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Whipple procedure at the University Hospital of North Norway (UNN)

A retrospective study describing clinical pathways for all patients undergoing the Whipple procedure during the time period 2008–2017 at UNN Tromsø

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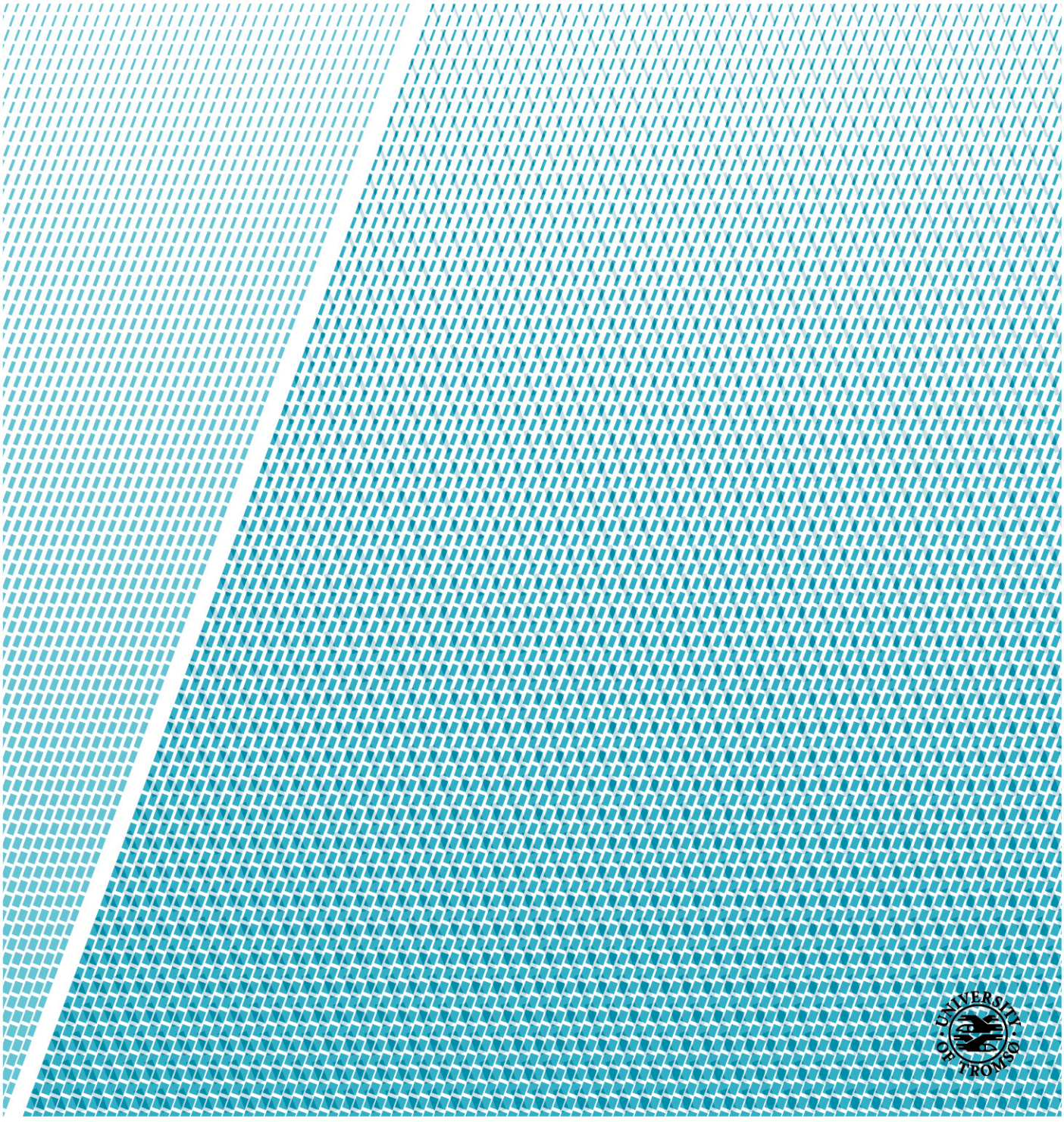

Preface

This thesis has considered different aspects of the Whipple procedures performed in northern Norway between 2008 and 2017. The purpose of the project was to investigate hard end points such as postoperative death and long-term survival. Internal audit, to which this thesis contributes, is one of several important means of quality assurance in health care.

The thesis is part of the module MED-3950 at the medical school of The Arctic University of Norway (UiT) in Tromsø. Dr. Kim Mortensen, supervisor at the Gastrointestinal Surgical Department at the University Hospital of North Norway Tromsø (associate professor, Department of Clinical Medicine), required an internal audit regarding the Whipple procedure.

A big thank you to Kim Mortensen for good help throughout the whole process and for being available for questions. He has contributed good points to the discussion and has proofread the thesis. Thanks are also due to associate professor Trond Iversen (Department of Community Medicine, UiT) for help regarding interpretation of the statistical analysis. The project had no financing.

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Abstract

Background

Pancreatic cancer is the fourth most common cause of cancer-related death in Norway. At the University Hospital of North Norway (UNN) Tromsø, the Whipple procedure is the preferred method of treating resectable pancreatic cancer. Results after surgical treatment are dependent on the volume of procedures undertaken, and UNN Tromsø is considered a low-volume hospital.

Our hypothesis is that a low-volume hospital such as UNN Tromsø can accomplish Whipple procedure with acceptable levels of complications and survival rates.

Material and methods

Outcomes after all Whipple procedures performed between 2008 and 2017 at UNN Tromsø were collected from all hospitals in northern Norway. Descriptive statistics, a chi-square test, multiple and linear regression analyses, Kaplan–Meier survival analyses, and the log-rank test were performed to describe the data material.

The Whipple procedure was performed on 156 patients: 91 (58.3%) men. Average age was 66.3 years (SD 10.2).

Results

An R0 resection margin was achieved in 112 (71.8%) of the procedures. 90 (57.7%) patients were discharged to non-index hospitals. 32 (20.5%) patients were readmitted during the first 30 postoperative days, and 36 (23.1%) patients were reoperated on.

35.0% of the patients experienced an Accordion score of 3 or higher. Twenty (12.8%) patients experienced postoperative pancreatic fistula. Delayed gastric emptying was experienced in 31 (19.9%) patients, postoperative bile leakage in 10 (6.4%) patients, and postoperative hemorrhage in 10 (6.4%) patients.

74 (47.4%) patients had pancreatic ductal adenocarcinoma (PDAC) as a postoperative histology finding. During the period of follow-up, the postoperative 90-day mortality was 4 (2.6%) patients. The 5-year overall survival was 21.6% for PDAC patients.

Conclusion

With a 90-day postoperative mortality of 2.6% for all patients and a 5-year survival for PDAC patients of 21.6%, one may conclude that the treatment results are in line with international standards for high-volume centers.

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1 Background

Pancreatic surgery is frequently characterized as having a high-risk and low-volume outcome (1). Improvements in surgical results in the treatment of pancreatic cancer are associated with hospital volume, and adjusted mortality rates differ by over 12.0% from very low-volume hospitals to very high-volume hospitals (16.3% versus 3.8%, respectively) (2). The data available describe that experienced surgeons and high-volume hospitals are necessary to lower postoperative mortality (1). Even though there is a clear correlation between hospital volume and low mortality, there is no available consensus about what constitutes a "high-volume" center. A study by Meguid et al. (3) showed that an annual resection volume of 19 procedures was the best model for a "high-volume" hospital. In a study by Nathan et al. (4), the authors describe the relationship between the hospital and surgeon effect and the volume-outcomes effect. Low hospital volume for resection of the pancreatic head was associated with high mortality. In addition, low individual surgeon volume was associated with high mortality. The effect of annual hospital pancreas resection volume did not persist after adjustments for surgeon volumes. This suggests that the effect of hospital volume is largely driven by surgeon resection volume (4).

Although some studies show that major pancreatic surgery can be performed safely at low-volume, community hospitals (5), evaluation of the centralization of pancreatic resection in the Netherlands and Finland concludes that the concentration of pancreatic surgery in higher-volume centers is likely to improve the outcome regarding mortality rates and long-term survival (6, 7). A study from Stavanger in Norway shows that an increase in annual resection from <10/year to >20/year between 1986 and 2012 led to a significant improvement in postoperative mortality (from 16.1% to 3.5%) (8).

Historically, the incidence and mortality rates for pancreatic cancer have been largely unchanged over time. Incidence rates stood between 7 and 10 per 100,000 in the period 1965–2000. In the same period, the relative survival rate of untreated pancreatic cancer remained poor, with 1-year relative survival at 5.0–10.0% and 5-year relative survival at <3.0% (9). Since 2000 a small, but important, increase in the survival rate of pancreatic cancer in Norway has been documented. Between 2005 and 2007 the 1-year survival increased to 18.0% in males and 16.0% in females, with 5-year relative survival at 5.3% in males and 2.6% in females (9). In Norway, 713 new cases of pancreatic cancer were registered in 2016, 53.0% being men. The age-standardized incidence rate in the Norwegian population is 15.3 per 100,000 men and 11.5 per 100,000 women. Pancreatic cancer is more common in the

elderly, with a median age of 72 years at diagnosis. In Norway, pancreatic cancer is the fourth most common cause of cancer-related death in both genders, with a mortality rate of 15.8 per 100,000 men and 13.2 per 100,000 women (10).

Worldwide, 441,083 people die due to pancreatic cancer every year, and it is estimated that pancreatic cancer will be the second most important cause of cancer-related death in the USA in the year 2030 (11). The cause of pancreatic cancer remains unknown, even though there have been advances in the understanding of its biology. Tobacco is the only risk factor with a causal role, with 2.5–3.6 times increased risk in contrast to non-smokers (12). These results are in harmony with findings in the Norwegian population (13). Positive family history of pancreatic cancer also increases the risk, since 10.0% of pancreatic cancer cases have a familial basis (14). Also, chronic pancreatitis and diabetes have shown increased risk in some studies. There is also a positive association between pancreatic cancer and high body mass index (BMI) (14).

