ORIGINAL ARTICLE

Survival, Complications and Patient Reported Outcomes after Pancreatic Surgery

Bart M.G. Baekelandt[1], Morten W. Fagerland[2], Marianne J. Hjermstad[3], Turid Heiberg[4], Knut J. Labori[5] & Trond A. Buanes[1,5]

[1]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway, [2]Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Norway, [3]European Palliative Care Research Centre (PRC), Department Oncology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Norway, [4]Østfold University College, Norway, and [5]Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Norway

Abstract

Background: Long-term effects of complications in pancreatic surgery have not been systematically evaluated. The objectives were to assess potential effects of complications on survival and patient reported outcomes (PROs) as well as feasibility of PRO questionnaires in patients with periampullary and pancreatic tumors.

Methods: From October 2008 to December 2011, 208 patients undergoing pancreatic surgery were included in a prospective observational study. ESAS, EORTC QLQ-C30 and QLQ-PAN26 questionnaires were completed at inclusion, then every third month. Complications were recorded according to the Clavien-Dindo (CD) classification and Comprehensive Complication Index (CCI).

Results: 148 complications were registered in 100 patients (48%), 36 patients (17%) had CD IIIa or above. 125 patients (60%) completed baseline questionnaires, 80 (39%) responded after three and 54 (28%) after six months. Complications were associated with reduced long-term survival in patients with pancreatic ductal adenocarcinoma (PDAC) (p = 0.049) and other malignant diseases. No significant relationship was found between complications and PROs, except for anxiety, which was significantly increased in patients with complications.

Conclusion: Postoperative complications led to increased anxiety at 3 months after surgery and were associated with reduced long-term survival in patients with malignancy. A short, patient derived, disease specific questionnaire is required in the clinical research context.

Correspondence

Trond A. Buanes, Professor of Surgery Institute of Clinical Medicine, Faculty of Medicine, University of Oslo Department of Hepato-Pancreatico-Biliary (HPB) Surgery, Oslo University Hospital (OUS), Nydalen, N-0424 Oslo Norway. E-mail: trond.buanes@medisin.uio.no

Introduction

Long term survival in pancreatic and periampullary cancer is very unlikely without surgical resection[1,2]. Prognosis varies greatly between different histological diagnoses, but despite surgery, survival is poor in many patients, and quality of life (QoL) is important during their short residual lifetime. Postoperative complications may result in shorter survival and impaired QoL, and the outcome of surgery depends profoundly on the frequency, severity grade and management of complications.[3] Comprehensive efforts have been made to define and classify severity grade of complications after pancreatic surgery, and the consensus definitions have been widely implemented.[4] However, a need to refine the concepts and redefine specific complications has recently been recognized.[5,6] The Clavien-Dindo (CD) classification has defined severity grade for single complications[7,8] and the Comprehensive Complication Index (CCI) integrates all complications and offers a metric approach to measure the overall burden of postoperative complications in each patient.[9,10] The main objective of this study was to assess the impact of complications on survival and patient reported outcomes (PROs) in a patient cohort undergoing pancreatic surgery. Furthermore, we sought to test the feasibility of the Edmonton

Symptom Assessment System (ESAS), EORTC QLQ-C30 and the disease specific module QLQ-PAN26 as PRO-measures in a clinical research setting.

Methods

In October 2008, Oslo University Hospital established a multidisciplinary research program for patients undergoing investigation for pancreatic or periampullary tumours. Clinical data, including postoperative complications and PROs were recorded prospectively. Overall, 426 patients with suspected pancreatic or periampullary cancer were included from October 2008 to December 2011. 208 patients (49%) underwent surgery, whereas 218 did not due to benign diagnoses (n = 41) or unresectable malignant disease (n = 177).

Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 2008, ref 265-08412c) for registration of clinical data and sampling of blood and tumour tissue for research purposes. All patients were included after signed informed consent.

Preoperative work-up/treatment

All patients underwent evaluation at the multidisciplinary meeting, as described previously.[11] Preoperative workup included multidetector computed tomography (CT) with a standard protocol optimized for imaging pancreatic tumours, and chest CT. Tumours infiltrating the superior mesenteric vein (SMV) or portal vein (PV) were considered resectable if there was a patent vein above and below the infiltrated site to allow reconstruction.[12,13] Preoperative histological diagnosis was not required. Neoadjuvant chemotherapy was not given to any patient, and radiation therapy was not offered, pre- or postoperatively.

