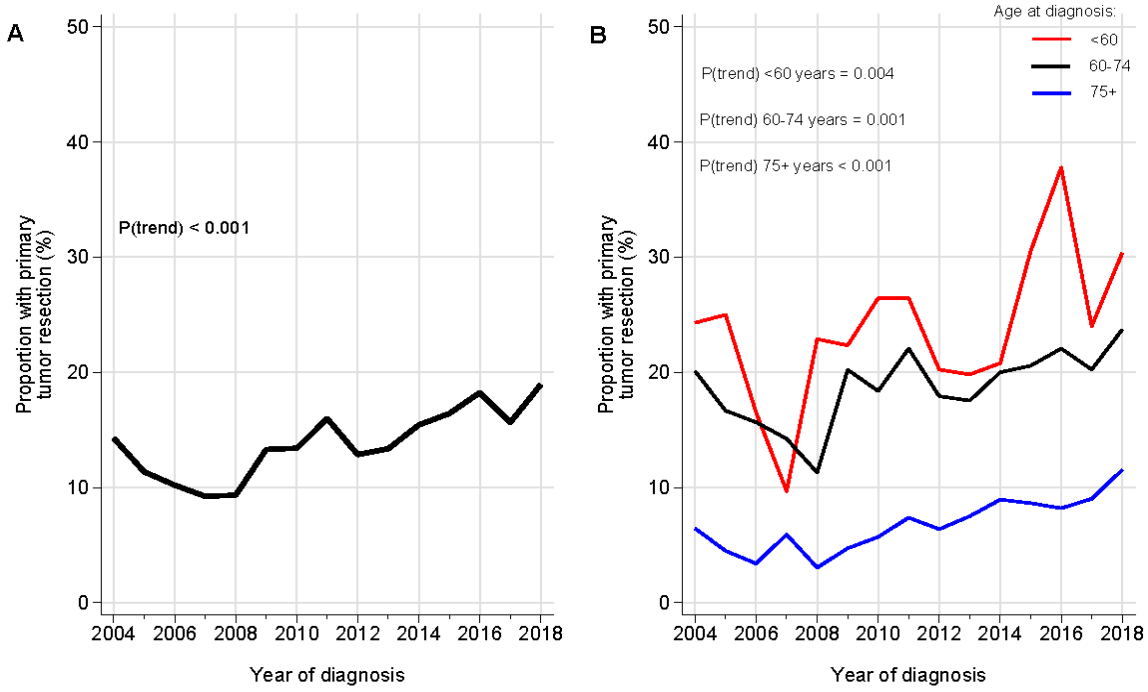


Figure 14: Trend in resection rate 2004-2018 for a) all ages and b) stratified by age group

A marked rise in provision of perioperative CTx was found, especially for neoadjuvant CTx (all ages) with OR (95% CI) of neoadjuvant CTx for 2014-2018 of 4.44 (2.58-7.63) compared

to 2010-2013. No change in provision of palliative CTx was observed (p=0.201) for the resected. An increase in use of palliative CTx for non-resected patients was demonstrated, mostly due to provision to patients aged 75+ with an OR (95% CI) for palliative CTx for 2014-2018 of 1.72 (1.35-2.20), with 2010-2013 as reference.

Median overall survival (IQR) for resected patients increased from 16.0 months (8.3 – 33.0) for 2004-2008 to 25.1 months (12.4 – 49.2) for 2014-2018, and the 3-year survival (CI) improved from 22.0 % (17.9-26.4) to 36.4 % (32.2-40.6).

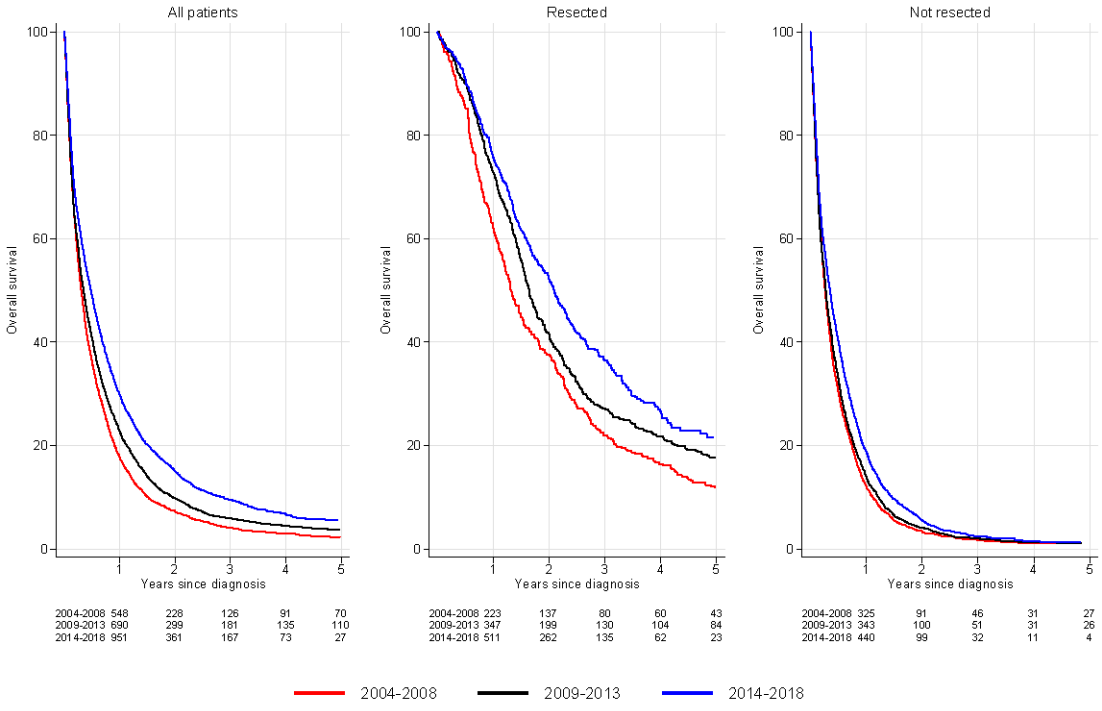


Figure 15: Survival plots (KM) for a) all patients, b) resected patients and c) non-resected patients with stratifies curves for the respective time cohorts. Numbers at risk provided in tables under each figure.

4.3.1 Supplementary results not included in paper III

Regional practice and survival

	Total (national)	RHA South-East	RHA West	RHA Central	RHA North	Statistical comparison
2004-2018						
Resection rate (%)	14.1	14.1	13.8	14.3	13.1	0.807
2010-2018 (-2017 for palliative chemotherapy)						
Provision of chemotherapy, n (%)						
Non-resected patients (palliative)	2077 (45.6)	1142 (46.2)	427 (45.4)	311 (50.6)	196 (37.1)	**<0.001**
Resected patients:						
-Neoadjuvant	125 (12.0)	72 (12.2)	13 (7.2)	29 (17.9)	10 (8.8)	**0.001**
-Adjuvant	676 (64.7)	392 (66.7)	111 (61.7)	103 (63.6)	69 (60.5)	0.521
- Palliative	475 (45.5)	267 (45.4)	80 (44.4)	73 (45.1)	55 (48.3)	0.827
-Any postoperative chemotherapy	787 (75.3)	447 (76.0)	132 (73.3)	118 (72.8)	89 (78.1)	0.761

Figure 16: Regional resection rates and provision of chemotherapy. Patients categorized by residing regional health authority (RHA). Missing data for residing RHA for 5% of patients, and these were excluded.

The resection rates were equal between the four regions. Besides provision of palliative CTx to non-resected patients (range from 37.1% in RHA North to 50.6% in RHA Central, $p<0.001$) and neoadjuvant CTx (range from 7.2% in RHA West to 17.9% in RHA Central, $p=0.001$) there was no difference in provision of CTx between the regional populations.

Regional survival (2004-2018)

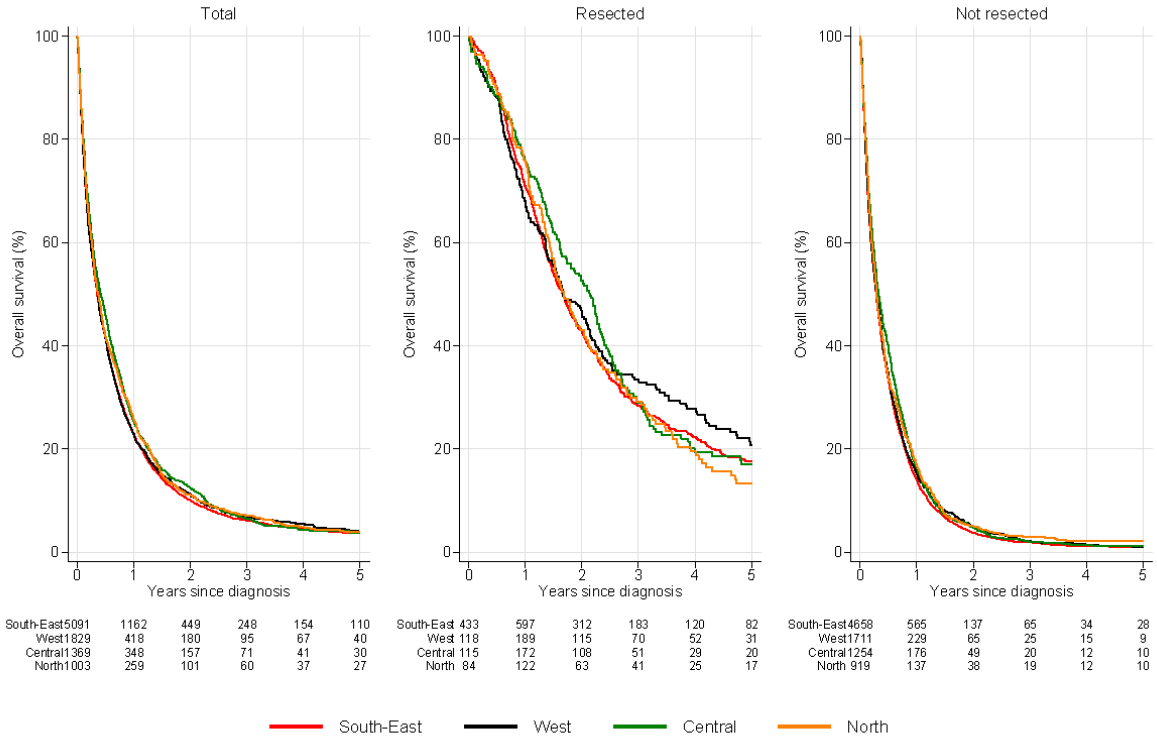


Figure 17: Kaplan-Meyer plots for overall survival 2004-2018 stratified by residing regional health authority, a) all patients with PDAC diagnosis, b) resected patients and c) non-resected patients.

There was no difference in survival between the complete PDAC populations in the four regions (p=0.063), nor between the regional subgroups of resected patients (p=0.536).

5 DISCUSSION

5.1 National short-term outcomes (Paper I and II)

The contemporary results and practice of pancreatoduodenectomy in Norway are reassuring in comparison to other recent population-based reports. (29, 56, 68, 69) The complete, unselected 5-year cohort (2012-2016) analysed in paper I demonstrated a national mortality rate in line with publications from expert centres. (48) Of note, the follow-up in paper I included treatment given in any transfer or re-admitting hospital and deaths occurring outside hospitals and extended in time beyond the more commonly evaluated *in-hospital* data. The dataset for paper II allowed for more granular analyses of procedure-specific complications for the latter two years of the cohort previously studied in paper I. Sánchez-Velázquez et al published in Annals of Surgery in 2019 an international multi-centre study from expert centres where outcomes from PD in a cohort of low-risk patients were used to benchmark cut-offs for acceptable levels of postoperative outcomes, including procedure-specific complications. (48) By comparison, we showed in paper II that both the single high-volume unit and the four medium-low volume units in Norway combined (i.e., the complete national cohort) scored within their benchmarked cut-offs for operation duration, blood transfusion, length-of-stay, POPF, PPH and mortality. The specific FTR rate for the high-volume centre was higher in terms of observed absolute figures (20%), but the national FTR-rate (11%) was on par with the benchmark value (9%). This was in spite of the fact that the abovementioned benchmarked levels were based on data from a low-risk cohort defined by strict criteria that excluded almost one in two patients, while our data included every single patient treated across the nation during the given time span: lock, stock and barrel. In addition, the benchmark values (48) also included complications scored as Clavien-Dindo grade 3a in the denominator of the FTR-rate, while our studies only included complications corresponding to Clavien-Dindo grade 3b or higher. The absence of patient selection, the extended follow-up time in paper I, and the completeness in follow-up in both papers further support the finding of an acceptable level of short-term complications following pancreatoduodenectomy in Norway today.

Analyses of postoperative mortality after pancreatic surgery have also been reported from other principally coeval population-based and unselected national cohorts. The national 90-day mortality rates after PD was in France 9.2% (68) and in Germany 9.1% after any major

pancreatic resection. (56) Both countries have a combination of public and private health care services and despite overt intentions (49, 54, 56, 68) have not yet carried out the centralization process in practice. Both Sweden and the Netherlands practice organizational models similar to the Norwegian one and report results more comparable to our findings, with a 3.5% 90-day mortality rate after PD for periampullary malignancies or pancreatic cancer (14) and 4% in-hospital mortality after PD on any indication (26), respectively.