Despite extended knowledge about risk factors, staging, and treatment of the early stages of pancreatic cancer in recent times, there has been minimal progress in the prevention and treatment of advanced disease (12).

1.1 Pancreatic cancer symptoms and investigation

The pancreas is placed in an abdominal region where a tumor does not necessarily give symptoms. Between 2012 and 2016, 51.0% of Norwegian men presenting with pancreatic cancer did so at an advanced stage. At the same time, only 7.0% presented with localized disease (10). 70.0–80.0% of patients had an advanced stage disease when symptoms occurred.

The symptoms of pancreatic cancer are vague. The pancreatic head is the origin of the majority of tumors, and about 70.0% of cases present with icterus. 75.0–80.0% also have pain at the time of diagnosis. Involuntary weight loss (>5.0–10.0%) is reported in 50.0–90.0% of patients, and 50.0–75.0% also report nutrition problems (11). Additionally, nausea and vomiting, bloating, dyspepsia, pruritus, and back and shoulder pain are reported as early symptoms (14). Since pancreatic cancer can obstruct the pancreatic duct, it is important to consider cancer risk in patients with acute pancreatitis and newly diagnosed diabetes (12).

A clinical investigation should determine tumor size and localization to decide favorable treatment. The best way to provide this information is by computed tomography, with different protocols to represent vascular infiltration in arteries and veins. Magnetic resonance imaging does not add crucial information about staging, but endoscopic ultrasound can be used to acquire information about smaller lesions (15). Routine blood samples have

generally non-specific results. CA-19-9 is the only biomarker with clinical benefits. CA-19-9 is not recommended to use as a screening tool but is used in monitoring and follow-up of known disease (12).

1.2 Pancreatic cancer pathology and oncology

Pancreatic ductal adenocarcinoma (PDAC) constitutes >90.0% of all pancreatic tumors and has worse survival rates than other ampullary tumors (12, 16). Tumors evolve from premalignant lesions to invasive cancer, and it is suggested that the sporadic occurrence of gene mutations is the cause in the majority of cases. About 10.0% of cases are due to inherited germ-line mutations. In familial pancreatic cancer, an inherited mutation in BRCA2 is probably the most common cause (17). One, or more, of four genetic defects is detected in almost all patients with fully established pancreatic cancer. Mutation in the KRAS2 oncogene, inactivation of the CDKN2A gene, an abnormal p53 gene, or loss of DPC4 expression are the genetic defects described, but the key mutations differ between tumors (12).

Staging of pancreatic cancer is according to the tumor, node, and metastasis (TNM) classification (Table 1). Stage T1, T2, and T3 tumors are potentially resectable, while T4 tumors are considered unresectable. If the tumor affects veins that can be reconstructed (superior mesenteric vein or portal vein), it is considered resectable (12). In addition to the TNM stage, the Union for International Cancer Control (UICC) staging system can be used to define the prognosis of survival defined by the tumor characteristics (TNM). Generally, stages I and II are considered resectable according to the UICC system, whereas stage IV is viewed as unresectable. Stage III is in most cases evaluated as unresectable, but in some special centers, patients with a stage III tumor can be treated as “borderline resectable” (1). Table 2 presents resectability, median survival, and 5-year survival dependent on UICC stage.

Chemotherapy after surgery, i.e., adjuvant chemotherapy, is meant to reduce the risk of relapsed disease after radically operated pancreatic cancer. The large European Study Group for Pancreatic Cancer-1 study showed that adjuvant chemotherapy after radical surgery resulted in better survival compared with surgery only (18). There was no difference in total survival after radical surgery between the two chemotherapy regimes: 5-FU and gemcitabine (19).

In Norway, surgery and adjuvant chemotherapy is the standard of care. The Norwegian Pancreatic Cancer Trial-1 (NorPACT-1) aims to investigate whether overall mortality can be reduced with chemotherapy before surgery, i.e., neoadjuvant chemotherapy. Neoadjuvant

chemotherapy enables early treatment of micrometastasis. This can help selection of the correct patients for surgical treatment, since rapidly progressing tumors can be excluded before major surgery is performed. This can increase the chance of receiving adjuvant chemotherapy, which is shown to significantly increase survival rates (20).

1.3 Preoperative procedures

Preoperative biliary drainage is not recommended as a routine procedure, since the procedure is associated with an increased rate of complications, for instance, infection (17). However, if cholangitis is present, there is an indication for preoperative biliary drainage. A serum bilirubin level above 250 μmol/L increases the risk of postoperative liver failure and is therefore considered by some as an indication for biliary drainage. Patients with symptoms of icterus and pruritus, together with raised serum bilirubin, are also candidates for drainage (11).

Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC), which are the two preoperative biliary drainage procedures, can both cause life-threatening complications. Hemorrhage, perforation, cholangitis, and pancreatitis can all delay, and in the worst case exclude, further surgical treatment (21, 22). Biliary drainage in patients with cholestatic icterus can lead to increased risk of complications during the procedure in addition to the postoperative course (23, 24). ERCP is usually the preferred procedure, as it has a high rate of success, with no need for an external drain and a low rate of complications compared with PTC (25).

Prophylaxis for thrombosis and appropriate antibiotics use is considered important for reduced frequency of postoperative thrombosis and infections (11). A somatostatin analog is used to suppress pancreas function. This has been shown to reduce the frequency of postoperative complications and length of hospital stay, but there is no evidence that it affects postoperative mortality (11). To help clinicians predict operative risk, the American Society of Anesthesiologists (ASA) has developed a classification system to categorize the physical status of the patient before surgery – the ASA classification. Although the ASA classification has some well-known limitations, it is extensively used to describe the overall preoperative condition of the patients (26). Table 3 shows which variables are considered for patients in ASA classes 1–6.

1.4 Surgical procedures

Pancreatoduodenectomy (PD) is the established surgical procedure for resection of tumors originating in the pancreatic head and neck. PD implies the removal of the pancreatic head and uncinate process, the duodenum and first segment of the jejunum, the common bile duct and gallbladder, and sometimes the pylorus and/or antrum of the stomach (27). This necessitates the reconstruction of 1) the pancreatic remnant to the small bowel or stomach, 2) the main hepatic duct to the small bowel, and 3) the gastric remnant (or postpyloric duodenum) to the small bowel (11).

The classic PD, considered the Kausch–Whipple procedure, was established in 1935 when Allen O. Whipple described the method of PD. In 1941, Whipple modified his method, so both resection and reconstruction could be performed as a one-step procedure (28). Also, the Traverso–Longmire method, or pylorus-preserving PD, was established in 1972. There are no differences between the two methods considering survival, postoperative mortality, complications, and quality of life (29). In Tromsø, all patients with resectable pancreatic cancer undergo the classic Whipple procedure.

Less than 20.0% of patients with pancreatic cancer have a potentially curable stage upon presentation. Therefore, it is important to have selection criteria for which patients are suitable for surgery. The National Comprehensive Cancer Network has developed criteria for this that are acknowledged internationally and are used in the Norwegian guidelines for pancreatic cancer (11). A resectable tumor characteristically has no arterial tumor contact (celiac axis, superior mesenteric artery, or common hepatic artery) and no contact between tumor and veins (superior mesenteric vein or portal vein) (17). The resection margin is an important factor to describe the postoperative course. The International Study Group of Pancreatic Surgery (ISGPS) defines an R0 resection margin to be a cancer-free margin of 1 mm. R1 resection involves cases with a margin of <1 mm. The ISGPS recommends consideration of tumor clearance in eight margins (anterior, posterior, medial or superior mesenteric groove, superior mesenteric artery, pancreatic transection, bile duct, and enteric) (17). This definition of R0 and R1 from the ISGPS can be used as a prognostic factor, where patients with an R0 resection have significantly increased survival compared with those with an R1 resection margin (28, 30).

Complete resection of the tumor is the most important prognostic factor predicting long-term survival. Due to the anatomical location of veins near the pancreatic head, venous resection is the only curative therapy in patients with vascular infiltration. This necessitates

reconstruction of the superior mesenteric vein, portal vein, and the superior mesenteric–portal vein confluence, dependent on the degree of tumor invasion. According to the classification system presented by Tseng et al. (Figure 1), venous resection can be divided into five categories: tangential resection with a saphenous patch (V1); segmental resection with splenic vein ligation and primary anastomosis (V2) or interposition grafting (V3); segmental resection without splenic vein ligation and primary anastomosis (V4) or interposition grafting (V5) (31). The benefits of venous reconstruction have been controversial, but during recent years the literature has shown that experienced centers can accomplish PD with venous resection with acceptable morbidity and mortality rates in addition to complication rates similar to classic PD (32). The short-term outcome of venous reconstruction with venous allograft is no different to primary end-to-end anastomosis (33). The most important factor for long-term survival after venous resection is the resection margins. A Norwegian retrospective study found an R0 rate of 4.0% in patients who experienced venous resection and 22.0% in patients without venous resection (34).

1.5 Postoperative complications

Pancreatic surgery is considered a relatively safe treatment for pancreatic cancer. Postoperative mortality is 2.0–5.0% (11). Postoperative complications are common (30.0–50.0% of patients), but the majority can be treated conservatively. The most common complications after PD are 1) delayed gastric emptying (DGE) (9.0–23.0%), 2) postoperative pancreatic fistula (POPF) (5.0–16.0%), 3) wound infections (3.0–11.0%), 4) intra-abdominal abscess (1.0–4.0%), and 5) postpancreatectomy hemorrhage (PPH) (5.0–10.0%) (11). In addition to these common complications, age, ASA class, node status, resection margin, and the severity of complications are all prognostic variables in the treatment of pancreatic cancer (11).

The Accordion Severity Grading System is used to quantify the severity of postoperative complications (35). Table 4 presents the revised Accordion classification from 1) mild to 6) death.

The ISGPS definition of a POPF is “a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity” (36). Table 5 describes the grading of a POPF. There are some known predictors for development of pancreatic fistulas: a small pancreatic duct size, soft gland texture (ampullary, duodenal, or cystic pathology), and intraoperative blood loss >1000 mL (37).