Quality of life and symptom score assessment

The general cancer questionnaire QLQ-C30 comprises 30 questions constituting 5 functioning and 3 symptom scales, 6 single items and one global health/QoL scale. QLQ-PAN26 is a diagnosis-specific module with 26 questions developed for pancreatic cancer. Both forms are scored on 1–4 categorical scales ranging from; not at all, a little, quite a bit and very much, except for the global health/QoL scale (going from 1 to 7). The EORTC QLQ-C30 and QLQ-PAN26 raw scores were converted to a 0–100 scale using recommended EORTC procedures.[14] The at the time most frequently used Norwegian version of the Edmonton Symptom Assessment System (ESAS) was applied.[15] It differs from the original by including a question about oral dryness and a second question about pain at movement, supplementing the item on pain at rest. Symptoms are scored on numerical rating scales, ranging from 0 (no

symptom, normal/good) to 10 (worst possible). Similar to the original version, the Norwegian does not specify the timeframe for rating of symptoms, but patients were informed that the ESAS should reflect current symptoms, according to our common practice.[16]

Baseline PRO and longitudinal follow-up

Inclusion of patients and baseline clinical data were collected in the outpatient clinic, or upon preoperative admission at the latest. Baseline PROs were preferably collected in the outpatient clinic, but if patients found the forms too comprehensive, they met a second request at admission. Follow-up questionnaires on PROs and symptoms were mailed to each patient every third month postoperatively with no end date, no reminders were sent and no external incentives were provided. The resulting response rates were considered an indicator of feasibility of the combination of QLQ-C30/QLQ-PAN26 and ESAS forms, for this patient cohort in a clinical setting.

Complications

Pancreatic fistula,[17] delayed gastric emptying[18] and postoperative haemorrhage[19] were classified according to the criteria set by the International Study Group for Pancreatic Surgery (ISGPS). Severity grade, based on required therapeutic consequences according to CD[8] was also recorded with particular focus on patients with severity grade III-V, requiring radiological, endoscopic or surgical intervention, experiencing organ failure or suffering lethal consequences. The CD grading was used to calculate the CCI by means of the online tool (www.assesssurgery.com). This is an index ranging from 0 (no complication) to 100 (death) based on CD grades for every single complication, summarized to a metric score for the total complication burden. Survival was defined as time from surgery to death of any cause or the end of follow-up through 30 June 2017, whichever came first.