Besides the established centralization of surgery, the explanation behind the low mortality rates and overall beneficial contemporary short-term outcomes after pancreatic surgery in Norway, as demonstrated in paper I and II, is not obvious. Intuitively, a conservatism in selection of candidates for surgery might be suspected, but there are few signs of this. By narrowing the "clinical operability" frame to exclude patients with characteristics or comorbidity signifying a perioperative high-risk profile, it is possible to select towards beneficial short-term outcomes after surgery. The inherent consequence will be lower procedure incidence rates per population. The incidence of PD per population (any indication) in Norway was 3.6 procedures per 100 000 inhabitants for 2012-2016 in comparison to the abovementioned French cohort with 3.3 procedures per 100 000 inhabitants between 2007 and 2012. The age among patients resected with PD in Norway is higher or in line with other western countries. (14, 56, 68) In paper I, more than one fifth of patients were aged 75+ at the time of the PD and were found to have an increased risk for mortality within 90 days compared to patients aged <65 years (OR 13.8 (95% CI 4.2-63.0). The extent of the surgical procedure may also influence on the achieved short-term outcomes. In line with the literature (12, 13) our data confirmed that concomitant multi-visceral resection (MVR) was an independent predictor of both relaparotomy and mortality. There are few population-based reports on the incidence of concomitant MVR that can serve as adequate comparisons to the cohort from paper I and an associated analysis of DPs in Norway (16) (5% MVR-rate for PDs and 2.9% for DPs). A publication from the US NSQIP database, using a broader definition than ours, reported a rate of 3% of concomitant MVR in PDs. (12) The majority of literature suggests that vascular resection (arterial or venous) during pancreatic resection increases both morbidity and mortality. (9, 42, 70) Others (10) have demonstrated no increased complication burden after venous resection in PD, which is in line with our findings where vascular resection during PD was not a predictor of neither relaparotomy nor mortality in paper I and found only to be a predictor of PPH grade B/C in paper II. Nevertheless, the rate of vascular resection during PD in Norway was 15% from 2012-2016, and 33.5% in PD for PDAC in

2015-2016, which is on par with or higher than comparable cohorts (70, 71) and even series from expert centres. (72) Although previously validated (73), the method used for computing the Charlson comorbidity index (CCI) in paper I relies on the quality of coded diagnoses within the NPR, which we believe to be of questionable accuracy. Hence it cannot serve as a reasonable means of external comparison of the comorbidity burden to other cohorts. In sum, considering the population-based incidence of pancreatic resections, the relatively high age among the resected Norwegian patients and little evidence of less extensive surgery, our results do not point to a conservative resection practice as an explanatory factor to the obtained beneficial outcomes and the low short-term mortality in particular.

5.2 National trends in treatment and survival from pancreatic ductal adenocarcinoma (paper III)

The literature on treatment of PDAC from the past decades suggest that survival is improving. Novel strategies for expanding the resectability criteria have been taken up into routine practice including techniques for vascular resection and downstaging of locally advanced disease by preoperative CTx. The introduction of FOLFIRINOX in both palliative and adjuvant settings have demonstrated marked survival benefits in comparison to traditional regimens. Of note, these claims of progress are based on highly selected cohorts of patients who either fit the strict inclusion criteria for surgical or drug trials, or who have access to treatment at expert surgical centres. Even in western countries the vast majority of patients with PDAC do not fit into either category due to either high age or other frailty, advanced tumour stage at time of diagnosis or organizational or economic concerns.

Whether the abovementioned progress is visible when assessing population-based cohorts, including every single patient and health care provider, is less explored. In paper III we analysed trends in treatment practice and long-term survival in a national 15-year cohort of all patients diagnoses with PDAC. The studied time frame covered the centralization of decision on resectability and provision of surgery to oncological HPB units, and establishment of a national onco-surgical clinical society and official practice guidelines. We found that the proportion of patients diagnosed with PDAC who *did not* receive tumour-directed therapy did decrease over time. Yet, by 2018 still four in ten Norwegian patients diagnosed with PDAC did not reach neither surgery nor CTx. To no surprise, their survival was practically unaffected over time with a sparse net rise in median survival of about one week from 2010-

2013 to 2014-2018. As stated by many others, biology is still king of this disease and novel preventive strategies, or tools of treatment are sorely needed to obtain a substantial increase in long-term survival from PDAC. Although technical surgical progress as mini-invasive PD and complex vascular resections should be applauded, it is probably not herein the solution to the steadily grim survival prospects from PDAC lies.

From early to late study period the odds of reaching resection increased by 54% and peaked with a resection rate (all ages and stages) for 2018 of 18.9%. An increasing proportion of resected patients were provided with perioperative CTx, and in particular neoadjuvant CTx (four-fold increase in late vs early part of the study period that included data on CTx). Simultaneously, in spite of more and older patients being resected and a steep rise in neoadjuvant CTx signifying at least borderline resectability, the median survival after resection increased by 9 months up to a median OS of 25.1 months (IQR 12.4 – 49.2) and a 3-year OS of 36.4 % (IQR 32.2-40.6) for 2014-2018. The reasonable morbidity burden and steadily low mortality following pancreatic resections in Norway have probably over time allowed skewing the "clinical operability" frame to a situation that nowadays include older and more frail patients with early-stage disease, and thereby contributed to increased resection rates. The increased provision of neoadjuvant CTx, which is advocated and practiced only for borderline or selected patients with locally advanced tumours or in experimental protocols, is contraindicative of a general stage drift towards more early-stage disease and cannot serve as a reasonable explanation to the observed increased survival among resected patients. However, we know that the quality of radiology is improving, and that high-resolution and contrast-enhanced CT, MRI and ultrasound aids in detecting occult metastatic disease especially in the liver (74, 75) and also can provide an enhanced evaluation of tumour resectability. The introduction of mandatory HPB-unit decision on resectability also includes centralization of the radiological assessments. One might hypothesize that this has led to a superior selection of surgical candidates, with more actual non-metastatic (within the limits of radiological assessment) patients being resected, and that this contributes positively to the survival in the resected cohort. I.e., while the surgical and oncological progress seemingly have led to *more* (and older) patients reaching resection, the radiological improvement may have aided in selecting the *right* patients for surgery. The increased use of perioperative CTx regimens might also influence positively to the increased survival post resection.

For the non-resected the rate of provision of palliative CTx increased, especially among the elderly, whereas their survival remained largely unchanged over time. As FOLFIRINOX was

not used in a broad scale in Norway before 2018, the potential survival gain from this regimen is not assessable within this study cohort. Importantly, the observed, though modest, increase over time in proportion of patients who reach resection have likely left the cohort of *non-resected* with a converse drift towards a heavier disease burden and/or comorbidity. Although we documented that a larger proportion of these embark on palliative CTx regimens, the potential benefit in survival from the available CTx regimens might be camouflaged by an increased cancer load and other frailty in the cohort left without resection. The data on CTx from NPR did not allow analysing the completeness of the planned cycles.

A similar and principally coeval nationwide evaluation from the Netherlands showed parallel trends to our results (21), with increased resection rates, use of CTx and 3-year survival. In comparison, with reservation regarding analytical dissimilarities between the two datasets, the Norwegian PDAC cohort apparently received more treatment (in particular palliative CTx for the non-resected), and at the end of the study periods the median and 3-year OS after resection were higher in Norway (18.1 months (IQR 17.1-19.1) vs 25.1 months (IQR 12.4 – 49.2) and 25.4% (IQR 23.3 – 27.8) vs 36.4% (IQR 32.2 - 40.6), respectively). Another nationwide cohort from Sweden, a country practicing an organizational model very similar to the Norwegian one, reported resection rates and a 3-year OS for PDAC almost identical to our results, but a lower 5-year OS (6% vs 17.5%). (14) The same reservation regarding analytical dissimilarities applies to this comparison. Noteworthy, the population-based median survivals post resection reported from Sweden (14) and Norway (present paper III, submitted) are in line with what was obtained in the ESPAC trial (76) (all included patients assigned to adjuvant CTx and with a low protocol violation rate), but inferior to single institution series from expert centres. (77)

Will a PDAC population *as a whole* benefit from higher resection rates or increased survival when treated in a PD service practicing a high rate of concomitant vascular resection? We showed in paper I and II that the uptake population of the sole high-volume centre more often had a simultaneous vascular resection during their PD procedure, with only a negligible cross-regional patient drift that was adjusted for in the analyses. In paper III we could not find evidence of neither corresponding higher resection rates nor superior survival after resection in the regional population treated at the high-volume unit. Importantly, regarding the regional survival, the analyses were only performed on the complete study cohort from 2004-2018 as a whole, and vascular resection techniques did not gain territory in everyday practice until the latter half of this period. Herein lies a possibility of overlooking an effect that would have

been identifiable in subgroup analyses of more granular time periods. Concerning the threshold for simultaneous vascular resection for pancreatic malignancies, no comprehensive criteria are included in the national guidelines. While the present studies (paper I and II) suggest that vascular resection can be practised without an excessive overall complication burden, most evidence support the contrary (42, 78). In light of the exceedingly high R1-rate in PDAC specimens in general and for specimens from PDs with vascular resection in particular (currently in Norway four in five are R1, see supplementary results paper II and other publications (79, 80)), a certain sobriety should probably be maintained towards the long-term survival benefit from this additional procedure, beyond allowing resection at all, as an R0-resection is rarely achieved anyway. (79)

5.3 On regional disparities and the level of centralization (Paper I-III)

It is a declared goal from the national health care governments that access to, and quality of the health care provided should be equal for all citizens and non-dependent of one's region of residency. There exists no valid argument to defend large discrepancies in population-based procedure incidence of pancreatic resection, resection rates for PDAC or key surgical outcome metrics between the four administrative regional health regions (RHAs) in Norway. Reassuringly, we found little evidence of such. In spite of a large span in regional population density and size, as well as unit surgical case volume, the present studies do not point out any major discrepancies in the amount or quality of provided health care services in terms of pancreatic resection or PDAC treatment across the nation.

In paper I we demonstrated practically identical regional procedure incidences of PD between the four regional populations and equal 90-day mortality rates, pointing to a uniformity in practice of evaluation of resectability and selection for surgery. A difference in rate of relaparotomy was however identified. Interestingly, the region reporting the highest relaparotomy rate experienced no deaths within 90 days after PD, and contrariwise the region with the lowest relaparotomy rate saw the highest 90-day mortality rate. This might be a coincidence and a result of small absolute figures but spurs a speculation of different approaches to non-major anastomotic leaks. Although a relaparotomy is never a desired event it may be necessary, and a timely reintervention for intraabdominal complications is key to maintain low FTR-rates. Both paper I and II confirmed that patients treated in one of the regions (RHA South-East, surgical unit OUS Rikshospitalet) were more likely to have a

concomitant vascular resection with their PD. This held true after adjusting for interregional patient drift and is hence likely a consequence not of patient case mix but of diverging attitudes between the surgical milieus towards the theoretical survival benefits from this adjunctive procedure (beyond allowing for pancreatic resection at all). Of equal importance, with limitations due to small absolute figures and limited data on extent of the reconstruction, having a concomitant vascular resection at a medium/low volume unit was not associated with an increased risk of postoperative adverse events in comparison to the high-volume unit.

For PDAC, no regional differences were found in key outcomes such as resection rates and survival. However, there was some variation in provision of both palliative CTx for the unresected as well as neoadjuvant CTx for patients who later underwent tumour resection. These discrepancies are probably not attributed to patient factors, but rather reflect intended diverging practice patterns between the regions and this deserves further attention. On the other hand, the observed variations in use of neoadjuvant CTx were not reflected in regional survival rates after resection. Also, in light of the modest survival gain and impact on quality of life, embarking on palliative CTx for PDAC should not be considered an unnuanced quality metric. It is somewhat a question of "temperament" or perspective of life in both patients and health care providers, and despite national guidelines it remains susceptible to individual judgement.

To recapitulate, the amount and quality of pancreatic resections and PDAC treatment is alike across all regions in Norway, and the unselected national short-term outcomes from surgery and PDAC survival is beneficial in comparison to other national cohorts and established benchmarks, and in some respects even in line with expert center series. So, has the current organizational model struck the balance between geographical/organizational concerns and postoperative outcomes for pancreatic resections, or would the national outcomes improve further by practicing an even higher degree of centralization? In light of the strict adherence within the surgical society and the current beneficial nationwide results obtained, the centralization process of pancreatic surgery in Norway has so far been a success.