The ISGPS definition of DGE is “the need for nasogastric tube after 4–7 days or reinsertion after postoperative day (POD) 3. Unable to tolerate solid oral intake by POD 7, and/or vomiting and/or use of prokinetics” (38). Table 6 describes the grading of DGE.

The ISGPS definition of PPH is “early (<24h) or late (>24h) onset of intra- or extraluminal hemorrhage. Low severity when blood volume loss leads to a decrease in hemoglobin concentration <3g/dL, and high severity when blood volume loss leads to a decrease in hemoglobin concentration >3g/dL.” (39). Table 7 describes the grading of PPH.

The ISGPS definition of bile leakage is “fluid with an increased bilirubin (>3 times greater than the serum bilirubin) concentration in the abdominal drain or the intra-abdominal fluid on or after postoperative day 3, or as the need for radiologic intervention or relaparotomy resulting from bile peritonitis” (40). Table 8 describes the grading of bile leakage.

1.6 Norwegian guidelines

The treatment of pancreatic cancer is regulated by national consensus guidelines published by the Norsk Gastrointestinal Cancer Gruppe (www.ngicg.no). Treatment results are monitored by a national registry, the Norwegian Registry for Gastrointestinal Surgery (NoRGast). NoRGast has published guidelines for acceptable and target rates considering different gastrointestinal surgical procedures. The Whipple procedure has an acceptable mortality rate of <8.0% but a target level of <5.0%. The most common procedure-related complication, pancreatic fistula, has an acceptable rate of <20.0% but a target level of <15.0%. Reoperation should be below 20.0% (41).

NoRGast also publishes yearly reports about surgical procedure outcome in Norway, including the Whipple procedure. In 2016, the registry had a coverage of 88.0% of Whipple procedures in Norway and 100% coverage of the procedure performed at the University Hospital of North Norway (UNN) Tromsø. The reports describe all complications: within the first 30 postoperative days, the 90-day mortality, and all reoperations within the first 30 days (42, 43).

1.7 Literature regarding complications, readmission, and survival

Whipple procedure is considered a safe surgical procedure, with a postoperative mortality between 2.0% and 5.0% (11). Postoperative complications are common and are experienced in 30.0–50.0% of patients. The most common complications are DGE (9.0–23.0%), POPF

(5.0–16.0%), wound infection (3.0–11.0%) and postpancreatectomy hemorrhage (5.0–10.0%) (11).

The readmission rate is used as a quality metric after advanced surgery such as the Whipple procedure. In a large study from the American College of Surgeons National Surgical Quality Improvement Program, the overall readmission rate is described to be 18.7% (44). PD-specific complications, such as DGE and POPF, increased the readmission rates (44).

According to the report from NoRGast in 2018, UNN Tromsø had the highest rate of relaparotomy after Whipple procedure in Norway between 2016 and 2018, with 24.0% in contrast to the national average of 15.0% (41). However, UNN Tromsø has the lowest 90-day mortality after Whipple procedure in Norway (2016–2018), with 2.0% in contrast to the national average of 4.0% (41). This is a low mortality rate compared with other larger studies from Europe (41). 5-year survival rates are described to be between 6.0% and 24.0% in newer studies from Norway, Canada, and the USA (11).

1.8 Aim and hypothesis of the study

Clinicians need to have updated information about their outcome in advanced surgery such as pancreatic surgery. Therefore, internal audit is one of several important means of quality assurance in health care. By comparing the findings from the present retrospective study with published literature from national and international high-volume centers, we aim to evaluate treatment outcomes after Whipple procedures performed at UNN Tromsø in the time period 2008–2017. Our hypothesis is that a low-volume hospital can accomplish advanced surgery with acceptable levels of complications and survival rates.

2 Material and methods

2.1 Material

A total of 156 patients underwent the Whipple procedure at UNN Tromsø in the period 2008–2017: 91 (58.3%) men and 65 (41.7%) women. The average age was 66.3 years (SD 10.2). Average BMI at the time of operation was 24.5 (SD 4.2). 89 (57.1%) of the patients were classified as ASA 2 and 65 (41.7%) as ASA 3. One (0.6%) patient was ASA 1 and one was ASA 4.

2.2 Methods

The assignment was approved by application to the data protection officer in Tromsø municipality (*personvernombudet*) October 17, 2018 (project ID 2185). During autumn 2018 the introduction was written. With permission from the data protection officer, follow-up data were collected from all hospitals in northern Norway through the user role "Helse Nord Read Only." Data were collected from the electronic patient journals in the Northern Norway Regional Health Authority (Helse Nord) (Dips). Patients were identified from a list of patients undergoing surgical procedure code JLC30 (Whipple) during the time period 2008–2017. There were no exclusion criteria. Time of follow-up was from January 1, 2008 until data collection was complete on January 1, 2019. The list with patient identification was stored on a research server at the hospital and only anonymized data were used further. Variables were collected and registered in Microsoft Excel during winter 2019. The spreadsheet was exported and analyzed in the Statistical Package for the Social Sciences (SPSS) version 25 (IBM, Armonk, NY, USA) during autumn 2019. During winter 2020 the results and discussion were written, and the assignment was completed in spring 2020. References were handled in the reference management program EndNote X9. During the whole period of work, supervisor Kim Mortensen was available for guidance and help, both in meetings and via e-mails.

2.3 Variables

Appendix 1 shows the list of variables collected from Dips.

2.4 Statistical methods

All analyses were performed with SPSS version 25. Frequencies and averages were analyzed to describe the data. Crosstabs and a chi-square test were used to analyze development of a POPF. Multiple linear regression and logistic regression analyses were used to describe

predictors of readmission, development of a POPF, and survival. Kaplan–Meier survival analyses and log-rank test were performed to describe survival regarding adjuvant chemotherapy and histology.

3 Results

3.1 Perioperative variables

156 patients underwent the Whipple procedure at UNN Tromsø during the time period 2008–2017. In total, nine different surgeons performed the procedure as the main surgeon, but three of them accounted for >70% of the operations. The average operation time was 302.5 minutes (SD 81.8) and average blood loss was 508.3 mL (SD 621). Blood transfusion was given to 19 (12.2%) patients. The average hospital stay at the index hospital, UNN Tromsø, was 12.5 days (SD 13.9). The patients that were discharged to non-index hospitals in the postoperative course were hospitalized for a further 5.25 days (SD 8.8) on average. The total postoperative length of stay was therefore 17.8 days (SD 15.7). 90 (57.7%) patients were discharged to non-index hospitals in northern Norway. The distribution of patients discharged to non-index hospitals is presented in Table 9.

3.1.1 Preoperative drainage

77 (49.4%) patients were treated with preoperative drainage of bile: 48 (62.3%) of them by ERCP and the remaining 29 (37.7%) by PTC.

3.1.2 Resection margins

112 (71.8%) of the procedures resulted in an R0 resection. 35 (22.4%) resections were R1 and 2 (1.3%) R2. The localization of the R1/R2 resections is given in Table 10.

3.1.3 Venous reconstruction

A venous resection was performed in 15 (9.6%) patients due to invasive growth of tumor. Eight (53.3%) of these patients were histologically radically operated, 6 (40.0%) patients had an R1 resection and one (6.7%) patient had an R2 resection.

In 12 (80%) of the 15 patients that underwent venous resection, the postoperative histology showed PDAC. Venous resection corresponding to ISGPS type 4 was performed in 7 (46.7%) patients, ISGPS type 1 in 5 (33.3%) patients, and ISGPS type 5 in 3 (20.0%) patients. Vein suture without graft was used in 11 (73.3%) patients, while Gore-Tex graft was used in 2 (13.3%) patients. Calves pericard and native venous graft were used in one (6.7%) patient each.

2 (13,3%) patients experienced a portal vein thrombosis after a venous resection.

3.2 Complications

A total of 55 (35.3%) of the 156 patients experienced a postoperative Accordion score of 3 or higher, as presented in Figure 2.

General complications of the surgery were experienced in 37 (23.7%) patients. Of these, 8 (21.6%) patients developed postoperative pneumonia. Postoperative sepsis and pulmonary emboli were both experienced in 4 (10.8%) patients. Table 11 presents the general postoperative complications.

3.2.1 Postoperative pancreatic fistula

20 (12.8%) patients experienced a POPF with clinical significance (types B and C). They were equally distributed with 50% being type B and 50% type C.

15 (75%) of the patients with a POPF were treated at the index hospital, UNN Tromsø. Of them, 10 (67%) were reoperated on, 2 (13%) were treated with percutaneous drainage, and 3 (20%) were treated conservatively. One (7%) patient with a POPF was reoperated on at Hammerfest Hospital. At Nordland Hospital, Bodø, one (7%) patient with a POPF was treated by percutaneous drainage. The last 3 (20%) patients with a POPF were treated conservatively at UNN Narvik and Helgeland Hospital, Mo i Rana. Table 12 presents the treatment of patients that experienced a POPF.

Logistic regression was conducted to assess whether the eight predictor variables – year of surgery, age, sex, BMI, operating time, preoperative drainage of bile, venous resection, and PDAC histology – significantly predicted whether or not the patient developed a POPF. When all eight predictor variables were considered together in the model, they did significantly predict whether or not the patient developed a POPF (χ^2=19.74, *df*=8, N=75, p=0.011). Logistic regression analysis did not find any single predictors for which patients would develop a POPF. PDAC histology and year of surgery were both borderline significant predictors. Table 13 presents the odds ratio and p values.

To investigate whether year of surgery affects whether the patients developed a POPF, a chi-square test was conducted. Assumptions were checked and were met. Table 14 shows the Pearson chi-square results and indicates that year of surgery significantly affected whether or not the patients developed a POPF (χ^2=17.53, *df*=9, N=156, p=0.041). Year of surgery was more likely than expected under the null hypothesis to have lower or higher frequency of POPF. In 2015 and 2016 there were more pancreatic fistulas than in the other years, with respectively 35% and 25% in contrast to 0–10% in the other years.