Statistical analysis

Wilcoxon rank-sum (Mann–Whitney) test was used to compare independent variables without assuming a normally distributed dependent variable. Chi-square test was used to examine the relationship between categorical variables. The Kaplan Meier estimator was used to estimate median survival times. Cox regression was used to assess a variable's association to survival. Change in longitudinal PRO was examined, using box-plots and scatterplots. We used linear regression comparing CCI as the dependent variable of difference in PROs from baseline to 3 and 6 months. For longitudinal PROs, only ESAS was used, to reduce data-fishing. Correlation between CCI and length of hospital stay (LOS) was estimated with Spearman correlations. Required level of significance was set at 5%. Unless specified otherwise, numbers in parentheses represent 95% confidence intervals.
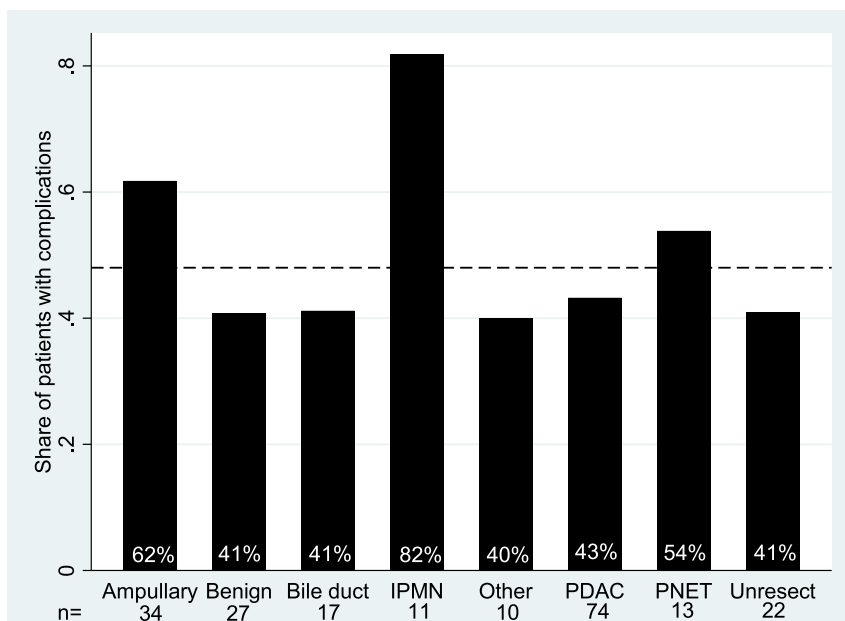
Figure 1 Share of patients with postoperative complications in each diagnostic subgroup, horizontal line reflecting the share of total patients with complications (48%). Ampullary: carcinoma in the ampulla of Vater. Bile duct: extrahepatic bile duct carcinoma. IPMN: intraductal papillary mucinous neoplasm. PDAC: pancreatic ductal adenocarcinoma. PNET: pancreatic neuroendocrine tumour
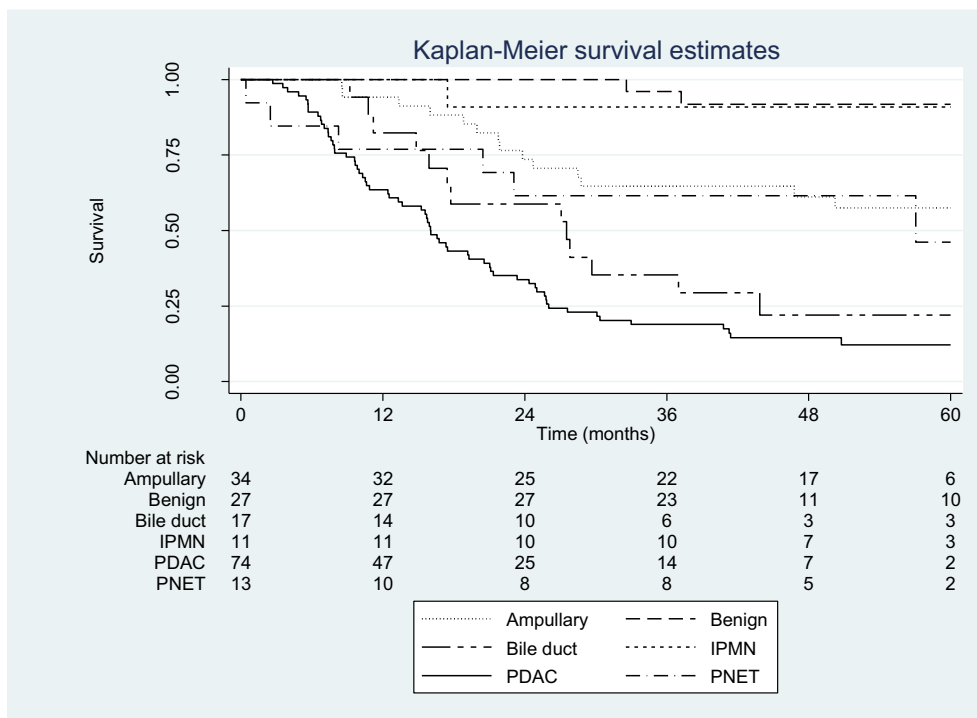

Figure 2 Postoperative overall survival after pancreatic resection by diagnosis. Ampullary: carcinoma in the ampulla of Vater. Bile duct: extrahepatic bile duct carcinoma. IPMN: intraductal papillary mucinous neoplasm. PDAC: pancreatic ductal adenocarcinoma. PNET: pancreatic neuroendocrine tumour

Results

Patient characteristics, procedures and histological diagnosis

In 208 operated patients, median age was 70.5 years (range 36−91), and 51% were female. 156 patients (75%) underwent a pancreatoduodenectomy or total pancreatectomy and 23 (11%) distal pancreatectomy with splenectomy. 15 patients underwent resection of the SMV/PV or the common hepatic artery/superior mesenteric artery (CHA/SMA). Seven patients (3%) were operated with other surgical methods (enucleation, duodenal resection). During laparotomy, 22 patients (11%) were found unresectable. Two patients were reoperated, one due to PV thrombosis after a pancreatoduodenectomy with SMV/PV resection and reconstruction with interposition graft, and the other because of pancreatic fistula, grade C, necessitating remnant pancreatectomy.