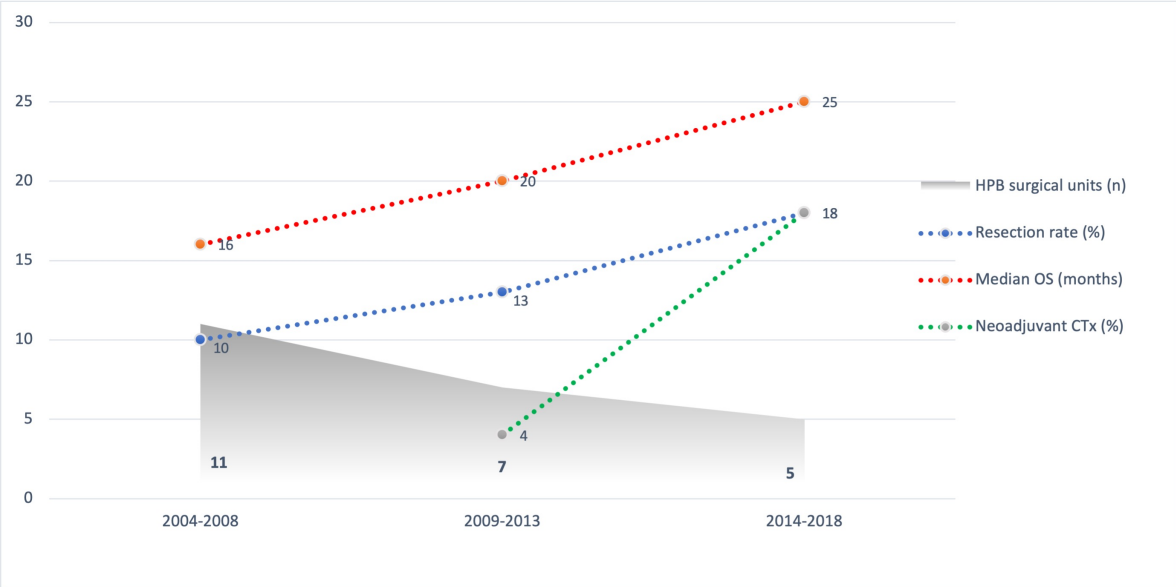
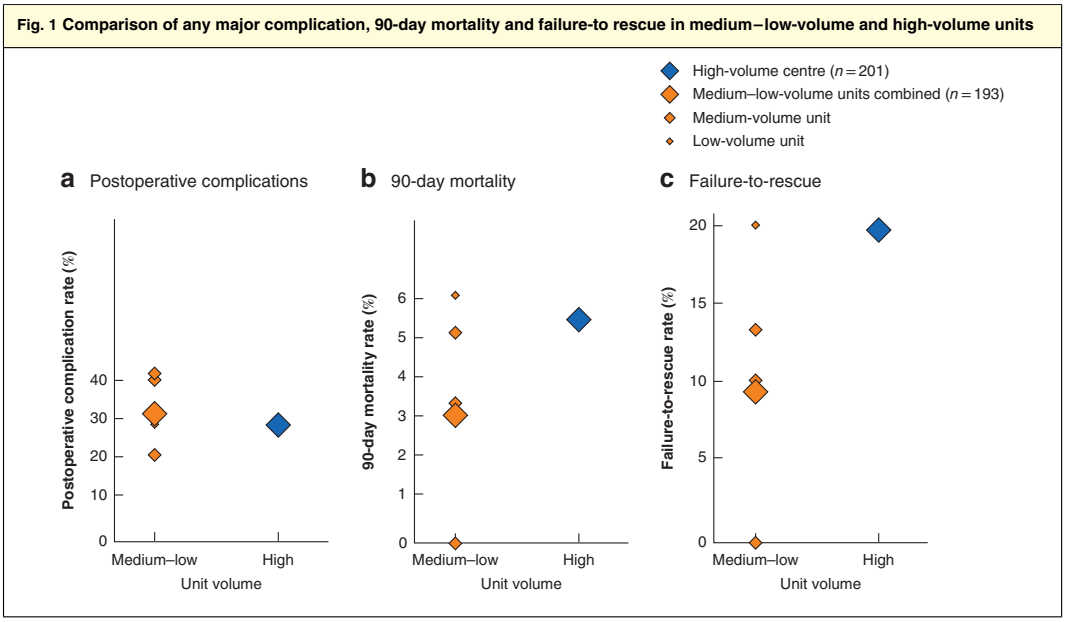


Figure 18: Concurrent development during the study period for HPB service organization and core treatment metrics and outcomes for resectable pancreatic adenocarcinoma (from paper III)



a Postoperative complications (Accordion grade 3–6); **b** 90-day mortality; **c** failure-to-rescue. Multivariable analysis with high volume as reference (odds ratio (OR) 1·00): **a** OR 1·28 (95 per cent c.i. 0·82 to 1·98), $P = 0·274$; **b** OR 0·24 (0·07 to 0·82), $P = 0·023$; **c** OR 0·49 (0·26 to 1·63), $P = 0·243$.

Figure 19: Accordion grade 3 or higher, 90-day mortality and failure-to-rescue after pancreatoduodenectomy 2015-2016, stratified for high-volume vs medium/low volume units (from paper II).

In paper II we used 40 PDs a year as a cut-off for high volume and showed that the four medium-low volume units combined overall did not score inferior to the single high-volume unit in terms of key short-term outcomes from PD. (Figure 12). The rate of POPF was indeed lower in the high-volume unit and their index length-of-stay (before transfer) was shorter, but

their 90-day mortality and FTR-rate was higher (mark, the latter not statistically significant). Subacute complications to pancreatic surgery may well be discovered after primary discharge from the operating unit and considering vast geographical distances the proximity to and post-discharge auspice from the operating facility may be of importance to secure timely treatment or surgical reintervention. Of note, various definitions of a high-volume pancreatic surgical unit exist, and according to the more commonly applied one (>20 PDs a year) 95.9% of patients in this two-year cohort (paper II) were treated in a high-volume facility.

Moreover, sound arguments *against* an unlimited centralization do exist. Among reasonings towards a practice of moderate centralization are administrative organizational issues and patient concerns beyond short-term surgical outcomes. (81) These especially hold true for sparsely inhabited and vast geographical areas. (82) Also, in contradiction to the perceived linear relationship between unit volume and short-term outcomes, some studies have failed to prove additional gain between medium and high-volume units (29, 46, 83), which suggest that a ceiling effect in terms of unit volume may be reached. Surgeon experience with other anatomical related surgery is also proposed to compensate for a lower volume of pancreatic resections (84), and all the five Norwegian HPB units have an annual volume of other major HPB and upper GI resections of more than four-fold their PD volume.

With some reservation regarding the sole low-volume unit, our data do not suggest that a further centralization of pancreatic surgery in Norway will benefit the outcomes to a degree that would outscore the negative side effects on organizational and administrative concerns.

5.4 Follow-up beyond index stay and the value of complete population-based cohorts including "warts and all"

In paper I we showed that after PD one in five relaparotomies occurred outside the index unit, and that two in five deaths within 90 days occurred in a transfer hospital, in a primary health care facility or at home. An increase of 25% in relaparotomy rate and almost 70% in mortality rate from that of the operating (index) unit is substantial. As previously shown by others (85), the 90-day mortality was double that of the 30-day mortality rate. From another publication by our group we learned that by including transfer and readmission stays the length-of-stay after PD in Norway increased by more than 50% as opposed to the commonly reported index unit length-of-stay. (30) Caution must be taken when comparing diverging results for e.g.,

mortality or complications as long as the entities themselves are not alike or well-defined, and the completeness and quality of follow-up data diverge or are not reported on.

Scientific publications even in high impact journals, especially single institution resection series, sometimes scarcely touch upon or even lack any description of the data quality of follow-up after surgery. Many include only in-hospital data for both morbidity and mortality (86), which we know from paper I, and as discussed above, can lead to an underestimation of the real-life complication burden. A single-unit resectional cohort of major pancreatic resections from Heidelberg, Germany assessed institutional data only and reported a)n in-hospital mortality rate of 3.8%. (86) In comparison, a complete, nationwide audit of all major pancreatic resections in Germany using national administrative data only, published an in-hospital mortality ranging from 6 to 13% between high and low volume units. (56) The dissimilarity this exemplifies can in theory reflect different completeness, quality and methods for data gathering, as discussed in the previous section, but also the difference between results obtained in a selected patients series treated in a high-volume expert centre contra a whole nation, including all patients, surgeons and hospitals; warts and all. As long as the data quality and completeness in follow-up are not alike or not even accounted for, we cannot decide. These two seemingly alike outcome variables ("in-hospital mortality") should be compared with much caution, or not compared at all. Both hold scientific value but most likely reflect different clinical situations and populations, and the foundation of the data sets are not akin.

Case series publications on the surgical feasibility of, and the survival obtained in patients undergoing extensive radical surgery for PDAC (i.e., arterial resection) often overlook the selection bias inherent to such selected patient series. Not only do these patients have access to surgery at expert centres, but from being found fit enough for any treatment (chemotherapy with high toxicity *and* extensive surgery) and having a tumour biology responsive to CTx, they are biological winners to begin with. By performing intention-to-treat analyses where all patients with advanced tumour stage considered for, or at least those started with, downstaging/neoadjuvant CTx are included in the denominator, it will be possible to display a more correct image of the survival benefits from these extensive and high-morbidity surgical procedures. (87) Randomized controlled trials on long-term survival after CTx alone vs CTx with surgical resection for locally advanced pancreatic cancer are lacking.

5.5 Methodological considerations

Observational studies of large cohorts like the three studies included in this thesis, and in particular when using administrative data, hold some inherent weaknesses and strengths. First, the variables that are available are often crude and other core variables that may influence on the studied outcome may be lacking. This stands in contrast to intervention studies allowing for real-time gathering of predefined and pinpointed granular clinical information. Another weakness is the necessity of making *assumptions* when defining variables without any reasonable cost-effective means of validation. For example, the definitions of relaparotomy and readmission used in paper I cannot exclude rare intercurrent and unrelated conditions, but we assumed that the vast majority of events were related to the index surgery. Likewise, the incidence of vascular reconstruction in paper I and provision and setting of provided chemotherapy in paper III relies on the accuracy of procedure coding, which we assumed was high. Core variables for both paper I and paper III were crosschecked against EPJ for minor subsets of patients and the algorithms were found to be of good quality. The uncertainty linked to the assumptions behind the definitions are also less important when comparing data across regions, or over time.

Among the obvious strengths of large-scale studies of unselected patient cohorts is the ability to provide a picture of the real-life practice. However, while cohort studies may benchmark outcome metrics and describe the effect measures of the assessed predictors, they cannot provide evidence of more than significant associations and only suggest or hypothesize causal effects. In contrast to randomized controlled trials, observational studies comparing patient groups are prone to unrecognized baseline biases that are not accounted for in the analyses or interpretations. This may be minimized by the sole use of inclusion and outcome metrics that are unequivocally defined, such as pancreatic resection and death.

In paper II, we did statistical comparisons of several rare events (specific postoperative complications, mortality and failure-to-rescue) in two like-sized but somewhat small cohorts. Herein lies the possibility of making a type II error by rejecting a true finding that simply did not reach statistical significance due to small sample sizes. In retrospect it is obvious that an expansion to a larger patient cohort would have strengthened the value of this study substantially.

6 CONCLUSIONS AND CLINICAL IMPLICATIONS

- The contemporary national short-term outcomes from pancreatoduodenectomy in Norway are beneficial in comparison to other national cohorts and in line with established clinical benchmarks for a standard patient population.

- Overall, the short-term outcomes after pancreatoduodenectomy obtained in the four medium-low volume hospitals were not inferior to the high-volume unit. We found no difference in survival for pancreatic ductal adenocarcinoma between the regional populations. The degree of centralization as practiced today seems balanced.

- A rising proportion of patients with pancreatic ductal adenocarcinoma reach resection and the median and 3-year survival is increasing.

- Although decreasing over time, the proportion of patients diagnosed with pancreatic ductal adenocarcinoma who do not reach any tumour-directed therapy is still close to 40% and this should be a focus of attention and further research.

7 FUTURE FOCUS OF RESEARCH AND PERSPECTIVES

Among the noteworthy findings during the work in this thesis was the high proportion (close to four in ten) of PDAC patients who by present time, and in a health care system with few economical limitations, still do not reach any form of tumour-directed treatment. Even though they numerically outscore the resected cohort by a two-fold, they receive a bare minimum of resources from the surgical and oncological clinicians and are left in the care of community health care resources and occasionally an ambulant palliative care team. Another aspect worthy of attention is the increasing proportion of non-resected PDAC patients aged 75 or older who commence on palliative CTx (currently in Norway about 30%). In light of the limited prospects of survival gain from this treatment, its innate implications on quality of life especially for the elderly and frail and including often long travel distances to treatment facilities, it is entirely possible that we provide "too much" treatment to this group. Further studies focusing on the balance between quality-of-life against the limited survival gain from such treatment would be useful. In 2020 a dedicated quality registry for patients with pancreatic ductal adenocarcinoma was funded as a sub-registry of the Cancer Registry of Norway and will hopefully provide data that will allow for further future investigations into these matters.

The modern long-term survival prospects from PDAC are uniquely poor in comparison to most other cancers. Refining the presently available treatment options, exemplified by more extensive surgery, debates on the optimal graft material for vascular reconstructions, centralization of surgery to high-volume units and novel but toxic chemotherapy (as FOLFIRINOX) will highly likely not turn the table. A large proportion of PDAC patients are nevertheless not in the position to receive either. Research resources should probably instead be directed towards the emerging initiatives exploring novel biomarkers to identify premalignant disease, genetic tumour profiling, and immune-based and targeted therapy.

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PAPER I

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ORIGINAL ARTICLE

The effect of centralization on short term outcomes of pancreatoduodenectomy in a universal health care system

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Abstract

Background: Centralization of pancreatic resections is advocated due to a volume-outcome association. Pancreatic surgery is in Norway currently performed only in five teaching hospitals. The aim was to describe the short-term outcomes after pancreatoduodenectomy (PD) within the current organizational model and to assess for regional disparities.