To investigate whether preoperative drainage of bile affects whether the patients developed a POPF, a chi-square test was conducted. Assumptions were checked and were met. Table 15 shows the Pearson chi-square results and indicates that the type of preoperative drainage significantly affected whether or not the patients developed a POPF (χ^2=5.78, *df*=1, N=77, p=0.016). Preoperative drainage was more likely than expected under the null hypothesis to have lower or higher frequency of POPF. The risk of pancreatic fistula was lowest in patients that were drained using ERCP (2.01%) in contrast to PTC (17.24%).

3.2.2 Other complications related to pancreatic surgery

Postoperative DGE was experienced in 31 (19.9%) patients. 21 (68%) of them had type B and 10 (32%) type C. There was no significant association between development of DGE and a POPF.

Postoperative bile leakage was experienced in 10 (6.4%) patients: 6 (60%) type B and 4 (40%) type C.

Postoperative hemorrhage was experienced in 10 (6.4%) patients: 7 (70%) type B and 3 (30%) type C.

3.3 Readmissions and reoperations

Logistic regression was conducted to assess whether the 11 predictor variables (days admitted, age, sex, Accordion score, POPF, postoperative bile leakage, postoperative hemorrhage, DGE, other postoperative complications, ASA class, BMI) significantly predicted whether or not the patients were readmitted. When all 11 predictor variables were considered together in the model, they did significantly predict whether or not the patients were readmitted or not (χ^2=22.58, *df*=11, N=153, p=0.020). Logistic regression analysis found POPF (p=0.005) and DGE (p=0.011) to be predictors for which patients were readmitted. Nagelkerke R^2=0.22, indicating that the model explains 22% of all readmissions. Table 16 presents the odds ratio and p values.

32 (20.5%) of the 156 patients were readmitted to hospital during the first 30 postoperative days. Eighteen (56%) of these patients were readmitted to non-index hospitals in northern Norway, while the remaining 14 (44%) were readmitted to the index hospital, UNN Tromsø. Seven (21.9%) were readmitted with abdominal abscess, 6 (19%) with DGE, and 6 (19%) with anastomosis leakage (of whom 4 had pancreaticojejunal leakage, one had gastrojejunal leakage, and one hepaticojejunal leakage). Of the 6 patients with anastomosis leakage, 5 were readmitted to non-index hospitals and later transferred to UNN Tromsø for

assessment. No patients were operated on during readmission. Table 17 presents readmission location.

Reoperation within 30 postoperative days was performed in 36 (23.1%) patients. Leakage from the pancreaticoduodenal anastomosis was the dominant cause, with 16 (44.4%) patients. Hemorrhage was the cause in 6 (16.7%) of the reoperations. Wound dehiscence and abscess accounted for 3 (8.3%) patients each.

Of the 36 patients that were reoperated on, 32 (89%) were reoperated on at the index hospital, UNN Tromsø. At the non-index hospitals in Hammerfest, Narvik, Harstad, and Bodø, one (2.8%) patient was operated on at each location. Table 18 presents reoperation location.

3.4 Pathology

Seventy-four (47.4%) patients had PDAC as a postoperative histology finding. Twenty (12.8%) patients had ampullary cancer. Seventeen (10.9%) patients had intraductal papillary mucinous neoplasm without carcinoma. The histology is presented in Table 19.
T status was T2 in 44 (28.2%) patients and T3 in 65 (41.7%) patients. N status was N0 in 67 (42.9%) and N1 in 61 (39.1%) patients.

3.5 Oncology

Only 2 (1.3%) patients received neoadjuvant chemotherapy, whereas 69 (44.2%) received adjuvant chemotherapy. A log-rank test was run to determine whether there were differences in the survival distribution for the different types of intervention: adjuvant chemotherapy and no adjuvant chemotherapy. The survival distributions for the two interventions were statistically significantly different ($\chi^2(1)=7.40$, $p=0.007$). There was significantly better survival in the group who received adjuvant chemotherapy. Figure 3 presents the survival function of patients that experienced adjuvant chemotherapy versus no adjuvant chemotherapy.

As adjuvant chemotherapy, 56 (81.2%) patients received FLV (5-FU) and 13 (18.8%) gemcitabine. A log-rank test was run to determine whether there were differences in the survival distribution for the different types of intervention: FLV and gemcitabine. The survival distributions for the two interventions were not statistically significantly different ($\chi^2(1)=0.119$, $p=0.730$). There was no significant difference between the two types of adjuvant chemotherapy. However, gemcitabine is a newer regime and accordingly has a shorter observation time in this study.

3.6 Survival

During the period of follow-up, in January 2008 to January 2019, the postoperative 30-day mortality was 3 (1.9%) patients. All of these patients died of cardiac arrest. The postoperative 90-day mortality was 4 (2.6%) patients. None of them had PDAC. The patient that died between days 30 and 90 died during reoperation due to pancreatic fistula at UNN Tromsø.

Survival rates for PDAC patients after surgery are presented in Table 20. Five-year overall survival was 21.6%.

A log-rank test was run to determine whether there were differences in the survival distribution for the different types of final histology: PDAC and all other histology. The survival distributions for the two interventions were statistically significantly different ($\chi^2(1)=23.101$, $p=0.000$). Figure 4 presents the survival functions.

Multiple regression was conducted to determine the best linear combination of year of surgery, reoperation, age, sex, histology, T status, N status, R status, adjuvant chemotherapy, and BMI for predicting survival. The averages, standard deviations, and intercorrelations can be found in Table 21. The table shows that 12 predictors are significantly. This suggests high colinearity. This combination of variables did not predict survival ($F(10.74)=1.353$, $p=0.219$). The adjusted R-squared value was 0.040. This indicates that only 4% of the variance in survival was explained by the model. However, histology ($p=0.030$) and resection margin ($p=0.035$) were significant coefficients in the model related to survival.

4 Discussion

The aim of this study was to examine, through a retrospective review of journals in Helse Nord, different aspects of the Whipple procedure performed at UNN Tromsø in terms of complications and survival. The hypothesis was that a low-volume hospital like UNN Tromsø, with an annual average of 15 Whipple procedures (in the time period of this study), will result in acceptable outcomes according to national guidelines.

90-day postoperative mortality was 2.6%, while the national "recommended" level in NoRGast is <5%. This is highly acceptable. Three patients died of cardiac arrest, while one died as a direct result of a procedure-related complication. The 5-year overall survival of patients with PDAC was 21.6%. This is also highly acceptable. Only 1.3% of the patients received neoadjuvant chemotherapy. This is an area for possible further improvement in survival, as discussed in the NorPACT-1 study. Neoadjuvant chemotherapy can help select the correct patients for surgery and qualify even more patients to receive adjuvant chemotherapy (20).

Patients who received adjuvant chemotherapy, 69 (44.2%) patients, had a significantly better survival rate, which is well known in the literature. The only predictors of survival after surgery were histology and resection margins. This is also well described in the literature. Readmission was 32 (20.5%) patients during the first 30 postoperative days. This is in accordance with literature from high-volume centers. Abscess, anastomosis leakage, and DGE were the most frequent causes. Of the 17 patients that were discharged to non-index hospitals postoperatively, only 2 (11.7%) patients were readmitted directly to UNN Tromsø. Nevertheless, all 4 patients with severe problems, like anastomosis leakage, were transferred to UNN Tromsø for assessment after readmission at non-index hospitals. This describes a well-functioning system of patient follow-up.

36 (23%) patients were reoperated on during the first 30 postoperative days. This is above the goal set by NoRGast of <20%. According to the 2018 report from NoRGast, UNN Tromsø has the highest rate of relaparotomy in Norway. Nevertheless, 32 out of 36 (89%) patients reoperated on were reoperated on at the index hospital, UNN Tromsø. One may certainly argue that this rate is justified when looking at the results of the most important hard end points, namely a postoperative 90-day mortality of only 2.6% and a 5-year survival of 21.6% among PDAC patients.

The rate of POPFs was 12.8%. This is within the acceptable level regarding guidelines from NoRGast and other literature. Non-PDAC histology was borderline significant for

development of a POPF (p=0.07). A hard gland, as with adenocarcinoma, is described to have a lower fistula rate. This could be a type II error because of a small population, with 74 PDAC patients, and a larger population could have made PDAC significant for not developing pancreatic fistulas. There was a significant association between year of surgery and development of pancreatic fistulas (p=0.04). In 2015 and 2016, a total of 25% and 35% of the operated patients, respectively, developed a POPF, unlike 0–10% the other years in the follow-up period. This could be due to the necessary training of two new surgeons in the years 2015 and 2016. The increased rate of POPF in 2015 and 2016 could also be due to unknown factors.

11 out of 20 (55%) patients with a POPF were reoperated on. It is known that UNN Tromsø has a high rate of surgical treatment of pancreatic fistulas. Nevertheless, with a low mortality and high 5-year survival rate it can be described as good clinical practice. Of the 11 patients reoperated on due to pancreatic fistulas, 10 were reoperated on at UNN Tromsø. In total, 15 of the 20 (75%) patients with a POPF were treated at the index hospital, UNN Tromsø. This describes a low rate of failure to rescue for the patients operated on in northern Norway.

Venous reconstruction was performed during 15 (9.6%) of the procedures. 80% of venous reconstruction was performed on patients with histology of PDAC. Of these patients, 8 (53.3%) patients achieved R0 resection. This is a high rate compared with the literature.

Preoperative drainage of cholestasis was performed on 49.4% of patients, with 62.3% of them through ERCP. Regression analysis describes a lower risk of developing a POPF if the patient is drained with an endoscopic procedure. This is in agreement with the literature from studies with a larger patient population.

The main strength of this study is that it is a complete regional cohort study accounting for all patients operated on with the Whipple procedure and their follow-up in northern Norway. Each patient is accounted for at their local hospital in the postoperative course. All readmissions and reoperations are included, even if the patients were treated at non-index hospitals in northern Norway.

The thesis has some weak sides due to the collection of data from the patient journals, especially during the early period of follow-up when there were inadequate journal notes to collect all the data needed. Grading of complications such as pancreatic fistulas, bile leakage, and postoperative hemorrhage was dependent on the interpretation of journal entries.