Histological diagnoses were pancreatic ductal adenocarcinoma (PDAC) in 74 patients (36%), ampullary carcinoma in 34 (16%), extrahepatic bile duct carcinoma in 17 (8%), pancreatic neuroendocrine tumor (PNET) in 13 (6%), invasive carcinoma associated with intraductal papillary mucinous neoplasm (IPMN) in 11 (5%) and 10 patients (5%) had other periampullary malignancies. 27 patients (13%) had benign conditions. According to the American Joint Committee on Cancer (AJCC) system of tumor, node and metastasis staging for PDAC, 10 (13%) were stage 1, 62 (83%) were stage 2 and 2 (3%) were stage 3. The most common diagnosis for patients considered unresectable at laparotomy was PDAC, accounting for 16 of 22 patients, with the remaining 6 diagnosed with other malignancies.

Complications, hospital stay and adjuvant chemotherapy

At least one postoperative complication was recorded in 100 patients (48%). Overall 148 complications were documented, with some patients having three, four or five different complications. Of the 148 complications, 21 (14%) were CD grade I, 83 (56%) grade II, 24 (16%) grade IIIa, 12 (8%) grade IIIb and 7 (5%) grade IVa, no complications were grade IVb and one was grade V (postoperative death). Median CCI in the whole cohort was 0 (0−8.7), in the 100 patients with complications it was 20.9 (20.9−26.2). Median age in patients without and with complications was 68 (66−72) years versus 72.5 (70−75) years, respectively (p = 0.04). There was no statistically significant difference in gender or type of procedure between these groups. Despite apparent differences in complication frequency in different diagnostic groups (Fig. 1), these differences were not statistically significant, likely as a result of small numbers of patients in each group. Length of stay (LOS) in patients without and with postoperative complications was a median of 10[9,10] versus 18[15−21] days respectively (p < 0.001). CCI correlated with LOS r_s = 0.590 (0.487−0.694) (p < 0.001).

Among 74 patients with PDAC, 32 had postoperative complications. Adjuvant chemotherapy was delivered to 21 of these 32 patients, versus 30 of the 42 patients without complications. In both groups the portion is two thirds of the patients, with no significant difference. For these 74 patients, there was no significant difference in AJCC stage between patients with and without complications.

Survival

By June 2017, 132 (63%) patients were dead. Periampullary carcinomas of different tumor origin and histological subtype had significantly different prognosis. Invasive carcinoma associated with IPMN lesions had an estimated 91% 5-year survival versus 14% for PDAC (Fig. 2). The estimated median postoperative overall survival in PDAC was 16 (13−21) months versus 26 (21−37) months for all carcinomas, analysed together.

The impact of postoperative morbidity on survival was negative in resected PDAC patients, as shown in Fig. 3a,
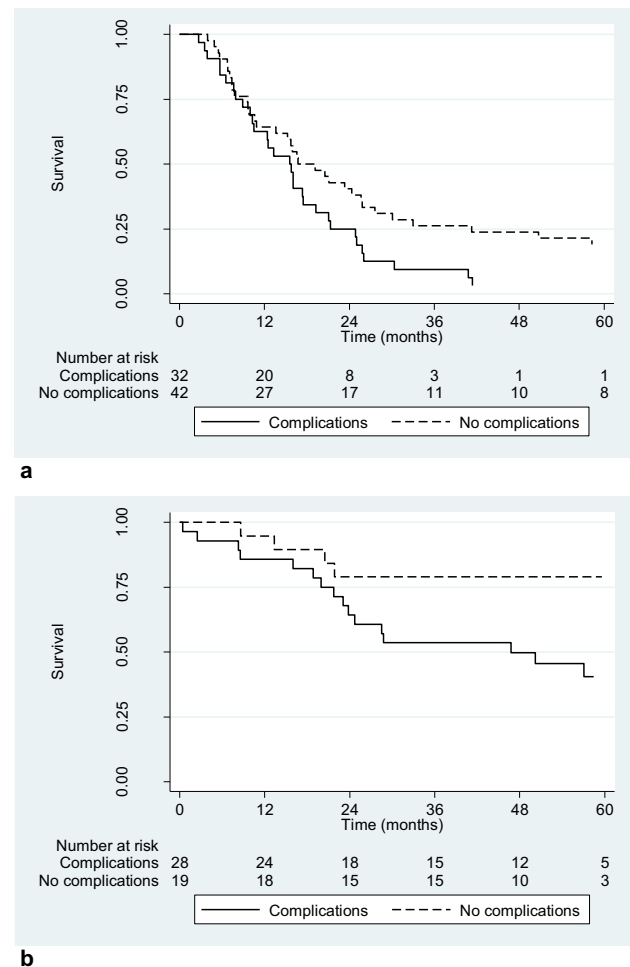