Methods: All patients who underwent PD in Norway between 2012 and 2016 were identified. Mortality (90 days) and relaparotomy (30 days) were assessed for predictors including demographic data and multi-visceral or vascular resection. Aggregated length-of-stay and national and regional incidences of the procedure were also analysed.

Results: A total of 930 patients underwent PD during the study period. In-hospital mortality occurred in 20 patients (2%) and 34 patients (4%) died within 90 days. Male gender, age, multi-visceral resection and relaparotomy were independent predictors of 90-day mortality. Some 131 patients (14%) had a relaparotomy, with male gender and multi-visceral resection as independent predictors. There was no difference between regions in procedure incidence or 90-day mortality. There was a disparity within the regions in the use of vascular resection ($p = 0.021$).

Conclusion: The short-term outcomes after PD in Norway are acceptable and the 90-day mortality rate is low. The outcomes may reflect centralization of pancreatic surgery.

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Introduction

PD is considered a complex surgical procedure and associated with significant postoperative morbidity and mortality, even in modern series.[1–3] The long-term survival from surgery is very limited for adenocarcinoma,[4] and uncertain for cystic neoplasms,[5] and quality-of-life following PD can be substantially impaired.[6,7] Therefore, it is important that short term outcomes are monitored and optimized if such surgery is to be justified. Single-centre series from expert centres have consistently reported improved outcomes and low mortality figures for PD.[8,9] Notably, high-volume, tertiary centres may not reflect the *average* centre or surgeon performance, and nationwide audits have shown inferior outcomes compared to expert centre reports.[1,3] Only complete, unselected cohorts including all patients and all surgeons, with follow-up extending beyond in-hospital data can provide a correct picture of the real-life outcomes. Several analyses of volume–outcome relationships indicate inferior outcomes after PD performed in low-volume centres, and different cut-off values for the minimum annual case load have been proposed.[1,3,10–12] Internationally there is currently a

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large variation in organizational models and degree of centralization of pancreatic surgery.[1,3,10,13] Recent nation-wide reports from both France and Germany propose that superior short-term outcomes may be achieved with further centralization of major pancreatic resections.[1,3] However, most papers exclusively report outcomes from health systems with non-centralized pancreatic surgery, and studies of outcomes achieved after centralization are lacking. Pancreatic surgery in Norway is strictly centralized to a limited number of university hospitals. Neither the incidence, nor the short-term outcomes of PD in Norway have previously been evaluated and the impact of vascular and multivisceral resection remain unknown.

The aim of this study was to describe the short-term outcomes after PD in a complete, contemporary national cohort within the current organizational model, and secondly to assess for relevant regional disparities in practice or outcomes.

Methods

Ethics

Centre for Clinical Documentation and Analysis (SKDE) in Tromsø holds a licence from the national Data Protection Authority allowing access to and analysis of NPR-data, and additional research committee application to evaluate these data was waved according to Norwegian law.

Study design

This study was an observational cohort study of all patients who underwent PD in Norway during the five-year period of January 2012 to December 2016. Resections for both malignant and benign disease were included. The study was conducted and reported in accordance with the STROBE guidelines for observational studies.[14]

Health care in Norway

Norway has a universal, public health care system covering some 5.3 million inhabitants. The nation is organized into four independent regional health authorities (RHAs). All hepato-pancreato-biliary (HPB) surgery is performed within five public university hospitals; one HPB unit in each of the four RHAs, with the exception of RHA West which has two collaborating units. All five pancreatic centres have access to advanced intervention radiology, expertise on vascular surgery and multidisciplinary intensive care wards. There is no official national referral unit for complex pancreatic resections. However, as Oslo University Hospital Rikshospitalet carries the national transplantation unit, selected patients with complex surgical challenges may be referred there for a second opinion. HPB-surgeons from all five units are represented in the HPB-section of the Norwegian Gastrointestinal Cancer Group, and involved in the continuous development of national guidelines,[15] and study protocols (e.g. the NorPACT study).[16] The national guidelines,[15] describe a mandatory preoperative work-up and include definitions of resectability and of locally advanced disease. Neither operative technique nor perioperative care is strictly standardized.

Data gathering

All hospitals in Norway report data to the National Patient Registry (NPR) for reimbursement, including details on diagnoses, procedures and hospital stays. Data are identifiable on patient-level by a unique personal identification number that enables tracking of treatment episodes across time and centres. The NPR was searched for NCSP-codes (NOMESCO Classification of Surgical Procedures),[17] denoting PD (JLC 30 or JLC 31) and the following unique patients journeys were tracked. Both the patients residing RHA and treating RHA were registered to allow for recording of interregional patient drift and referral practices. Charlson comorbidity index (CCI) was computed using a previously validated search algorithm for ICD-10 codes in NPR.[18–20] Data from NPR are not sufficiently detailed to address complications specific to the procedure, and hence rates of postoperative fistula or haemorrhage were not possible to identify.

Definitions

Mortality was assessed at 90 days as a primary outcome indicator, but all deaths following index surgery were recorded up to 180 days. Relaparotomy was defined by a search for a fixed set of NCSP procedure codes denoting any laparotomy registered within 30 days from index surgery during index or any subsequent stay, performed in any Norwegian hospital.[21] Length-of-Stay was evaluated as aggregated length-of-Stay (a-LoS), defined as cumulative number of days after index procedure spent in any hospital within 30 days, including transfers and readmissions to own or other institutions. Readmission was defined as any additional stay in any hospital (direct transfers not included) within 30 days after index procedure. Details concerning the search algorithms and definitions used for the above-mentioned outcomes are described previously.[21] Vascular resection during index procedure was defined by the presence of NCSP codes denoting any major arterial or venous resection. Codes denoting only vascular suture, ligature or simple angioplasty were not classified as vascular resection.[22] Multi-visceral resection was defined by the presence of NCSP codes denoting simultaneous formal resection of either stomach (extending beyond resection of distal stomach as performed with non-pylorus preserving PD), small bowel or colon during index procedure. Wedge resections of either of these organs were not included. Use of procedure codes from the National Patient Registry has previously been validated, and are considered as complete and robust data.[23] The incidence of the procedure was defined as number of patients in whom PD was performed per 100 000 registered inhabitants, nationally and in the four respective geographical regions (regardless of where the resection was performed) after adjusting for age- and gender composition in the regional populations.

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Statistical analysis

Crude outcome measures are reported in rates (per cent), means with standard deviation (SD) or medians with interquartile range (IQR). Annual procedure-volume per region is reported in means. Univariate analysis was done using chi-square or Fischer exact test. The impact of age, gender, Charlson comorbidity index, vascular resection, multi-visceral resection and RHA where treated were analysed for mortality and relaparotomy using models for binary logistic multivariable regression analysis (step-wise, backwards selection model). For mortality the impact from relaparotomy was also included. The results are presented as odds ratios (OR) with 95 per cent confidence intervals (CI) and p-values. Regional incidences of the procedure were adjusted for age and gender composition by direct method, and reported as number of resections per 100 000 inhabitants per year. Regional use of multi-visceral resection and vascular resection and incidence of PD were compared by Chi-square-test and significant results were adjusted for multiple testing (Bonferroni method). Regional results in a-LoS were compared using Kruskal–Wallis test. All p-values were two-tailed and a $p < 0.050$ considered statistical significant. The software used for all statistical analysis was SAS 9.4 (SAS Institute, Cary NC).

Results

A total of 930 patients underwent PD during the study period. Follow-up on patient-level was 100% complete. There was a gradual increase in number of procedures performed per year from 144 procedures in 2012 to 187 procedures in 2016 ($p = 0.006$), with a peak of 227 procedures in 2015.

Demographics

There were 497 (53%) male patients. The median age was 68 years (IQR 60–73) with 357 patients (38%) aged <65 years, 379 patients (41%) aged between 65 and 74 years and 194 patients (21%) were 75 years or older. Some 689 patients (74%) had a primary pancreatic malignancy. The Charlson comorbidity index was <2 for 238 patients (26%), 2 for 453 patients (49%) and 239 (26%) had an index score of >2. A vascular resection or multi-visceral resection was performed simultaneously to the PD in 139 (15%) and 44 (5%) patients, respectively.

Mortality

The 90-day mortality rate was 34 out of 930 (4%). Mortality rates up to 180 days from surgery are presented in Fig. 1. Stratified 90-day mortality rates are presented in Table 1 and Fig. 2. The over-all mortality rate was significantly higher among men, and the largest gender difference was observed for patients aged 75 or older ($p = 0.019$). Vascular resection did not result in a raised mortality rate, whereas multi-visceral resection did. Patients who experienced a relaparotomy had a more than five-fold higher mortality rate. Male gender, higher age, and relaparotomy remained independent significant predictors of 90-day mortality after multivariable analysis (Table 1).

Relaparotomy

The number of patients who had a relaparotomy within 30 days from index surgery performed in any hospital and for any indication, was 131 (14%). Median number of days from index surgery to (first) relaparotomy was 4 (IQR 1–9). Stratified relaparotomy rates and results from multivariable analysis are

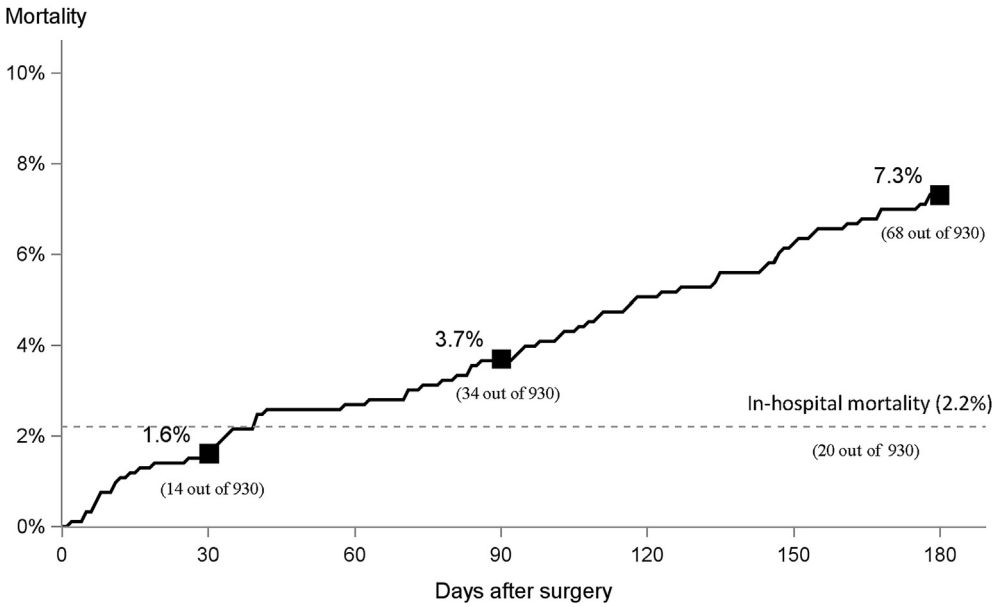

Figure 1 Over-all postoperative mortality for 2012–2016 (n = 930). Rates at 30, 90 and 180 days after surgery are marked with black boxes and in-hospital mortality is marked in dotted grey horizontal line. The 90-day mortality rate is substantially higher than the in-hospital mortality

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Table 1 Predictors of 90 day mortality

	Number of patients n (%)	Mortality within 90 days n (%)	Univariable odds ratio (95% CI)	Multivariable odds ratio[a] (95% CI)
All	930	34 (4)		
Age group			**p = 0.003**	**p < 0.001**
<65	357 (38)	3 (1)	ref	ref
65–74	379 (41)	17 (5)	5.5 (1.8–23.9)	5.0 (1.6–22.0)
≥75	194 (21)	14 (7)	9.2 (2.9–40.2)	13.8 (4.2–63.0)
Gender			**p = 0.003**	**p = 0.007**
all females	434 (47)	7 (2)	ref	ref
<65	159 (37)	0 (0)		
65–74	171 (40)	4 (2)		
≥75	97 (23)	3 (3)		
all males	496 (53)	27 (6)	3.5 (1.6–8.8)	3.4 (1.5–9.0)
<65	195 (42)	3 (2)		
65–74	191 (41)	13 (6)		
≥75	83 (18)	11 (12)		
Vascular resection			p = 0.968	p = 0.625
no	791 (85)	29 (4)	ref	ref
yes	139 (15)	5 (4)	0.98 (0.3–2.4)	1.3 (0.4–3.5)
Multi-visceral resection			**p = 0.009**	p = 0.054
no	886 (95)	29 (3)	ref	ref
yes	44 (5)	5 (11)	3.8 (1.3–9.6)	3.4 (0.9–9.0)
Relaparotomy			**p < 0.001**	**p < 0.001**
no	799 (86)	18 (2)	ref	ref
yes	131 (14)	16 (12)	6.0 (3.0–12.2)	5.9 (2.7–12.8)
Treating RHA			p = 0.816	p = 0.561
South-East	513 (55)	18 (4)	ref	ref
West	197 (21)	9 (5)	1.3 (0.6–3.0)	0.7 (0.3–1.8)
Central	136 (15)	7 (5)	1.5 (0.6–3.6)	1.7 (0.6–4.2)
North	84 (9)	0 (0)	0 (0–0.4)	0 (0–0.4)

[a] Predictors included in multivariable logistic regression model: Age, gender, vascular resection, multi-visceral resection, Charlson Comorbidity Index, regional health authority (RHA) and relaparotomy.

presented in Table 2. Males experienced a relaparotomy more often than women, and the largest gender contrast was observed between patients aged 75 years or older, where 19 out of 94 men (20%) had a relaparotomy compared to 7 out of 100 women (7%), p = 0.007.