5 Conclusion

This work describes the outcomes after Whipple procedures performed at UNN Tromsø in the time period 2008–2017. With a 90-day postoperative mortality of 2.6% for all patients and a 5-year survival rate of 21.6% (for PDAC patients) one may conclude that the treatment results are well in line with international standards from high-volume centers. In addition, this thesis demonstrates that UNN Tromsø has a satisfactory follow-up of patients discharged to local hospitals in northern Norway, avoiding failure to rescue.

6 Tables

Table 1. Tumor, node, and metastasis (TNM) staging of pancreatic cancer. Table published after Hartwig et al. (15).

TNM classification	
T = primary tumor	
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor restricted to the pancreas, <2 cm in greatest dimension
T2	Tumor restricted to the pancreas, ≥2 cm in greatest dimension
T3	Tumor extends beyond the pancreas, no involvement of the celiac axis or superior mesenteric artery
T4	Tumor affects the celiac axis or superior mesenteric artery
N = regional lymph node	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M = distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Table 2. Survival data for resected pancreatic adenocarcinoma. Staging according to the Union for International Cancer Control, 7th edition. NA = data not available. Table published after Hartwig et al. (1).

	Resectability	*Median survival (months)*	*5-year survival (%)*
Stage 0 *(Tis, N0, M0)*	Carcinoma in situ, resectable	NA	NA
Stage IA *(T1, N0, M0)*	Localized, resectable	24–42	31–39
Stage IB *(T2, N0, M0)*	Localized, resectable	20–26	22–27
Stage IIA *(T3, N0, M0)*	Locally invasive, resectable	15–30	16–25
Stage IIB *(T1-3, N0-1, M0)*	Locally invasive, resectable	12–21	8–10
Stage III *(T4, N0-1, M0)*	Locally advanced, borderline resectable	11–14	0–7
Stage IV *(T0-4, N0-1, M1)*	Distant metastasis, palliative	5–12	0–4

Table 3. The American Society of Anesthesiologists (ASA) physical status classification system. Table published after Doyle and Garmon (26). BMI = body mass index.

American Society of Anesthesiologists Classification	
ASA 1	A normal healthy patient. Example: Fit, nonobese (BMI under 30), a non-smoking patient with good exercise tolerance.
ASA 2	A patient with a mild systemic disease. Example: Patient with no functional limitations and a well-controlled disease (e.g., treated hypertension, obesity with BMI under 35, frequent social drinker or is a cigarette smoker).
ASA 3	A patient with a severe systemic disease that is not life-threatening. Example: Patient with some functional limitation as a result of disease (e.g., poorly treated hypertension or diabetes, morbid obesity, chronic renal failure, a bronchospastic disease with intermittent exacerbation, stable angina, implanted pacemaker).
ASA 4	A patient with a severe systemic disease that is a constant threat to life. Example: Patient with functional limitation from severe, life-threatening disease (e.g., unstable angina, poorly controlled chronic obstructive pulmonary disease, symptomatic congestive heart failure, recent (less than 3 months ago) myocardial infarction or stroke).
ASA 5	A moribund patient who is not expected to survive without the operation. The patient is not expected to survive beyond the next 24 hours without surgery. Examples: ruptured abdominal aortic aneurysm, massive trauma, and extensive intracranial hemorrhage with mass effect.
ASA 6	A brain-dead patient whose organs are being removed with the intention of transplanting them into another patient.

Table 4. Revised Accordion classification. Table published after Porembka et al. (35).

Grade		*Revised Accordion classification*
Mild	1	Requires only minor invasive procedures that can be done at the bedside, such as insertion of intravenous lines, urinary catheters, and nasogastric tubes, and drainage of wound infections. Physiotherapy and antiemetics, antipyretics, analgesics, diuretics, and electrolytes are permitted.
Moderate	2	Requires pharmacological treatment with drugs other than such allowed for minor complications, e.g., antibiotics. Blood transfusions and total parenteral nutrition are also included.
Severe	3	No general anesthesia: requires management by an endoscopic, interventional procedure or reoperation without general anesthesia.
Severe	4	General anesthesia or single organ failure.
Severe	5	General anesthesia and single organ failure or multisystem organ failure (>2 organ systems).
Death	6	Postoperative death.

Table 5. Postoperative pancreatic fistula (POPF) International Study Group of Pancreatic Surgery grading. Presented after Bassi et al. (36). CT = computed tomography; US = ultrasound.

Grade	*A*	*B*	*C*
Clinical conditions	Well	Often well	Ill appearing
Specific treatment	No	Yes/No	Yes
US/CT (if obtained)	Negative	Negative/Positive	Positive
Persistent drainage (>3 weeks)	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/No	Yes/No

Table 6. Delayed gastric emptying International Study Group of Pancreatic Surgery grading. Presented after Wente et al. (38). POD = postoperative day.

Grade	*Nasogastric tube required*	*Unable to tolerate solid intake by POD*	*Vomiting/ gastric distension*	*Use of prokinetics*
A	4–7 days or reinsertion POD 3	7	+/−	+/−
B	8–14 days or reinsertion POD 7	14	+	+
C	14 days or reinsertion POD 14	21	+	+

Table 7. Postpancreatectomy hemorrhage (PPH) International Study Group of Pancreatic Surgery grading. Presented after Wente et al. (39). CT = computed tomography; US = ultrasound.

Grade	*Time of onset, location, severity*	*Clinical condition*	*Diagnostic consequence*	*Therapeutic consequence*
A	Early, intra- or extraluminal, mild	Well	Observation, blood count, ultrasonography and, if necessary, CT	No
B	Early, intra- or extraluminal, severe Late, intra- or extraluminal, mild	Often well/ intermediate	Observation, blood count, US, CT, angiography, endoscopy	Transfusion of fluid/ blood, ICU, therapeutic endoscopy, relaparotomy for early PPH
C	Late, intra- or extraluminal, severe	Severely impaired, life-threatening	Angiography, CT, endoscopy†	Localization of bleeding, angiography and embolization or relaparotomy, ICU

Table 8. Bile leakage International Study Group of Pancreatic Surgery grading. Presented after Koch et al. (40).

Grade	
A	Bile leakage requiring no or little change in patient's clinical management
B	Bile leakage requiring a change in patient's clinical management (additional diagnostic or intervention) but manageable without relaparotomy, or Grade A leakage lasting >1 week
C	Bile leakage requiring relaparotomy

Table 9. Postoperative discharge to non-index hospitals.

Postoperative discharge to non-index hospitals	*Frequency*	*%*
Kirkenes	9	5.8
Hammerfest	9	5.8
Narvik	2	1.3
Harstad	13	8.3
Stokmarknes	12	7.7
Gravdal	1	0.6
Bodø	19	12.2
Mo I Rana	16	10.3
Mosjøen	1	0.6
Sandnessjøen	8	5.1
Total	90	57.7

Table 10. Localization R1/R2 resections.

Localization R1/R2 resection	*Frequency*	*%*
Multiple affected margins	11	7.1
Retroperitoneum	10	6.4
Pancreas remnants	8	5.1
Dorsal resection surface	5	3.2
Ventral resection surface	2	1.3
Ductus choledochus	1	0.6
Total	37	23.7

Table 11. Postoperative complications.

Postoperative complications	*Frequency*	*%*
Wound infection	3	1.9
Pneumonia	8	5.1
Myocardial infarction	2	1.3
Pulmonary embolism	4	2.6
Cardiac arrest	3	1.9
Abscess	6	3.8
Sepsis	4	2.6
Respiration failure	1	0.6
Thrombosis vena porta	2	1.3
Other	4	2.6
Total	37	23.7

Table 12. Pancreatic fistula treatment.

Pancreatic fistula treatment location	Treatment			
	Conservative	Percutaneous drainage	Operation	Total
Hammerfest	0	0	1	1
Narvik	2	0	0	2
Bodø	0	1	0	1
Mo I Rana	1	0	0	1
Tromsø	3	2	10	15
Total	6	3	11	20

Table 13. Logistic regression prediction of postoperative pancreatic fistula. BMI = body mass index; B = unstandardized regression weight; OR = odds ratio; PDAC = pancreatic ductal adenocarcinoma; SE = standard error.

Variable	*B*	*SE*	*OR*	*p*
Year of surgery	1.26	0.75	3.51	0.093
Age	0.05	0.08	1.05	0.489
Sex	2.97	2.00	19.48	0.139
Operating time	−0.01	0.01	0.99	0.490
Preoperative drainage	2.00	1.48	7.42	0.175
Venous resection	1.42	2.33	4.15	0.541
PDAC	4.00	2.27	54.68	0.077
BMI	−0.10	0.22	0.91	0.648

Table 14. Chi-square analysis of prevalence of postoperative pancreatic fistula (POPF) depending on year of surgery.

		POPF			
Variable	*N*	No	Yes	χ^2	*p*
Year of surgery				17.53	0.041
2008	8	6	2		
2009	17	16	1		
2010	16	16	0		
2011	17	17	0		
2012	10	10	0		
2013	15	14	1		
2014	16	14	2		
2015	22	15	7		
2016	23	18	5		
2017	12	10	2		
Total	156	136	20		

Table 15. Chi-square analysis of prevalence of postoperative pancreatic fistula (POPF) depending on preoperative drainage of bile. ERCP = endoscopic retrograde cholangiopancreatography; PTC = percutaneous transhepatic cholangiography.

		POPF			
Variable	*N*	No	Yes	χ^2	*p*
Preoperative drainage				5.78	0.016
ERCP	48	47	1		
PTC	29	24	5		
Total	77	71	6		

Table 16. Logistic regression prediction of readmission. ASA = American Society of Anesthesiologists; BMI = body mass index; B = unstandardized regression weight; OR = odds ratio; SE = standard error.