a

b

Figure 3 a) Survival in PDAC-patients with and without complications (p = 0.049). b) Survival in patients with pancreatic neuroendocrine or ampullary carcinoma, with or without complications (p = 0.036)

p = 0.049. Median overall survival was 15.6 (10.0–19.3) months in complicated compared to 16.8 (10.9–25.7) months in uncomplicated procedures, 5-year survival 1% versus 19%. Patients with PNET and ampullary carcinoma had almost identical postoperative survival curves and a similar frequency of postoperative complications. These groups were combined in the analysis of the relationship complications/long-term survival. Fig. 3b illustrates that also in this combined group, patients with an uncomplicated postoperative course survive significantly longer (p = 0.036). In patients with IPMN or benign tumor, there is no such difference. When all resected patients were analyzed together as one heterogeneous group, survival was the same with or without postoperative complications.

Short term and long term patient reported outcome

At baseline, 125 patients (60%) completed ESAS forms, 123 (59%) the QLQ-C30, and 132 (63%) QLQ-PAN26. After three (n = 205) and six (n = 193) months, the corresponding numbers were 80 (39%), 79 (39%), 82 (40%) and 54 (28%), 58 (30%), 58 (30%) respectively, as shown in Fig. 4.

Return rates of PRO questionnaires was not associated with survival, neither was there any difference in response rates associated with adjuvant chemotherapy, complications or histological diagnosis.

Comparing PRO, measured with ESAS, in patients with (n = 100) and without (n = 108) complications using box-plots,

or comparing PRO with severity of complications (CCI) using scatter-plots, revealed no difference at 3 and 6 months.

In PDAC patients with uncomplicated postoperative course (n = 42), we received completed PRO measures from 27, 20 and 16, preoperatively, at 3 and 6 months respectively, versus 19, 16 and 11 for patients with complications (n = 32). The only significant difference in specific PRO items between these two groups was anxiety (p = 0.013) with higher levels of anxiety for patients with complications after three months, whereas the high priority items pain and fatigue showed no difference in scores (Fig. 5).

Mean pain score for all patients (n = 125) preoperatively, at 3 and 6 months were 2.0, 1.8 and 1.6, respectively. For fatigue, corresponding scores were 3.3, 3.0 and 3.4. Mean general wellbeing (high score indicates poorer wellbeing) was 3.1, 2.8 and 3.1. There were no statistically significant differences in preoperative and postoperative values. Only 17 patients returned completed questionnaires at the long term follow-up (12–48 months). General wellbeing was improved in 13 patients, whereas four patients described reduced wellbeing.