For 24 out of 131 (18%) patients who had a relaparotomy, this was performed outside the index hospital. The 90-day mortality among these was 2 out of 24 as opposed to 14 out of 107 (13%) among those who had their relaparotomy at the index unit, p = 0.521. When relaparotomies performed outside the index hospital were included, the overall relaparotomy rate increased from 12% (in-hospital) to 14%.

Aggregated length-of-stay and readmissions

Including all transfer- and readmission stays within 30 days raised the conventional LoS from median 9 days (IQR 7–15) to an a-LoS of median 14 days (IQR 10–21). The median a-LoS was 13 days (IQR 10–20), 15 days (IQR 11–21) and 14.5 days (IQR 11–22) for patients aged <65, 65–74 and ≥75 years respectively, with no significant difference between the age groups, p = 0.122. There was no gender difference with median a-LoS for women of 14 days (IQR 10–19) compared to 14.5 days (IQR 10–22) for men, p = 0.112. A-LoS for patients who underwent a relaparotomy was 29 days (IQR 21–30) compared to 13 days (IQR 10–18), p < 0.001. The median a-LoS differed significantly between the RHAs with 13 days (IQR 9–19) in RHA South-East, 17 days (IQR 12–23) in RHA West, 16 days (IQR 12–22) in RHA Central and 15 days (IQR 10–21) in RHA North, p < 0.001. The proportion of patients who were still admitted 30 days after index surgery was 65 out of 131 (50%) among those who had a relaparotomy in contrast to 41 out of 791 (5%) among those without. The 30-day readmission rate was 115 out of 930 (12%).

Regional activity and outcomes

Procedure demographics stratified by treating RHA are presented in Table 3, and mortality and relaparotomy rates for each region are shown in Tables 1 and 2, respectively. Mean annual case load in each region varied largely. There was a significant regional difference in use of vascular resection, but the rate of performed multi-visceral resection did not differ between the RHAs. In multivariable analysis there was no significant difference between regions in rate of 90-day mortality, but there was a significant spread in relaparotomy rate.

Population-based use of PD and vascular- and multi-visceral resection

The national incidence of PD was 3.6 per 100 000 inhabitants per year for the complete five-year cohort, and increasing during the study period, see Fig. 3. Table 3 presents regional population-based incidences of the procedure and use of vascular and multi-visceral resection. During the five year study period only eighteen patients (2%) had their procedure performed outside their residing RHA, the majority being referrals to RHA South-East. When the eighteen guest patients were grouped within their geographical home RHA population, there was no difference in age- and gender adjusted incidence of PD between the populations of the four geographic regions. The rate of multi-visceral resection offered to the inhabitants of the four geographical regions did not differ. However, there was a significant difference in use of vascular resection between the regions, where patients living in RHA South-East who had a PD had a more than two-fold rate

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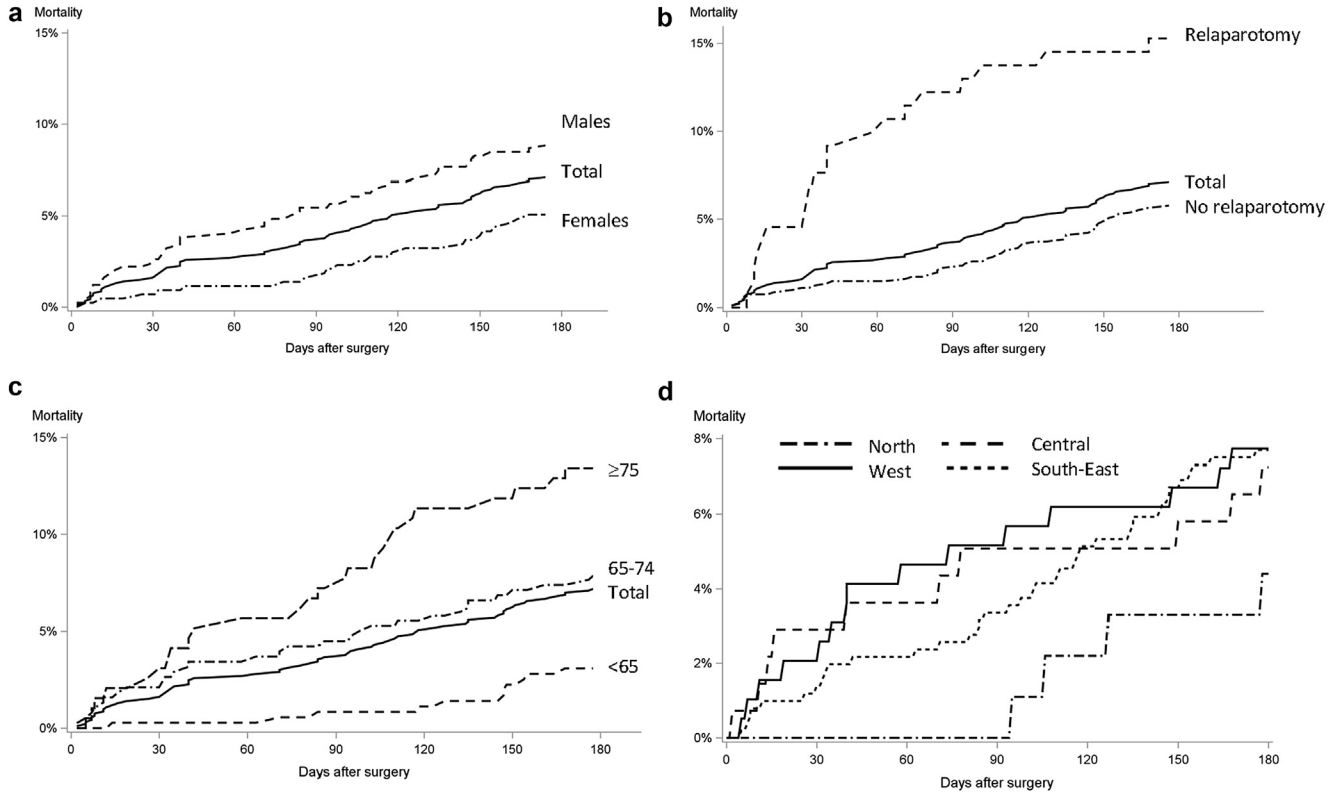

Figure 2 a–d: Stratified mortality rates the first 180 days after surgery. Stratification by gender, age group, relaparotomy and Regional Health Authority where treated. Gender, age group and having a relaparotomy were all significant independent predictors of mortality in multivariable analysis, whereas Regional Health Authority was not (Table 1)

of concomitant vascular resection when compared to the inhabitants of RHA West.

Discussion

This complete and unselected national cohort demonstrates low mortality rates across all regions. There was no disparity in use of PD between the regional populations despite a variation in procedure volume. The contemporary results and practice of PD in Norway are reassuring when compared to other recent population-based reports,[1,3,11] and the mortality rate is even in line with publications from expert centres.[8,9] The follow-up in this study includes treatment given in any transfer or re-admitting hospital and deaths occurring outside hospitals. The follow-up extends in time beyond the more commonly evaluated in-hospital data. This further supports the finding of an acceptable level of short-term complications following PD achieved within the Norwegian model of centralized pancreatic surgery, as practiced today.

An evaluation of the short-term mortality after pancreatic resections in France from 2007 to 2012 reported a 90-day mortality rate after PD of 9% and described a national practice with a low degree of centralization of pancreatic surgery.[1] Likewise, a recent German national cohort with volume-outcome analysis reported an in-hospital mortality after major pancreatic resection ranging from 13% in very-low volume centres to 6% in very high volume centres.[3] Authors of both publications advocated a further centralization of pancreatic surgery. An analysis from the National Cancer Database covering 70% of pancreatic resections in U.S. from 2007 to 2010 reported a 90-day mortality rate from major pancreatic resections of more than 8%, and also confirms a volume–outcome relationship.[24] In the other range of the scale, the Dutch Pancreatic Study group reported an in-hospital mortality rate of 4% for 2014-2015[2], and an evaluation of all PDs performed in Japan between 2007 and 2010 revealed an in-hospital mortality rate of 3% with a significant volume-outcome correlation.[11] In comparison, the in-hospital mortality rate in this complete, national cohort was even lower (2%), and also included deaths occurring during transfer stays.

The reasons for the low mortality rates in this cohort, besides centralization of pancreatic surgery, are not obvious. A restrictive practice in selection of candidates for surgery could in theory influence on the beneficial outcomes in Norway, but there are few, if any, indications of this. Concomitant multi-visceral resection has previously been shown to increase morbidity and mortality after PD,[25,26] and was a significant predictor of both relaparotomy and mortality also in the current study. Few other population-based studies reports rate of concomitant multi-

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Table 2 Predictors of relaparotomy within 30 days after index surgery

	Number of patients n (%)	Relaparotomy n (%)	Univariable odds ratio (95% CI)	Multivariable odds ratio[a] (95% CI)
All	930	131 (14)		
Age group			p = 0.674	p = 0.689
<65	357 (38)	47 (13)	ref	ref
65–74	379 (41)	58 (15)	1.2 (0.8–1.8)	1.2 (0.8–1.8)
≥75	194 (21)	26 (13)	1.0 (0.6–1.7)	1.1 (0.6–1.8)
Gender			**p = 0.001**	**p = 0.001**
female	434 (47)	44 (10)	ref	ref
male	496 (53)	87 (18)	1.9 (1.3–2.8)	1.9 (1.3–2.9)
Vascular resection			p = 0.523	p = 0.304
no	791 (85)	109 (14)	ref	ref
yes	139 (15)	22 (16)	1.2 (0.7–1.9)	1.3 (0.8–2.2)
Multi-visceral resection			**p = 0.001**	**p < 0.001**
no	886 (95)	117 (13)	ref	ref
yes	44 (5)	14 (32)	3.1 (1.5–5.8)	3.2 (1.6–6.3)
Treating RHA			p = 0.055	**p = 0.034**
South-East	513 (55)	66 (13)	ref	ref
West	197 (21)	35 (18)	1.5 (0.9–2.3)	1.5 (0.9–2.4)
Central	136 (15)	13 (10)	0.7 (0.4–1.3)	0.7 (0.4–1.3)
North	84 (9)	17 (20)	1.7 (1.0–3.1)	1.8 (1.0–3.3)

[a] Predictors included in multivariable logistic regression model: Age, gender, vascular resection, multi-visceral resection, regional health authority (RHA) and Charlson Comorbidity Index.

visceral resection. The rate of multi-visceral resection in this cohort (5%) was higher than in an analysis of more than 9900 PDs from the US NSQIP database reporting a rate of 3%, despite that this study included resections of kidneys and adrenal glands in their definition.[25] The reported rates of multi-visceral resections performed in referral centres treating highly selected patients with advanced disease are much higher,[26] but these cannot serve as a direct comparison to a national, unselected cohort. Vascular resection did not significantly predict mortality or relaparotomy in the current cohort, despite of minor resections (e.g. simple venoraphy) being omitted in the definition. This is in contrast to both a recent meta-analysis on the benefits of synchronous vein resection,[27] and a recent report from a Norwegian high-volume centre,[28] where both studies found

Table 3 Volume and practice stratified by regional health authority

	National	RHA South-East	RHA West	RHA Central	RHA North	Statistical comparison
***Treating* regional health authority**						
Procedure volume:						
Number of resections, (mean, annual)	930 (186)	513 (103)	197 (39)	136 (27)	84 (17)	n.a.
Vascular resection, n (%)	139 (15)	102 (20)	14 (7)	15 (11)	8 (10)	**p < 0.001**
Multi-visceral resection, n (%)	44 (5)	25 (5)	10 (5)	7 (5)	2 (3)	p = 0.782
***Residing* regional health authority**[a]						
Procedure incidence (per 10^5 inhabitants per year)	3.6	3.6	3.6	3.8	3.4	p = 0.929
Vascular resection, n (%)	139 (15)	97 (19)	15 (8)	16 (12)	11 (12)	**p = 0.021**
Multi-visceral resection, n (%)	44 (5)	23 (5)	10 (5)	7 (5)	4 (4)	p = 0.968

P-values lower than 0.05 are shown in bold.
[a] All patients are grouped within their geographical home RHA (eighteen patients were operated outside their residing region). The regional incidences are adjusted for age and gender composition in the regional populations.