Variable	*B*	*SE*	*OR*	*p*
Days admitted	0.11	0.015	1.011	0.464
Age	−0.012	0.024	0.988	0.620
Sex	−0.131	0.469	0.877	0.780
Accordion score	0.001	0.154	1.001	0.997
Postoperative pancreatic fistula	1.789	0.707	5.983	0.011
Bile leakage	−0.583	1.052	0.558	0.579
Postoperative hemorrhage	1.243	0.835	3.467	0.136
Delayed gastric emptying	1.475	0.525	4.369	0.005
Other complications	0.011	0.558	1.011	0.985
ASA score	0.317	0.471	1.373	0.500
BMI	−0.070	0.061	0.932	0.248

Table 17. Readmission location.

Readmission location	*Frequency*	*%*
Kirkenes	1	0.6
Hammerfest	3	1.9
Narvik	1	0.6
Harstad	3	1.9
Stokmarknes	2	1.3
Bodø	1	0.6
Mo I Rana	3	1.9
Sandnessjøen	4	2.6
Tromsø	14	9.0
Total	32	20.4

Table 18. Reoperation location.

Reoperation location	*Frequency*	*%*
Hammerfest	1	0.6
Narvik	1	0.6
Harstad	1	0.6
Bodø	1	0.6
Tromsø	32	20.5
Total	36	22.9

Table 19. Histology. IPMN = intraductal papillary mucinous neoplasm; NET = neuroendocrine tumor.

Histology	Frequency	%
Pancreatic ductal adenocarcinoma	74	47.4
Bile duct cancer	8	5.1
Duodenal cancer	8	5.1
Ampullary cancer	20	12.8
Other malignant disease	9	5.8
IPMN without carcinoma	17	11.0
Pancreatitis	3	1.9
Other benign disease	10	6.4
NET	7	4.5
Total	156	100

Table 20. Survival rates for pancreatic ductal adenocarcinoma (PDAC) patients after surgery.

Survival PDAC after surgery	Frequency	%
1/2 year	69	93.2
1 year	56	75.7
2 years	31	41.9
3 years	21	28.4
4 years	17	23.0
5 years	16	21.6

*Table 21. Means, standard deviations (SDs) and intercorrelations for survival and predictor variables (N=85). *=p<0.05, **=p<0.01. BMI = body mass index.*

Variable	*Mean*	*SD*	*1.*	*2.*	*3.*	*4.*	*5.*	*6.*	*7.*	*8.*	*9.*	*10.*
Survival	20.94	14.84	−0.15	0.10	−0.02	−0.13	0.18*	−0.03	−0.14	0.19*	−0.03	0.08
Predictor variable												
1. Year of surgery	5.27	2.42	–	0.06	0.08	−0.04	−0.08	0.16	0.24**	−0.18*	0.13	0.06
2. Reoperated	0.27	0.45		–	−0.03	0.10	0.18*	0.08	−0.15	−0.04	−0.24**	0.19*
3. Age	68.39	9.11			–	0.02	0.24**	0.01	−0.12	−0.23*	−0.39**	−0.02
4. Sex	0.66	0.48				–	0.19*	−0.12	−0.03	−0.05	−0.12	0.00
5. Histology	2.07	1.94					–	−0.03	−0.06	−0.22*	−0.37**	−0.70
6. T status	2.65	0.70						–	0.37**	0.17	0.04	0.12
7. N status	0.56	0.54							–	−0.02	0.09	−0.13
8. R status	0.34	0.52								–	0.01	−0.14
9. Adjuvant chemotherapy	0.54	0.50									–	−0.05
10. BMI	23.90	3.72										–

7 Figures

Figure 1. Illustration of the five forms of venous resection and reconstruction. Figure presented by Tseng et al. (31.

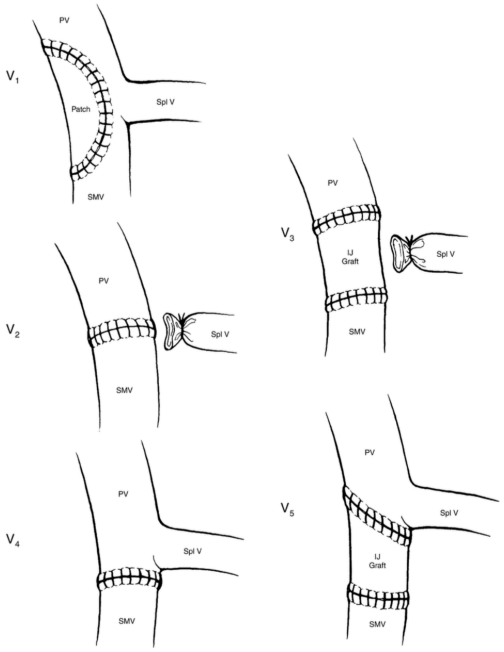


Figure 2. Accordion score.

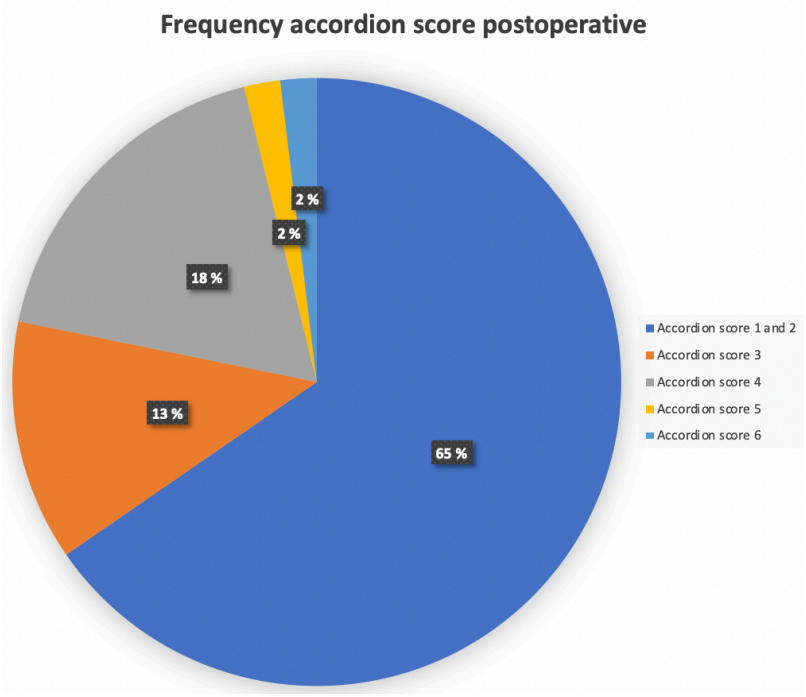


Figure 3. Survival curve regarding adjuvant chemotherapy.

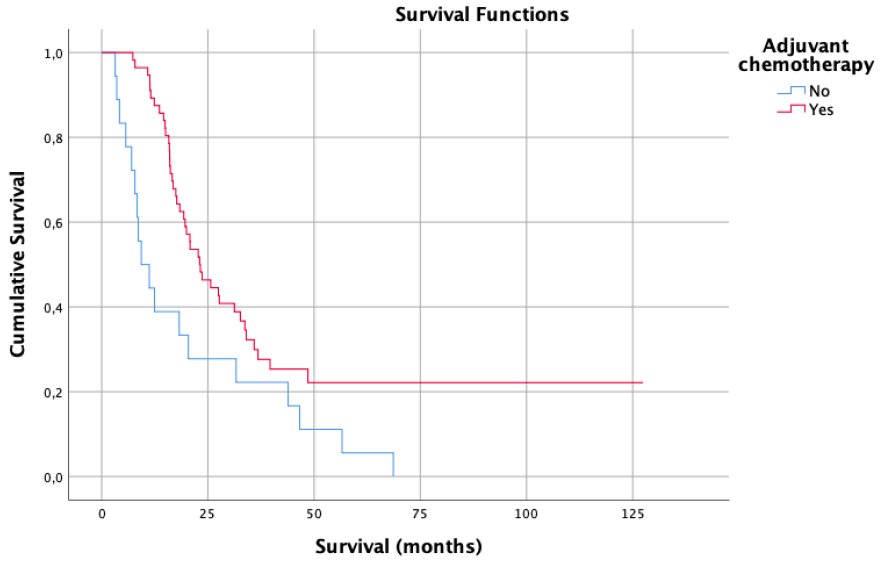
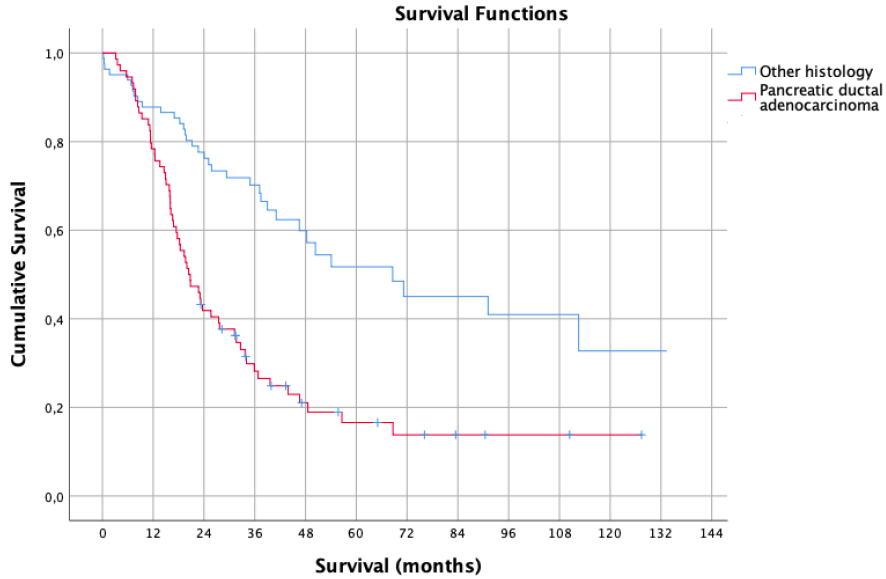


Figure 4. Survival curve regarding histology.



8 Summaries and evaluation of literature (in Norwegian)

Referanse:
Kleive D, Labori KJ, Line PD, Gladhaug IP, Verbeke CS. Pancreatoduodenectomy with venous resection for ductal adenocarcinoma rarely achieves complete (R0) resection. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2019.