Discussion

The current study shows that postoperative complications did not significantly impact PRO at 3 and 6 months after pancreatic surgery, except for anxiety, which was significantly increased in
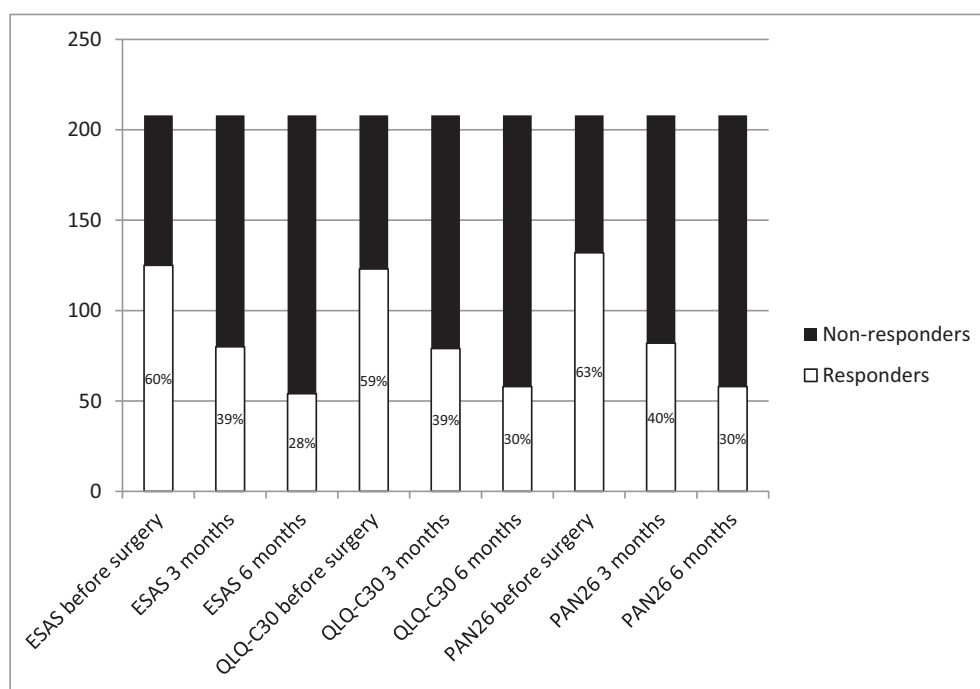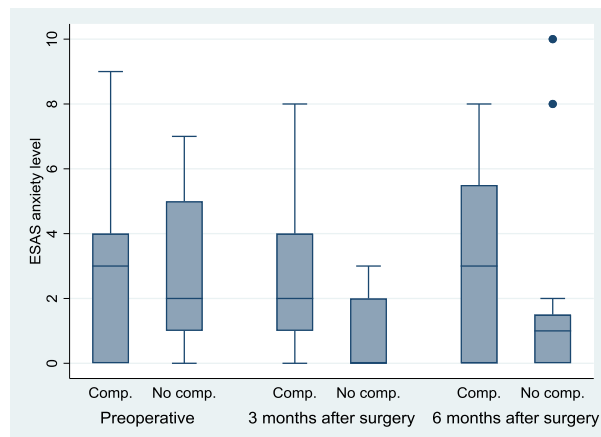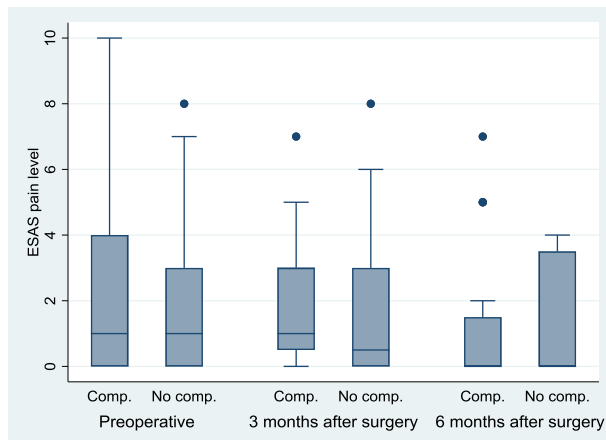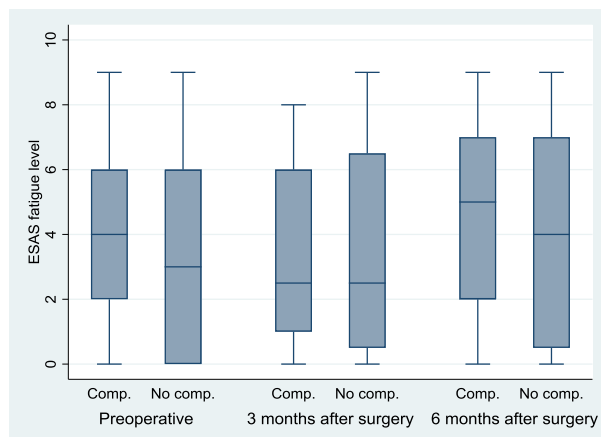