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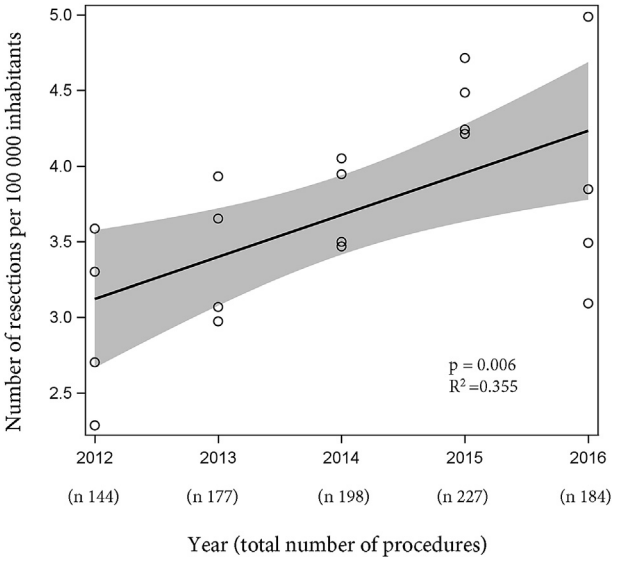

Figure 3 Trend in national incidence of pancreatoduodenectomy 2012–2016. Resections per 100,000 inhabitants per year is shown in continuous black line, with 95% confidence interval in grey. Regional incidences (marked with "o") are adjusted for age- and gender differences in the respective populations. There was a significant increase in the national incidence of pancreatoduodenectomy during the study period, p = 0.006

higher complication rates after synchronous venous resection. Few reports of rate of vascular resection in a complete population exist to date. Two recent analyses from the US NSQIP database used a similar definition and methodology to the current study, and reported equal,[22] or lower,[29] rates of vascular resections. Considering that the current cohort also included resections for benign or premalignant disease, both multi-visceral and vascular resections were quite frequent. More than one fifth of patients in this study were 75 years or older when they had their PD performed. The proportion of elderly patients in the current study is in line with or higher than other population-based reports,[1–3] which rules out selection by age as a potential bias. Reports evaluating over-all procedure incidence in complete populations are scarce. The annual incidence of PD in France between 2007 and 2012 was lower than in the current cohort (5.8 pancreatic resections per 100 000 inhabitants of which 57% patients underwent PD equals 3.3 patients undergoing PD per 100,000 inhabitants).[1] A recent international evaluation of national resection rates for patients with malignancy of the pancreas places Norway in the lower end of the scale,[30] but there are methodological issues pertaining to the way non-operated cancer patients were identified and it is the authors' belief the results should be interpreted with caution. Over-all, there are no good data to suggest that the contemporary PD incidence rate or use of vascular resection or multi-visceral resection techniques in the Norwegian population is lower than what is reported from other comparable cohorts. Hence, there would not appear to be any evidence that the favourable short-term outcomes in Norway are due to a conservative selection practice for patients to undergo PD.

Male gender was found to a predictor of both relaparotomy (two-fold increase) and mortality (more than three-fold increase). While several earlier reports have also reported males to have higher rates of postoperative complications,[31–33] and mortality,[24] after PD, robust explanations have not been presented. The excess morbidity and mortality risk for especially older males should nevertheless be recognized and taken into account in the process of selecting candidates for surgery.

There was a large variation in mean annual PD case load between the four regions, ranging from a mean of 17 (low-to-medium volume centre) to 103 procedures (high-volume centre). Despite the volume variation, all regions had low mortality rates with no significant disparities. There was, however, a significant variation in rate of relaparotomy. The region with the highest relaparotomy rate experienced no deaths within 90 days, and conversely the region with the fewest relaparotomies had the highest 90-day mortality rate of all regions (5%). This may reflect different in-centre approaches to postoperative adverse advents (e.g. attitude towards relaparotomy for moderate anastomotic leaks).[34,35] The observed a-LoS in the four regions did not correspond to the regional pattern in mortality or relaparotomy rates, and may be due to different perioperative care regimens and use of enhanced-recovery principles.[36] Nationwide practice is likely to be become more uniform in the years to come due to a common perioperative registry and increased cooperation, see below.

The observed equity in population based incidence of resection between the independent regions points to a uniform practice in terms of evaluation of resectability and selection for surgery. As the regional organizational model neutralizes differences in patient or tumour factors, the variation between regions in rate of vascular resection is probably due to divergent in-centre practice and attitudes towards the theoretical gains from vascular resection.

Centralization of HPB surgery in Norway started almost two decades ago. Still, in a sparsely inhabited country with large geographical distances, the size of the catchment areas of the HPB-units varies between 0.5 million and 2.5 million inhabitants. This study was a comparison of outcomes between a low number of single centres with variable annual case load and the performance of each centre may interfere regardless of volume. The regional results should therefore be used with caution in a debate of volume-outcome causality. However, the well-documented volume–outcome relationship for postoperative mortality was not confirmed in the current study. All five HPB-centres are academic teaching hospitals, which has been shown to provide superior outcomes after pancreatic surgery.[37,38] Notably, all the centres perform all other types of HPB surgery (except transplants) for their respective populations, and

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the total annual volume of major HPB resections per centre is at least four-fold that of their PD volume. The uniformity in practice and outcomes may also be influenced by a close academic cooperation in national resource groups. The discrepancy in rate of vascular resection offered to the regional populations will be further examined in prospectively gathered data that will be available from the Norwegian gastrointestinal resection registry (NoRGast) in the near future.[39] NoRGast will also provide more detailed data on patient comorbidity and re-interventions.

There are some limitations to this study that deserve to be mentioned. When addressing administrative data, the data quality depends on accuracy and completeness of coding. Diagnostic codes are susceptible to differences in coding practice, and therefore these were only used for CCI. The diagnostic codes used for pancreatic malignancy might also have been used for only suspected malignancy, and malignancy was therefore not analysed as a predictor of outcomes. Secondly, data for patient weight and height or granular information on the disease (e.g. histological type, size, TNM stage) or the pancreatic gland (e.g. texture, duct diameter) were not available for further risk stratification. Procedure codes denoting vascular resection were also crude, and did not allow for further grouping into arterial or venous resection. The lack in precision in coding for cause of relaparotomy did not allow for further exploration of the cause for reoperation. Data for radiological or endoscopic re-intervention for anastomotic leaks or bleeding were not available through the NPR.

One of the strengths of this study is the design that allows capture of complete patient journeys within the NPR. This extended follow-up, which included post-discharge data, substantially raised both mortality and relaparotomy rates as well as length-of-stay compared to in-hospital data alone. A significant proportion of deaths within 90 days occurred after primary discharge to home (from either index or transfer receiving unit), and almost one in five relaparotomies were done outside the index hospital. The length-of-stay increased more than fifty per cent when transfer stays and readmissions were included.[21]

When comparing the results from this cohort to other studies reporting solely in-hospital data these disparities in follow-up should be taken into account.

Disclaimer

Data from the Norwegian Patient Register has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Register is intended nor should be inferred.

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Conflicts of interest

None declared.

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PAPER II

Original article

BJS Open Open Access

Centralizing a national pancreatoduodenectomy service: striking the right balance

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Background: **Centralization of pancreatic surgery is currently called for owing to superior outcomes in higher-volume centres. Conversely, organizational and patient concerns speak for a moderation in centralization. Consensus on the optimal balance has not yet been reached. This observational study presents a volume–outcome analysis of a complete national cohort in a health system with long-standing centralization.**

Methods: **Data for all pancreatoduodenectomies in Norway in 2015 and 2016 were identified through a national quality registry and completed through electronic patient journals. Hospitals were dichotomized (high-volume (40 or more procedures/year) or medium–low-volume).**

Results: **Some 394 procedures were performed (201 in high-volume and 193 in medium–low-volume units). Major postoperative complications occurred in 125 patients (31·7 per cent). A clinically relevant postoperative pancreatic fistula occurred in 66 patients (16·8 per cent). Some 17 patients (4·3 per cent) died within 90 days, and the failure-to-rescue rate was 13·6 per cent (17 of 125 patients). In multivariable comparison with the high-volume centre, medium–low-volume units had similar overall complication rates, lower 90-day mortality (odds ratio 0·24, 95 per cent c.i. 0·07 to 0·82) and no tendency for a higher failure-to-rescue rate.**

Conclusion: **Centralization beyond medium volume will probably not improve on 90-day mortality or failure-to-rescue rates after pancreatoduodenectomy.**

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Introduction

A volume–outcome effect on mortality after pancreatoduodenectomy (PD) has been demonstrated repeatedly, with lower short-term mortality rates in high-volume centres[1–5]. The failure to prevent death in patients suffering from major postoperative morbidity (failure-to-rescue (FTR)) has been proposed as a mechanism behind the volume–outcome effect on mortality that is more important than the occurrence of postoperative complications[6,7]. Timely recognition and optimally sequenced treatment of complications after PD is a complex matter and requires a multidisciplinary approach[8,9]. A higher unit caseload necessarily reflects greater experience in the handling of complications. Academic teaching status of the treating hospital has also been proposed to influence FTR[7].

Covering a population of just 5·3 million inhabitants over a vast geographical area, pancreatic surgery in Norway has been restricted to only five hepatopancreatobiliary (HPB) units for more than a decade[10–12]. All are academic teaching hospitals with 24-h interventional radiology and endoscopy services available, and highly resourced ICUs. Although centralized, catchment areas vary substantially between

the units, from high- to medium-volume combined HPB and upper gastrointestinal units covering 0·5–1·0 million inhabitants each, to a single very high-volume dedicated HPB unit serving an uptake population of more than 2·6 million. The government funds the universal healthcare coverage, and there are no private institutions for resectional surgery.

A previous nationwide analysis[11] using administrative data documented a low contemporary 90-day mortality rate after PD in Norway, and negligible cross-regional patient drift. There were similar regional population-based incidences of the procedure and equal mortality rates among patients treated at the respective units, but variation in relaparotomy rates and use of vascular reconstruction was demonstrated[11]. A significant proportion of relaparotomies within 30 days (1 in 5) and deaths within 90 days (4 in 10) occurred after first discharge from hospital[11]. The centralization of surgery within a single-payer health system relies on patients being transferred back to general hospitals for parts of the postoperative phase and follow-up. Although still under the auspices of the operating (index) unit, these transfers reduce the patients' organizational and geographical proximity to the index surgical unit in the subacute recovery phase, where postoperative adverse events may still develop. This is an inherent consequence of centralization in all but the most densely populated countries.

This study assessed overall and procedure-specific outcomes in a complete national cohort of patients undergoing PD, and investigated for a volume–outcome effect in a country with longstanding centralization but a large variation in unit volume. The aim of the analysis was to examine a potential benefit from further centralization.

Methods

All patients registered in the Norwegian Registry for Gastrointestinal and HPB Surgery (NoRGast) have given written informed consent[13]. In addition, the project was granted allowance from the Norwegian Directorate of Health for additional access to electronic patient journal (EPJ) data. Approval of alignment of the multicentre data was given by the Data Protection Authority of Norway (reference number 17/33320-2).

Study design

This was an observational cohort study of complete nationwide data in a universal health coverage system. The STROBE guidelines[14] for reporting observational studies were adhered to, where applicable.

Accrual of data

NoRGast is a procedure-driven national quality registry with prospective gathering of core data for case mix and postoperative complications[13]. All five Norwegian HPB units contribute data to NoRGast. Data for all registered pancreatoduodenectomies performed between January 2015 and December 2016 were retrieved from the NoRGast database. Data from NoRGast were cross-checked at a patient level by performing an identical search for the same procedure codes in the local EPJs for each HPB unit, and data for missing patients were included. In addition, procedure-specific variables and complications not available in NoRGast (preoperative biliary drainage, duration of procedure, intraoperative haemorrhage, grade of postoperative pancreatic fistula (POPF), grade of postpancreatectomy haemorrhage (PPH) and histopathology data) were registered manually from the EPJ for all patients by a local HPB surgeon. Three of the four healthcare regions have a shared regional EPJ, allowing direct access to patient data for any transfer stays or readmissions outside the index unit; this ensures data quality for complications occurring after the index stay. In the one region where regional EPJ access was not available, discharge reports from transfer stays or readmissions were collected and evaluated. Date of death is available automatically in the EPJ via a direct coupling with the National Registry of Norway (Folkeregisteret).

Definitions

Co-morbidity

Severe cardiac disease (New York Heart Association class above 2 or severe arrhythmia) and pulmonary disease (forced expiratory volume in 1 s less than 50 per cent and/or vital capacity below 60 per cent) were defined in accordance with the modified form of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) system[15]. Diabetes mellitus was defined by preoperative use of any antidiabetic medication, administered either subcutaneously or orally.

Procedure details and postoperative complications

Any complication graded as 3 or above in the Accordion system[16] was considered a major complication. Briefly, Accordion grade 3 refers to percutaneous or endoscopic reintervention with or without general anaesthesia; Accordion 4 refers to relaparotomy or single-organ failure (SOF); Accordion 5 refers to relaparotomy and SOF, or multiple organ failure alone; and Accordion 6 refers to death. POPF[17], PPH[18] and venous resection[19] were scored in accordance with proposed guidelines from the International Study Group of Pancreatic Surgery.