Studiedesign: Pasientserie

Grade - kvalitet | Lav

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
Kartlegge andel R0-reseksjoner ved kirurgisk behandling av pancreastumor med vene-reseksjon.	**Populasjon** Alle pasienter med pancreatic ductal adenocarcinoma (PDAC) i caput pancreas som gjennomgikk åpen pancreatoduodenectomy (PD) med vene reseksjon i perioden 01.01.15-31.12.17. **Ekskulsjonskriterer:** - Pasienter som gjennomgikk andre typer reseksjon enn PD. - Pasienter med annen histologi enn PDAC. - Neoadjuvant kjemoterapi. - Samtidig arteriereseksjon og/eller multivisceral reseksjon. **Utfall – hoved utfall** -R0-reseksjon (>1mm fri reseksjonsrand) -Involvert margin ved R1 reseksjon **Viktige konfunderende faktorer** Pasientpopulasjon med ulikt stadie av pancreatic ductal adenocarcinoma. **Statistiske metoder** Kontinuerlige variabler er presentert som median eller gjennomsnitt. X^2 test eller Fisher's exact test for å sammenligne frekvenser. Man—Whitney U test og two-sample t test.	**Hovedfunn** I studieperioden ble det utført totalt 310 PD. 98 pasienter med PDAC fylte inklusjonskriteriene, og av dem hadde 25 gjennomgått PD med vene-reseksjon (VR). Av pasienter med VR oppnådde 1 av 25 (4%) av prosedyrene R0-reseksjon. Av pasientene uten VR oppnådde 16 av 73 (22%) R0-reseksjon (p=0,063). VMS-marginen hadde høyest frekvens av R1-reseksjon. 23 av 25 (92%) pasienter med VR hadde mikroskopisk innvekst i SMV-området, mens 37 av 73 (50,7%) av pasienter uten VR hadde innvekst (p<0,001).	**Sjekkliste:** • **Er formålet klart formulert?** Ja • **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? (seleksjons bias)** Ja • **Var inklusjonskriteriene klart definert?** Ja • **Var alle pasientene i samme stadium av sykdommen?** Nei • **Var responsraten høy nok? Frafallsanal.?** Ikke relevant • **Ble det brukt objektive kriterier for å vurdere/validere endepunktene? (Classfifc. Bias)** Ja, histologisk 1mm fri reseksjonsrate • **Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet?** Ja • **Er prognostiske/konfunderende faktorer beskrevet/tatt hensyn til i design/analyse?** Ja • **Var registreringen prospektiv?** Nei, retrospektiv • **Var oppfølgningen lang nok?** Ja • **Var oppfølgningen tilstrekkelig for å nå endepunktene? (attrition/follow-up bias)** Ja • **Stoler du på resultatene?** Ja • **Kan resultatene overføres til praksis?** Ja • **Annen litteratur som støtter resultatene?** Ja **Hva diskuterer forfatterne som:** • **Styrke:** Strenge inklusjonskriterer som gir en homogen pasient populasjon. • **Svakhet:** Retrospektiv studiedesign. Liten studiepopulasjon. **Har resultatene plausible biologiske forklaringer?** Ja
Konklusjon R0 reseksjon etter pancreaticoduodenectomi med vene-reseksjon for pancratic ductal adenocarcinoma oppnås sjelden på grunn av mikroskopisk innvekst i VMS.			
Land Norge			
År data innsamling 2015-2017			

Referanse:
Meguid RA, Ahuja N, Chang DC. What constitutes a "high-volume" hospital for pancreatic resection? Journal of the American College of Surgeons. 2008;206(4):622.e1-9.

Studiedesign: Pasientserie

Grade - kvalitet | **Lav**

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
Definere en objektiv, evidensbasert operasjons-volum terskel assosiert med bedret postoperativt forløp etter reseksjon av pancreas. **Konklusjon** Selv om volum har en viktig innvirkning på mortalitet, er volum en utilstrekkelig variabel for å beskrive dyktighet ved sykehus. Volum ser ut til å være en ufullstendig erstatter for andre variabler som bedre definerer sykehus sin dyktighet. **Land** USA **År data innsamling** 1998-2003	**Populasjon** Pasientdata samlet fra Nationwide Inpatient Sample (NIS) mellom 1998 og 2003. NIS har samlet omtrent 20% av alle sykehusutskrivelser i USA. Inklusjonskriterer var pasienter i NIS databasen >17 år, som har gjennomgått pancreas-reseksjon uavhengig av indikasjon. Type reseksjoner inkludert: - total pancreatectomy - radical pancreaticoduodenectomy - proximal pancreatectomy - distal pancreatectomy - radical subtotal pancreatectomy - other partial pancreatectomy **Utfall – hoved utfall** In-hospital dødelighet etter reseksjon av pancreas sett i sammenheng med årlig sykehus reseksjons-volum av pancreas. **Viktige konfunderende faktorer** Pasientene hadde ulik indikasjon for pancreasreseksjon, samt ulike typer reseksjon. **Statistiske metoder** Multivariabel logistisk regressjon. Forklaringsgrad av hver modell ble beskrevet med pseudo r^2.	**Hovedfunn** Basert på analyser av 7558 pasienter som gjennomgikk reseksjon av pancreas, var gjennomsnittlig årlig reseksjon-volum 15 pasienter pr sykehus. Den beste modellen for «høy-volum» senter og lav perioperativ død var et årlig reseksjon-volum på 19 eller høyere (r^2= 5,29%). **Bifunn** En modell uten noen volum-variabel hadde forklaringsgrad r^2 = 3,75%. Volum-variabelen beskriver dermed under 2% av variasjon i perioperative dødelighet ved pancreasreseksjon.	**Sjekkliste:** • **Er formålet klart formulert?** Ja • **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? (seleksjons bias)** Ja • **Var inklusjonskriteriene klart definert?** Ja • **Var alle pasientene i samme stadium av sykdommen?** Nei • **Var responsraten høy nok? Frafallsanal.?** Ikke relevant • **Ble det brukt objektive kriterier for å vurdere/validere endepunktene? (Classfifc. Bias)** Ja • **Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet?** Ikke relevant • **Er prognostiske/konfunderende faktorer beskrevet/tatt hensyn til i design/anal?** Nei • **Var registreringen prospektiv?** Nei retrospektiv • **Var oppfølgningen lang nok?** Ja • **Var oppfølgningen tilstrekkelig for å nå endepunktene? (attrition/follow-up bias)** Ja • **Stoler du på resultatene?** Ja • **Kan resultatene overføres til praksis?** Ja • **Annen litteratur som støtter resultatene?** Ja **Hva diskuterer forfatterne som:** • **Styrke –** valg av NIS-databasen pga dens store pasient-volum. • **Svakhet** – Retrospektivt studiedesign uten mulighet for å korrigere for erfaring hos kirurg, undersøke andre postoperative komplikasjoner enn død samt å beregne 30-dagers mortalitet. Ikke mulighet til å kontrollere diagnose- eller prosedyre-kode. Har resultatene plausible biologiske forklaringer? • Nei

Referanse:
Seppanen H, Juuti A, Mustonen H, Haapamaki C, Nordling S, Carpelan-Holmstrom M, et al. The Results of Pancreatic Resections and Long-Term Survival for Pancreatic Ductal Adenocarcinoma: A Single-Institution Experience. Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society. 2017;106(1):54-61.

Studiedesign: Pasientserie

Grade - kvalitet Lav

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
Evaluere utfall hos pasienter som gjennomgår pankreaskirurgi generelt, samt mulige fordeler i overlevelse hos pasietener operert for pancreas-kreft gjennom perioden med sentralisering til Helsinki Universitet sykehus. **Konklusjon** Etter sentralisering av pankreaskirurgi i Finland er overlevelsen for pasienter operert for pankreaskreft bedret. Pankreaskirurgi anses som trygt i et høy-volum senter. **Land** Finland **År data innsamling** Januar 2000 til september 2013. Data ble avlest september 2014.	**Populasjon** Alle pasienter som gjennomgikk pancreaskirurgi ved Helsinki Universitets sykehus mellom januar 2000 og september 2013. N=853. **Eksklusjonskriterie:** Pasienter som har gjennomgått necrosectomi. **Utfall** Postoperative dødelighet på sykehus (in-hospital death) og 30-dagers postoperativ dødelighet. 5- og 10-års overlevelse hos pasienter operert for pancreatic ductal adenocarcinom (PDAC) **Metode:** Data ble samlet fra pasientjournaler, det Finske folkeregisteret og dødsårsaksregisteret i september 2014. **Viktige konfunderende faktorer** Ulikt stadium av sykdom ved operasjon. **Statistiske metoder** Descriptive statistikk. Kaplan-Meier survival analysis, log rank test for sammenlikning. Cox hazard ratio regressjon analyse Alle resultater var alder og kjønnsjustert.	**Hovedfunn** Av de 853 pasientene som gjennomgikk pancreaskirurgi, var 581 (68%) pancreticoduodenectomies (PD) / Whippl-prosedyre. Av de 853 opererte pasientene hadde 309 (36%) pancreatic ductal adenocarcinom (PDAC) som postoperativ histologi. Sykehus-dødelighet (in-hospital death) etter PD var 12 (2,1%) pasienter. 30 dagers postoperative dødelighet etter PD var 7 (1,2%) pasienter. Langtidsoverlevelse for pasienter operert for PDAC var: 1-års overlevelse: 74% 3- års overlevelse: 36% 5-års overlevelse: 22% 10-års overlevelse: 14% **Bifunn** Postoperative pancreasfistel rate med klinisk betydning var 7% etter PD. Reoperasjonsrate var 5%. Av PDAC pasientene, gjennomgikk 52 (17%) pasienter neoadjuvant kjemoterapi. 151 (53%) av PDAC pasientene mottok adjuvant kjemoterapi. I multivariable analyser, hadde pasienter som mottak postoperative adjuvant kjemoterapi signifikant lavere HR.	**Sjekkliste:** • **Er formålet klart formulert?** Ja • **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? (seleksjons bias)*** Ja • **Var inklusjonskriteriene klart definert?*** Ja • **Var alle pasientene i samme stadium av sykdommen?** Nei, men alle var i et operabelt stadie. Ukjent preoperativ histologi. • **Var responseraten høy nok? Frafallsanal.?** Ikke relevant • **Ble det brukt objektive kriterier for å vurdere/validere endepunktene? (Classfifc. Bias)** Ja, harde endepunkter som mortalitet og overlevelse. • **Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet?*** Ikke relevant • **Er prognostiske/konfunderende faktorer beskrevet/tatt hensyn til i design?** Ja • **Var registreringen prospektiv?** Nei, retrospektiv • **Var oppfølgningen lang nok?** Ja for alle variabler utenom 10-års overlevelse. Data ble avlest sept 2014, derfor er det kun pasienter operert før 2004 man kan regne 10-års overlevelse på. • **Var oppfølgningen tilstrekkelig for å nå endepunktene? (attrition/follow-up bias)** Ja • **Stoler du på resultatene? J**a • **Kan resultatene overføres til praksis?** Ja • **Annen litteratur som støtter resultatene?** Ja **Hva diskuterer forfatterne som:** • **Styrke:** ikke diskutert • **Svakhet:** ikke diskutert **Har resultatene plausible biologiske forklaringer?** • Ja