Figure 4 The percentage of responders for QoL questionnaires ESAS, EORTC-QLQ-C30 and QLQ-PAN26 before surgery (n = 208), at 3 (n = 205) and 6 (n = 193) months after surgery

a

b

c

Figure 5 Box-plots for anxiety, pain and fatigue (ESAS) preoperatively (n = 19/27), at 3 (n = 16/20) and 6 months (n = 12/16) for PDAC patients with/without complications. a) Anxiety, group difference p = 0.013 at 3 months after surgery. b) Pain, no significant difference. c) Fatigue, no significant difference

patients with postoperative complications 3 months after surgery. Postoperative complications were also associated with reduced long-term survival in patients with malignancy. Moreover, the response rate to the PRO questionnaires was low. Postoperative complications in PDAC-patients resulted in significantly shorter survival but no such correlation could be found when the entire patient cohort was analyzed together. A couple of explanations are apparent. First, different histological diagnoses have different prognosis. Second, the frequency of postoperative complications seems to differ between diagnoses. Accordingly, the putative impact of complications on survival has to be analyzed among patients with homogenous histological diagnoses, or in groups with equal survival and similar complication rates. This applies for patients with PNET and ampullary carcinoma, and complications result in decreased survival when these groups were analyzed together. Poor survival in PDAC patients who do not receive proper adjuvant treatment due to postoperative complications after pancreatic surgery have previously been described.[20] The same effect of postoperative complications on long-term survival has been reported in intrahepatic cholangiocarcinoma.[21] However, adjuvant chemotherapy was given to equal portions of PDAC patients with or without complications, making this explanation in the present cohort less likely. A potential reason for decreased survival might be an immunological response from complications which in turn leads to increased tumor activity.[22]

An argument against the increased use of surgery in pancreatic cancer is that negative impact on postoperative QoL might outweigh the benefits in survival. However, already in 2005, return to preoperative or better values of QoL was reported 3 months after pancreatic resection.[23] Another report from the Netherlands stated that full recovery of QoL after pancreatic surgery took up to 6 months.[24] A recent investigation from Finland in 47 PDAC patients also found return to preoperative QoL levels within 3 months.[25] In the latter study, patients were followed for 24 months after pancreatoduodenectomy, when less than half were still alive (n = 23) and only 20 patients responded to the questionnaire. Many surviving patients probably suffered from recurrence after two years, illustrating a methodological problem associated with investigation of outcome of pancreatic surgery. Postoperative QoL may be influenced by surgical complications as well as the malignant disease. Accordingly, prospective studies with different design are mandatory. Our preference was to include all patients with intended pancreatic surgery in the study, as patients with favorable tumour biology represent the best opportunity to investigate long term PRO focused on the clinical impact of complications. We found no difference in PRO at 3 or 6 months after pancreatic surgery, compared to preoperative PRO. However, patients with complications had significantly higher anxiety at 3 months after surgery than patients with no complications. No other difference in PRO was found between these groups. Even if response rates were low in this study, it is important to notice that 13 of 17 long

term responders reported long term PRO above preoperative levels. This investigation therefore supports to push forward the borders of resectability, as resectional surgery increases survival and improves QoL in most patients.

The present study indicates that the comprehensiveness of PRO measures/symptom-scores is a major obstacle for high response rates in a routine clinical setting. A recent study with PROs as the primary endpoint after mastectomy reconstruction, achieved a response rate of 72.5% to the postoperative questionnaires BREAST-Q and PROMIS-29. This illustrates that low response rate is a challenge, even in a patient group with significantly better prognosis than pancreatic cancer.[26] A previous study of QoL in 51 patients with metastatic PDAC, included in a palliative care program at our center, utilized the same PRO measurements as we did in the present study. We obtained completed forms from all patients at baseline, as well as longitudinal response from more than half.[27] Low response rates to QLQ-C30, QLQ-PAN26 and ESAS questionnaires in the present study may in part be associated with the design of this study, as no incentives to respond were offered, beyond the letter every third month. It is an ambition at our center to record outcomes longitudinally in all patients in order to improve information to future patients on the risk of adverse outcome of pancreatic surgery. Therefore, one of our objectives was to evaluate the feasibility of these combined measures in a routine clinical setting. Studies investigating benefits or possible harm of pancreatic surgery should include longitudinal PROs with QoL as endpoint. This has been increasingly underlined worldwide.[2,28,29] However, the QLQC30/QLQ-PAN26 forms seem unfeasible, as they may be too long. Furthermore, many patients consider some items as irrelevant in their clinical condition. During the development of the Pancreatic Cancer Disease Impact (PACADI) score,[30] item selection was based on patients' priorities of which dimensions of PRO had greatest impact on their everyday QoL. This increase in relevance of questions as well as the short nature of the instrument, with only eight questions, is expected to improve the feasibility of PRO-measurement in a clinical research setting.

Conflict of interest

The authors have no conflicts of interest.

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