Table 1 Patient demographics

	Total (n = 394)	High volume (n = 201)	Medium–low volume (n = 193)	Unit range#	P††
Age (years)*	67·5 (60–73)	68 (61·5–74)	67 (58–72)	66–67·5	0·364‡‡
BMI (kg/m^2)*	24·5 (21·9–26·9)	24·1 (21·7–26·7)	24·6 (22·0–27·1)	24·2–25·5	0·271‡‡
Albumin (g/l)*	40·0 (36·0–43·0)	40·0 (35·5–43·0)	40·0 (36·0–43·0)	36·0–43·0	0·584‡‡
Weight loss†	n = 315	n = 149	n = 166		
Any	231 (73·3)	117 (78·5)	114 (68·7)	(62·5–71·7)	0·064
> 5%	185 (58·7)	101 (67·8)	84 (50·6)		
> 10%	90 (28·6)	62 (41·6)	28 (16·9)		
Diabetes mellitus‡	68 (17·3)	36 (17·9)	32 (16·6)	(6·3–22·6)	0·829
Neoadjuvant chemotherapy	22 (5·6)	11 (5·5)	11 (5·7)	(0–12·9)	0·922
Severe pulmonary disease§	15 (3·8)	3 (1·5)	12 (6·2)	(0–18·8)	0·014
Severe cardiac disease¶	23 (5·8)	11 (5·5)	12 (6·2)	(0–11·3)	0·753
Preoperative drainage	150 (38·1)	88 (43·8)	62 (32·1)	(25·8–37·1)	0·017
ERCP	134 (34·0)	88 (43·8)	46 (23·8)	(17·8–31·3)	
PTC	16 (4·1)	0 (0)	16 (8·3)	(0–15·6)	
ECOG score					0·083
0	288 (73·1)	157 (78·1)	131 (67·9)	(62·2–71·4)	
1	95 (24·1)	39 (19·4)	56 (29·0)	(25·7–37·5)	
> 1	11 (2·8)	5 (2·5)	6 (3·1)	(0–4·4)	
ASA grade					0·487
I–II	216 (55·0)	106 (53·0)	110 (57·0)	(46·8–75·0)	
≥ III	177 (45·0)	94 (47·0)	83 (43·0)	(25·0–53·2)	
Histopathology (extracted specimens)	n = 393	n = 201	n = 192**		0·072
Any malignancy	324 (82·4)	173 (86·1)	151 (78·6)	(67·1–93·8)	
PDAC	161 (41·0)	83 (41·3)	78 (40·6)		
Common bile duct cancer	58 (14·8)	36 (17·9)	22 (11·5)		
Duodenal cancer	36 (9·2)	25 (12·4)	11 (5·7)		
Ampullary/papillary cancer	30 (7·6)	9 (4·5)	21 (10·9)		
Other	39 (9·9)	20 (10·0)	19 (9·9)		
Any benign disease	69 (17·6)	28 (13·9)	41 (21·4)	(6·3–32·9)	
IPMN without adenocarcinoma	25 (6·4)	5 (2·5)	20 (10·4)		
Pancreatitis	11 (2·8)	9 (4·5)	2 (1·0)		
Other	33 (8·4)	14 (7·0)	19 (9·9)		

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Patient-reported weight loss in 6 months before surgery. ‡Defined by use of any antidiabetic medication, administered subcutaneously or orally. §Forced expiratory volume in 1 s less than 50 per cent or vital capacity less than 60 per cent. ¶New York Heart Association class 3–4 or arrhythmia requiring mechanical support. #Within medium–low volume category. **One patient died during surgery. ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography; ECOG, Eastern Co-operative Oncology Group; PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm. ††χ^2 test (high *versus* medium–low volume, dichotomized), except ‡‡Kruskal–Wallis test.

Failure-to-rescue

FTR was defined as any death within 90 days in patients with any major complication (Accordion grade 3 or above). Deaths with no recorded preceding major complication were included, in accordance with the original[20] and recommended[21] definition.

Hospital volume

Hospital units were dichotomized according to procedure volume, and defined as high volume for 40 or more procedures per year (1 unit) or as medium–low volume for fewer than 40 procedures per year (4 units). Others[3,5,6,22–24] have suggested this cut-off, and it allowed for meaningful comparison within the Norwegian setting. Length of stay was defined conventionally as the number of postoperative nights spent at the hospital after the procedure, omitting any transfer and/or readmission stays.

Primary outcomes

The primary outcomes of the study were incidence and type of major postoperative complications, overall 90-day

Table 2 Procedure characteristics

	Total (n = 394)	High volume (n = 201)	Medium–low volume (n = 193)	Unit range‡ (16–70)	P§
Estimated blood loss (ml) (n = 352)*	350 (700–1200)	200 (100–500)	490 (300–490)	300–1165	<0·001¶
Duration of surgery (min) (n = 383)*	322 (262–386)	341 (283–418)	300 (240–300)	240–431	<0·001¶
Without VR	308·5 (252–359)	323 (274–373)	300 (240–343)	240–354	<0·001¶
With VR	420 (355–454)	420 (369–454)	393 (337–465)	240–431	0·415¶
Classical PD†	206 (52·3)	60 (29·9)	146 (75·6)	(12·5–100)	<0·001
Peroperative blood transfusion	76 of 391 (19·4)	38 of 198 (19·2)	38 (19·7)	(10·0–35·5)	0·901
Any vascular resection	70 (17·8)	50 (24·9)	20 (10·4)	(5·7–17·7)	<0·001

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Classical pancreatoduodenectomy (PD) (Whipple procedure); all others were pylorus-preserving pancreatoduodenectomies. ‡Within medium–low volume group; the lowest case volume was 16 and the highest was 70. VR, vascular resection. §χ^2 test (high *versus* medium–low volume, dichotomized), except ¶Kruskal–Wallis test.

Table 3 Short-term outcomes

	Total (n = 394)	High volume (n = 201)	Medium–low volume (n = 193)	Unit range†	P‡
Any major complication	125 (31·7)	57 (28·4)	68 (35·2)	(31·2–42·2)	0·143
Accordion 3	46 (11·7)	21 (10·4)	25 (13·0)		0·436¶
Accordion 4	51 (12·9)	22 (10·9)	29 (15·0)		
Accordion 5	15 (3·8)	6 (3·0)	9 (4·7)		
Accordion 6 (30-day mortality)	10 (2·5)	8 (4·0)	5 (2·6)		
POPF	n = 393	n = 201	n = 192		
None or biochemical leak	327 (83·2)	180 (89·6)	147 (76·6)	(71·4–83·6)	
Grade B	41 (10·4)	13 (6·5)	28 (14·6)	(6·3–17·1)	<0·001#
Grade C	25 (6·4)	8 (4·0)	17 (8·9)	(3·3–12·5)	
PPH	n = 393	n = 201	n = 192		
None or grade A	349 (88·8)	177 (88·1)	172 (89·6)	(85·7–100)	0·741#
Grade B	22 (5·6)	10 (5·0)	12 (6·3)	(0–8·2)	
Grade C	22 (5·6)	14 (7·0)	8 (4·2)	(0–7·1)	
Relaparotomy	71 (18·1)	32 (15·9)	39 (20·3)	(8·2–28·6)	0·258
Haemorrhage	23 (5·9)	13 (6·5)	10 (5·2)		0·026¶
Pancreatic leak	17 (4·3)	5 (2·5)	12 (6·3)		
Biliary leak	8 (2·0)	1 (0·5)	7 (3·6)		
Wound dehiscence	4 (1·0)	4 (2·0)	0 (0)		
Other	19 (4·8)	9 (4·5)	10 (5·2)		
90-day mortality	17 (4·3)	11 (5·5)	6 (3·1)	(0–6·3)	0·323
Length of stay at index hospital (days) (n = 391)*	9 (7–16)	7 (6–11)	14 (9–21)	7–18	<0·001§
No major complication*	8 (6–13)	7 (6–8)	13 (8–15)	7–15	<0·001§
Any major complication*	18 (11–29)	14 (10–30)	21 (13–28)	13–24	0·129§

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.) with median unit range. †Within medium–low volume group. POPF, postoperative pancreatic fistula; PPH, postpancreatectomy haemorrhage. ‡χ^2 test (high *versus* median–low volume, dichotomized), except §Kruskal–Wallis test; ¶univariable χ^2 comparison of Accordion grade or reason for relaparotomy distribution; #univariable χ^2 comparison of presence of clinically relevant POPF or PPH grade B–C.

mortality, and 90-day mortality among patients with major postoperative complications (FTR).

Statistical analysis

Crude demographics, procedure details, major complications and histopathology data are presented as median (i.q.r.) values, or as absolute numbers with percentages. Crude comparison across volume categories was done using the χ^2 test for categorical variables and the Kruskal–Wallis (non-parametric) test for continuous variables.

Multivariable logistic regression analyses of the postoperative outcomes any major complication, relaparotomy,

Table 4 Multivariable analysis of predictors of postoperative complications*

	Odds ratios				
	Any major complication	Relaparotomy	90-day mortality	CR POPF	PPH grade B or C
Age (years)					
< 65	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)
65–74	1·19 (0·73, 1·91)	1·20 (0·68, 2·51)	4·63 (0·87, 24·22)	1·24 (0·69, 2·25)	0·95 (0·47, 1·92)
≥ 75	0·60 (0·31, 1·16)	0·57 (0·24, 1·34)	7·66 (1·14, 51·44)	0·62 (0·26, 1·49)	0·58 (0·20, 1·69)
P	0·112	0·212	0·098	0·271	0·594
Sex					
F	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)
M	1·21 (0·78, 1·89)	1·23 (0·72, 2·09)	3·69 (1·05, 13·02)	0·97 (0·51, 1·85)	1·77 (0·91, 3·45)
P	0·393	0·452	0·042	0·934	0·092
Indication					
Any malignancy	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)
Benign disease	1·75 (0·92, 2·98)	0·82 (0·39, 1·87)	0·41 (0·04, 3·84)	1·96 (0·94, 3·44)	0·86 (0·33, 2·27)
P	0·087	0·602	0·438	0·098	0·767
Vascular resection					
No	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)
Yes	1·30 (0·72, 2·34)	1·62 (0·84, 2·81)	1·33 (0·30, 5·81)	0·72 (0·30, 1·71)	4·27 (2·20, 8·28)
P	0·381	0·149	0·709	0·456	< 0·001
Preoperative biliary drainage					
No	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)
Yes	0·72 (0·45, 1·16)	0·79 (0·52, 1·64)	0·21 (0·05, 0·86)	0·50 (0·27, 0·92)	0·57 (0·28, 1·15)
P	0·178	0·781	0·030	0·025	0·117
Peroperative RBC transfusion					
No	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)
Yes	1·68 (0·99, 2·85)	2·12 (1·17, 3·82)	1·78 (0·49, 6·33)	1·28 (0·64, 2·57)	1·68 (0·81, 3·49)
P	0·053	0·013	0·376	0·481	0·164
Relaparotomy					
No			1·00 (reference)		
Yes			20·72 (6·03, 71·18)		
P			< 0·001		
Unit volume					
High	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)
Medium–low	1·28 (0·82, 1·98)	1·38 (0·82, 2·33)	0·24 (0·07, 0·82)	2·52 (1·43, 4·43)	1·10 (0·55, 2·19)
P	0·274	0·229	0·023	0·001	0·782

Values in parentheses are 95 per cent confidence intervals. *Other potential predictors evaluated in the multivariable logistic regression analysis, but not found to be significant predictors were BMI, weight loss greater than 10 per cent, albumin, diabetes mellitus, neoadjuvant chemotherapy, severe pulmonary disease, severe cardiac disease, Eastern Co-operative Oncology Group class above zero, ASA grade above II, duration of surgery and type of procedure. CR POPF, clinically relevant postoperative pancreatic fistula; PPH, postpancreatectomy haemorrhage; RBC, red blood cell.

clinically relevant (CR) POPF and PPH grade B/C were performed using a backwards stepwise approach, where centre volume was included as a predictor. A similar multivariable model was built to evaluate the predictors of death after major postoperative complications (FTR). The regression models were assessed for significant interactions and collinearity. Effect measures from multivariable analyses are reported as odds ratios (ORs) with 95 per cent confidence intervals. Level of significance for all final analyses was set to $P < 0{\cdot}050$.

IBM SPSS Statistics version 26.0 (IBM, Armonk New York, USA) was used for all statistical analyses.

Results

A total of 394 patients in Norway had a PD (all open resections) during the 2-year study period. Mean annual procedure volume ranged from 101 PDs in the high-volume centre to 35, 31, 23 and eight PDs respectively (median 27) in the four medium–low-volume

Table 5 Characteristics of 17 patients who died within 90 days of surgery

Sex	Age (years)	Unit	Co-morbidity	Procedure*	Pathology	Complications	Mortality (days)	Discharged from index unit alive
M	47	MV	None	CW, vein resection type 1	PDAC (R1)	Relaparotomy, POPF grade B, PPH grade C	30	No
M	67	HV	None	PPPD	Pancreatitis	Sudden cardiac arrest POD 5	30	No
F	85	HV	None	PPPD	PDAC (R1); extensive SMA dissection	Diarrhoea, renal failure	30	Yes
M	68	HV	None	PPPD	Duodenal adenocarcinoma	Relaparotomy, PPH grade C	30	No
M	76	HV	Cardiac disease	CW	Distal CC (R1)	Relaparotomy (wound dehiscence only)	30	No
M	76	MV	DM	PPPD	Other malignancy (R0)	Relaparotomy, POPF grade C, PPH grade C	30	No
F	71	MV	None	CW	Other malignancy (R0)	Relaparotomy (wound dehiscence only)	30	No
F	65	MV	DM	CW	No specimen retrieved	Peroperative death from haemorrhage	30	No
M	69	LV	None	PPPD	Distal CC (R0)	Relaparotomy, POPF grade C	30	No
F	70	HV	None	CW, vein resection type 3	Distal CC (R0)	Relaparotomy, POPF grade C, PPH grade C	30–90	No
F	71	HV	None	PPPD, vein resection type 3	PDAC (R1)	Relaparotomy, POPF grade C	30–90	Yes
M	63	HV	None	CW, vein resection type 3	PDAC (R1)	Infection after initiating adjuvant chemotherapy	30–90	Yes
M	78	HV	Cardiac disease	CW	Duodenal adenocarcinoma (R0)	Pneumonia, prolonged DGE	30–90	Yes
M	74	HV	DM	CW	Duodenal adenocarcinoma (R1)	Relaparotomy, POPF grade C, PPH grade C	30–90	No
M	74	HV	None	PPPD	Duodenal adenocarcinoma (R1)	Relaparotomy (wound dehiscence only)	30–90	Yes
M	74	MV	None	CW	PDAC (R0)	Relaparotomy, POPF grade C, PPH grade C	30–90	No
M	71	HV	None	PPPD	Distal CC (RO)	Relaparotomy, POPF grade C	30	No

*International Study Group of Pancreatic Surgery classification of vein resection. MV, medium volume; CW, classical Whipple procedure; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy haemorrhage; HV, high volume; PPPD, pylorus-preserving pancreatoduodenectomy; POD, postoperative day; SMA, superior mesenteric artery; CC, cholangiocarcinoma; DM, diabetes mellitus; LV, low volume; DGE, delayed gastric emptying.

units. Follow-up at 30 days (complications) and 90 days (mortality) was complete (394, 100 per cent).