Referanse:
Soreide K, Aagnes B, Moller B, Westgaard A, Bray F. Epidemiology of pancreatic cancer in Norway: trends in incidence, basis of diagnosis and survival 1965-2007. Scandinavian journal of gastroenterology. 2010;45(1):82-92.

Studiedesign: Pasientserie

Grade - kvalitet | Lav

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
Gi en oversikt av tidstrender angående insidens, diagnostikk, mortalitet og overlevelse av pancreascancer de siste fire tiår i den norske populajsonen **Konklusjon** Insidens og mortalitet for pancreascancer forblir vesentlig uendret, med lav 5-års overlevelse. Bedret korttids-overlevelse kan være et resultat av en mer aggressiv bruk av kirurgi og kjemoterapi. **Land** Norge **År data innsamling** 1965-2007	**Populasjon** 21.663 pasienter var inkludert fra kreftregisteret med pancreaskreft (ICD-10 kode C25) **Ekslusjonskriterier:** - Overlevelse <0 dager. Diagnose og død på samme dag. - Diagnostisert ved obduksjon - Pasient identifisert kun fra dødsattest - Tidligere kjent kreft-diagnose **Utfall – hoved utfall** - Insidens - Diagnosegrunnlag - Relativ overlevelse - Mortalitet **Konfunderende faktorer:** Ukjent dødsårsak. **Statistiske metoder** Relative survival, overlevelse uavhengig av dødsårsak, kalkulert vha: Relative survival (R(t)) = observert overlevelse ($S_O(t)$) / kalkulert beregnet overlevelse ($S_E(t)$) Insidens og mortalitetsrater ble alders-justert.	**Hovedfunn** Insidens og mortalitetsrater var 6-8 pr 100.000 gjennom studieperioden. Diagnostisering basert på klinisk undersøkelse alene falt fra 12,5% (1950-tallet) til <1% (2000-tallet). Diagnose basert på bildeundersøkelse (CT/MR) økte fra 3,6% til >30%. Den høye raten av obduksjons-verifisert kreft og ikke-terapeutisk kirurgi falt gjennom perioden. Flere primære tumorer (12,9% til 19,4%) og metastaser (12,5% til 22,4%) gjennomgikk histologisk undersøkelse. Relativ overlevelse av pancreas kreft var lav gjennom hele perioden, men i de senere år ses det en beskjeden bedring i korttids overlevelse, med 1-års overlevelse på 18% for menn og 16% for kvinner. 5-års relativ overlevelse på hhv. 5,3% hos menn og 2,6% hos kvinner.	**Sjekkliste:** • **Er formålet klart formulert?** Ja • **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? (selesksjons bias)*** Ja • **Var inklusjonskriteriene klart definert?** Ja • **Var alle pasientene i samme stadium av sykdommen?** Nei • **Var responseraten høy nok? Frafallsanal.?** Ikke relevant • **Ble det brukt objektive kriterier for å vurdere/validere endepunktene? (Classfifc. Bias)** Ja • **Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet?** Ikke relevant • **Er prognostiske/konfunderende faktorer beskrevet/tatt hensyn til i design/anal?** Ja • **Var registreringen prospektiv?** Nei • **Var oppfølgningen lang nok** Ja • **Var oppfølgningen tilstrekkelig for å nå endepunktene? (attrition/follow-up bias)** Ja • **Stoler du på resultatene?** Ja • **Kan resultatene overføres til praksis?** Ja • **Annen litteratur som støtter resultatene?** Ja **Hva diskuterer forfatterne som:** ◦ **Styrke:** ikke diskutert ◦ **Svakhet:** ingen histologisk revurdering av diagnose. **Har resultatene plausible biologiske forklaringer?** Ja

Referanse: Soreide JA, Sandvik OM, Soreide K. Improving pancreas surgery over time: Performance factors related to transition of care and patient volume. International journal of surgery (London, England). 2016;32:116-22.

Studiedesign: Pasientserie

Grade - kvalitet Lav

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
Vurdere indikasjoner og resultater av pancreas kirurgi gjennom overgangen fra lokalsykehus til universitetssykehus ved Stavanger Universitetssykehus. **Konklusjon** Overgangen til universitetssykehus og økt volum medførte signifikant bedring i flere kvalitetsindikatorer samt redusert postoperativ mortalitet. Bedret perioperative håndtering og fokusert, multidisiplinær omsorg anses viktig. **Land** Norge **År data innsamling** 1986-2012	**Populasjon** Alle pasienter som gjennomgikk pancreaskirurgi mellom 1986-2012 ved Stavanger Universitetssykehus ble identifisert fra sykehusets database. **Utfall – hoved utfall** Indikasjon for kirurgi Postoperative komplikasjoner Postoperativ mortalitet **Viktige konfunderende faktorer** Pasientene ble operert med ulike indikasjoner og ulikt stadium av sykdom. **Statistiske metoder** Ikke-parametriske tester. p<0,050 ansees som signifikant.	**Hovedfunn** Av de 219 inkluderte pasienten, gjennomgikk 150 (69%) pancreatoduodenectomy. Operasjonsvolumet steg fra <10/år til >20/år i perioden. 169 (77%) av pasientene ble operert for mistenkt malignitet. 30 dagers mortalitet sank signifikant for pasienter behandlet for pancreascancer i perioden fra 16,1% til 3,5% (p=0,012). Gjennomsnittlig hospitaliseringstid ble redusert fra 19 til 12 dager (p<0,001) og re-operasjons rate redusert fra 37,1% til 8,4% (p<0,001). Tid på intensivavdeling postoperativt ble redusert fra 3 til 0 dager (p<0,001). **Bifunn:** 71 (32,45) pasienter hadde komplikasjoner svarende til Clavien-Dindo grad III eller høyere. Det ble observert en reduksjon i reoperasjoner fra 37,1% (13/35 pasienter) i første tiår, til 19,1% (17/89 pasienter) i det andre tiåret og 8,4% (8/95 pasienter) i det siste tiåret (p<0,001).	**Sjekkliste:** • **Er formålet klart formulert?** Ja • **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe?** (selesksjons bias)* Ja • **Var inklusjonskriteriene klart definert?** Ja • **Var alle pasientene i samme stadium av sykdommen?** Nei • **Var responseraten høy nok?* Frafallsanal.?** Ikke relevant • **Ble det brukt objektive kriterier for å vurdere/validere endepunktene?** (Classfifc. Bias) Ja • **Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet?*** Ja • **Er prognostiske/konfunderende faktorer beskrevet/tatt hensyn til i design/anal?** Ja • **Var registreringen prospektiv?** Nei, retrospektiv • **Var oppfølgningen lang nok** Ja • **Var oppfølgningen tilstrekkelig for å nå endepunktene?** (attrition/follow-up bias) Ja • **Stoler du på resultatene?** Ja • **Kan resultatene overføres til praksis?** Ja • **Annen litteratur som støtter resultatene?** Ja **Hva diskuterer forfatterne som:** • **Styrke:** ingen seleksjonsbias på grunn av et statlig drevet helsevesen som gir alle lik tilgang til helsetjenester. • **Svakhet:** på grunn av retrospektivt studiedesign ikke mulig å finne pålitelig informasjon om hvert enkelt pasientforløp, feks rate av pancreasfistel. Gjennom en studietid på tre tiår, har det vært store endringer ifht bildediagnostikk og operasjonsteknikk, derfor kan ikke all forbedring tilskrives kun sentralisering av pancreaskirurgi. **Har resultatene plausible biologiske forklaringer?** Ja

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10 Appendices

Appendice 1: List of variables collected from Dips

Patient identification number
Admission date
Surgery date
Surgery year
Discharge UNN Tromsø
Discharge non-index hospital
Hospital stay UNN Tromsø
Readmitted
Readmission date
Readmission cause
Readmitted 30 days
Readmitted 90 days
Readmitted after 90 days
Reoperation
Reoperation date
Reoperation cause
Reoperation 30 days
Reoperation after 30 days
Dead
Date of death
Survival years
Survival months
Survival days
Age
Sex
Height
Weight
BMI
Surgeon
Surgery time
Preoperative drainage
Preoperative drainage type
ASA score
Blood loss
Blood transfusion
Venous reconstruction
Venous reconstruction type
Venous graft
Venous graft type
Accordion score
Postoperative pancreatic fistula
Postoperative pancreatic fistula degree
Bile leakage
Bile leakage degree
Postoperative hemorrhage
Postoperative hemorrhage degree
Delayed gastric emptying
Delayed gastric emptying degree
Complications 30 days
Complications 30 days type
Histology
Pancreatic ductal adenocarcinoma
T status
N status
R status
Resection margin affected
Neoadjuvant chemotherapy
Adjuvant chemotherapy
Adjuvant chemotherapy type