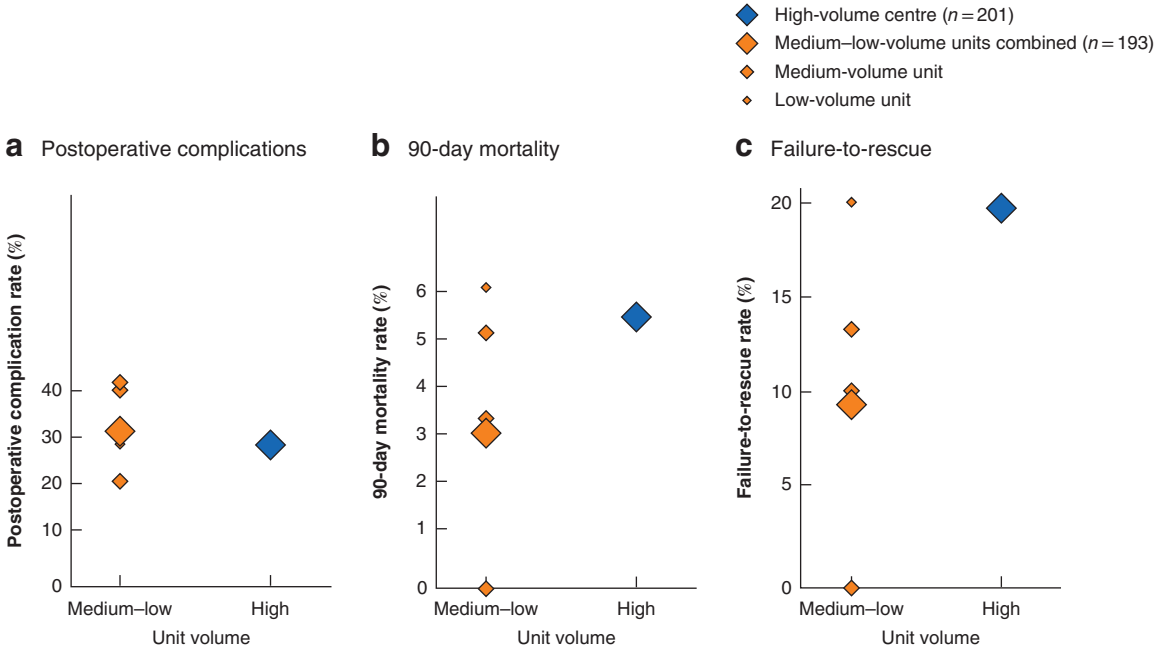
Patient demographics

Baseline patient data are presented in *Table 1*. The median age was 67·5 (i.q.r. 60–73) years, and 187 (47·5 per cent) of the patients were men. Of 393 extracted specimens (1 intraoperative death with no retrieved specimen), malignant disease was confirmed in 324 (82·4 per cent). Pancreatic ductal adenocarcinoma (PDAC) was found in 161 (49·7 per cent) of malignant specimens. Patients treated in the high-volume centre had a significantly higher rate of preoperative biliary drainage than those in the medium–low-volume units (88 of 201 (43·8 per cent) *versus* 62 of 193 (32·1 per cent) respectively; $P = 0·017$), and a lower rate of severe pulmonary disease (3 of 201 (1·5 per cent) versus 12 of 193 (6·2 per cent); $P = 0·014$). There were no other significant differences in patient characteristics between patients treated in the high- and medium–low-volume units, including no difference in proportions of specimens with malignant *versus* benign disease.

Procedure characteristics

Procedure characteristics are presented in *Table 2*. Concomitant vascular resection (vein or artery) was done in 70 (17·8 per cent) of the operations, and specifically in 54 of 161 (33·5 per cent) of resections for PDAC. Patients treated in the high-volume centre had significantly lower estimated blood loss and longer duration of surgery for all procedures

Fig. 1 Comparison of any major complication, 90-day mortality and failure-to rescue in medium–low-volume and high-volume units



a Postoperative complications (Accordion grade 3–6); **b** 90-day mortality; **c** failure-to-rescue. Multivariable analysis with high volume as reference (odds ratio (OR) 1·00): **a** OR 1·28 (95 per cent c.i. 0·82 to 1·98), $P = 0·274$; **b** OR 0·24 (0·07 to 0·82), $P = 0·023$; **c** OR 0·49 (0·26 to 1·63), $P = 0·243$.

and for PDs without concomitant vascular resection, a lower rate of classical PD (*versus* pylorus-preserving PD) and a higher rate of any vascular resection. Most arterial resections were performed in the high-volume centre (14 of 16); none of these 16 patients died within 90 days.

Postoperative complications

Crude rates of postoperative complications and univariable comparison between volume categories are presented in *Table 3*. Major complications occurred in 125 patients (31·7 per cent). Results from multivariable analyses are presented in *Table 4*. When analysing centre volume category as a predictor of postoperative outcomes, medium–low volume was a predictor of lower mortality within 90 days (OR 0·24, 95 per cent c.i. 0·07 to 0·82) but of a higher rate of CR POPF (OR 2·52, 1·43 to 4·43). Medium–low-volume unit did not independently predict occurrence of any major complication, relaparotomy or PPH grade B/C. Importantly, variation in the use of vascular resection between the volume categories was adjusted for.

Failure-to-rescue

Detailed patient data for all patients who died within 90 days are shown in *Table 5*. All but four of the patients who died within 90 days experienced at least one major surgical complication within 30 days: CR POPF (8 of 17), PPH grade B/C (6 of 17) and relaparotomy (12 of 17). The rate of FTR after any major complication was 13·6 per cent (17 of 125). The mortality rate after any relaparotomy and PPH grade B/C was 12 of 71 (17 per cent) and 7 of 44 (16 per cent). Overall mortality after CR POPF was eight of 66 (12 per cent), with separate mortality rates after POPF grade B and C of one of 41 (2 per cent) and seven of 25 (28 per cent) respectively.

The FTR rate in the high-volume centre was 11 of 57 (19 per cent), compared with six of 68 (9 per cent) in medium–low-volume units (*Fig. 1*). In multivariable analysis assessing the same predictors as for postoperative complications (*Table 4*), medium–low unit volume was not an independent predictor of higher FTR (OR 0·49, 95 per cent c.i. 0·26 to 1·63; $P = 0·243$).

Discussion

These data indicate that results similar to those in high-volume expert centres may be obtained within a single-payer PD service practising a moderate degree of centralization. The sole high-volume centre had outcomes on a par with those from internationally renowned

high-volume centres[24], but, importantly, so had the three medium-volume centres with 20–40 procedures per year. This suggests that a balance between beneficial short-term clinical outcomes and organizational concerns may have been obtained with this caseload.

The national outcomes in terms of rates of any major complication, POPF, PPH and FTR are comparable to the results and benchmarks cut-off values established from an international cohort of 23 high-volume expert centres[25]. Of note, whereas their benchmark values[25] were based on a subset of low-risk patients, excluding more than 50 per cent of their total patient cohort, the present study included 100 per cent of patients operated on across Norway during the study period (a true population-based cohort).

As shown previously[11], national 30- and 90-day mortality rates were low in comparison with contemporary cohorts from Germany, France and the USA, and in line with rates reported from Sweden and the Netherlands[1,2,26–28]. Rates of any major complication, CR POPF and PPH grade C were equal to coeval cohorts from the USA, Netherlands and Germany[22,29,30]. The relaparotomy rate in the present cohort (18·1 per cent) was similar to, or somewhat higher than, that reported from other studies[22,30,31]. Compared with similar population-based cohorts[29,30], the median operating time of 322 min was short and median estimated blood loss (350 ml) was low.

The national rate of FTR after PD of 13·6 per cent in the present cohort is in line with recent rates of 9 per cent reported from the US American College of Surgeons National Surgical Quality Improvement Program database[32] and 14·3 per cent in the Dutch Pancreatic Cancer Audit[6]. Importantly, the existing diversity in definitions of major postoperative morbidity used to calculate FTR rates hampers a direct comparison between studies. A Dutch study[33] of the management of POPF used a definition similar to that employed in the present study, and reported an in-hospital mortality rate after CR POPF of 17·8 per cent. In comparison, the present cohort demonstrated a 90-day mortality rate after CR POPF of 12 per cent.

The national mortality rate after PD achieved within the current organizational model in Norway is very low, and the improvement potential in terms of short-term mortality is not obvious. A root-cause analysis of mortality within 90 days after major pancreatectomy by Vollmer and colleagues[34] found pancreatic fistula or other surgery-related cause as the main reason for death in 13·8 and 26·6 per cent respectively, and the relaparotomy rate among the patients who died was 35·3 per cent. In contrast, the present cohort demonstrated that 14 of 17 patients who died within 90 days experienced surgical complications, and almost three in four had a relaparotomy within 30 days of the index operation. Despite the already reassuring national mortality rate, a potential for further decline may lie in a future focus on lowering the incidence, and timely and optimal handling, of surgical complications.

The medium–low-volume units had similar outcomes to those in the high-volume centre. This stands in contrast to a perceived more linear volume–outcome effect, as suggested in several earlier reports[1,5,31]. Moreover, and supporting the present observations, other reports[6,24,35] have also failed to show superior outcomes in high-volume units in comparison with medium-volume units. When assessing the literature of the volume–outcome relationship, one must be aware of the various definitions used for volume categories. Although the present analysis used 40 procedures a year as the cut-off for high volume, as have others[5,6,22], several other publications[4,36] have defined high volume as more than 20 procedures a year. According to this definition, the vast majority (95·9 per cent) of the procedures constituting the present cohort were performed in high-volume units, and hence the broadly accepted volume–outcome relationship would serve as an explanatory factor for the beneficial results. The single low-volume unit represents an outlier in the medium–low-volume category. It was included in the analyses in order to present a complete national cohort. The absolute numbers of resections performed in this unit (16 over 2 years) did not allow for statistical comparison in a separate low-volume category, but the degree of divergence in outcomes (*Fig. 1*) was deemed too low to skew the results in the medium–low-volume category combined.

The equity in key short-term outcome metrics observed across the large span in unit volume in the present cohort raises the question of whether other organizational factors can compensate for a moderate case load (20–40 procedures a year). A ceiling effect of the volume–outcome benefits may be reached within this interval, and several mechanisms may contribute to this. All five units performing pancreatic resections are academic centres, which have been shown previously to contribute more to lower mortality and FTR rates than unit caseload itself[7,37,38]. Further, all four medium–low-volume units annually perform other HPB and upper gastrointestinal resections in numbers at least fourfold of their caseload for PD. This frequent exposure to anatomically related surgery has been proposed to contribute to improved outcomes after PD, and even to compensate for a lower volume of pancreatic surgery[39]. The lower length of stay in the index unit (before transfer) in the high-volume centre, combined with higher 90-day mortality and (although statistically non-significant) almost twofold higher FTR rate, is also

of interest. It raises the question of whether follow-up in geographical and organizational vicinity to the index unit and operating surgeon, which is to a larger extent practised by the medium–low-volume units, is beneficial for optimal and timely recognition and handling of complications. Of note, the higher mortality rate in the high-volume centre found in the present cohort must be interpreted with caution, as the authors demonstrated previously[11], in a larger and partly overlapping cohort, that there was no difference in 90- and 180-day mortality between the regional health authorities in Norway.

From the patient's perspective, clinical outcomes after surgery are paramount, and outscore reasonable increases in longer travel distances to the treating hospital unit[40–42]. However, continuity in care during preoperative workup, surgery and long-term postoperative follow-up, as well as accessibility to specialized healthcare providers for contact and information, also weighs heavily[41], and is perhaps easier to obtain within an organizational model with a moderate level of centralization.

Several limitations deserve to be acknowledged. First, the present cohort is not large and, owing to a small absolute number of rare events, suffers from the risk of being underpowered. Second, as the analyses classified only one unit in the high-volume category, transferability to other high-volume units in general is weakened. Data on gland texture and duct diameter were not available, and a fistula risk score could not be included as a co-variable. However, as shown previously[11], both the identical population-based incidence of PD across the nation and the negligible regional patient drift, together with the similar proportions of malignant *versus* benign specimens found in the two unit-volume categories, make a large disparity in case mix and fistula risk score highly unlikely.

Disclosure

The authors declare no conflict of interest.

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PAPER III


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