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ORIGINAL RESEARCH

# Clinical Pathways For Pancreatic Surgery: Are They A Suitable Instrument For Process Standardization To Improve Process And Outcome Quality Of Patients Undergoing Distal And Total Pancreatectomy? - A Retrospective Cohort Study

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**Purpose:** Pancreatic surgery demands complex multidisciplinary management, which is often cumbersome to implement. Clinical pathways (CPs) are a tool to facilitate this task, but evidence for their utility in pancreatic surgery is scarce. This study evaluated if CPs are a suitable tool for process standardization in order to improve process and outcome quality in patients undergoing distal and total pancreatectomy.

**Patients and methods:** Data of consecutive patients who underwent distal or total pancreatectomy before (n=67) or after (n=61) CP introduction were evaluated regarding catheter management, postoperative mobilization, pancreatic enzyme substitution, resumption of diet and length of stay. Outcome quality was assessed using glycaemia management, morbidity, mortality, reoperation and readmission rates.

**Results:** The usage of incentive spirometers for pneumonia prophylaxis increased. The median number of days with hyperglycemia decreased significantly from 2.5 to 0. For distal pancreatectomy, the incidence of postoperative diabetes dropped from 27.9% to 7.1% (p=0.012). The incidence of postoperative exocrine pancreatic insufficiency decreased from 37.2% to 11.9% (p=0.007). There was no significant difference in mortality, morbidity, reoperation and readmission rates between groups.

**Conclusion:** Following implementation of a pancreatic surgery CP, several indicators of process and outcome quality improved, while others such as mortality and reoperation rates remained unchanged. CPs are a promising tool to improve quality of care in pancreatic surgery.

**Keywords:** clinical pathways, pancreatic surgery, distal pancreatectomy, pancreatectomy, quality of care

## Introduction

Pancreatic surgery demands complex and multidisciplinary perioperative management to mitigate the risk of potentially dangerous postoperative complications. Impaired exocrine and endocrine function after pancreatic resection can lead to malnutrition due to lipid malabsorption and diabetes mellitus. Especially after total pancreatectomy, some patients suffer from serious hypoglycemia which can be life-threatening.[1] In

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distal pancreatectomy and pancreatic head resection, there is a considerable risk of pancreatic stump leakage or pancreatic fistula. Distal pancreatectomy is often combined with splenectomy which is related to a higher rate of infectious complications.[2]

One possible approach to ensure a high quality of perioperative management is the implementation of clinical pathways (CPs).[3] CPs are intended to advance quality of processes and, consequently, of outcomes. They are a timeline protocol for all tasks that have to be performed in the course of a given treatment.[4–6] CPs usually involve all different disciplines that are part of the treatment team and aim to translate evidence into clinical practice.[7–9] CPs have shown favorable perioperative results for a number of operations in gastrointestinal surgery.[10] Kennedy et al (2012), Walters et al (2012) and Van der Kolk et al (2017) evaluated CPs for pancreaticoduodenectomy.[11–13] All showed a reduction in length of stay and Kennedy et al additionally reported a non-significant decrease of overall complication rates. Van der Kolk reported a significant decrease of major complications according to the Clavien-Dindo classification. There are three studies assessing CPs for distal pancreatectomy, and, to our knowledge, none for total pancreatectomy. While one of the studies for distal pancreatectomy showed no difference in outcomes and length of stay after CP implementation,[14] two studies demonstrated an improvement in length of stay and short-term outcomes.[15,16] Given the limited evidence, we conducted a study assessing if CPs are a suitable instrument for process standardization in order to improve process and outcome quality in patients undergoing distal or total pancreatectomy.

# Patients And Methods

## CP Design, Implementation, And Content

Since 2006, the Department of Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University has performed a stepwise implementation of CPs for different surgical procedures.[17–25] In February 2011, three CPs were introduced for pancreatic surgery: one for pancreaticoduodenectomy, one for distal pancreatectomy, and one for total pancreatectomy. The first mentioned CP has been assessed in a separate study.

The content of the CP is based on CPs for fast-track colorectal and bariatric surgery which had been previously established.[18,19] Specific treatment steps were modified to adapt this CP for use in pancreatic surgery. Both the original colorectal CP and the pancreatic surgery CPs are based on national and international treatment and nursing recommendations, as well as on best available evidence. The design and implementation processes were carried out by an interdisciplinary (surgery, anesthesiology, physiotherapy, nutritional services) and multi-hierarchical team.

First drafts of the respective CPs were elaborated after a literature review to identify evidence on perioperative treatment elements. In a second step, pre-existent institutional standards were integrated into the CPs. In a last step, a consensus meeting with all project participants was held to agree on a final CP version. Prior to definite implementation, all staff members were trained on how to work with the CPs. After implementation, continuous efforts were made to further develop and improve the CPs based on suggestions of staff members.

Full versions of the CPs are shown in the online Supplementary material. The main elements of the CPs included the following items: hospital admission was scheduled for the day before surgery. Epidural catheter placement was stipulated for all patients. A stepwise oral analgesia scheme, with a basis medication of non-opioids and on demand medication of potent opioids, was included in both CPs. Patients were monitored postoperatively in a surgical intermediate care unit for at least one night or in an intensive care unit, if considered necessary by the surgeon and/or anesthesiologist. All patients were encouraged to drink sweetened tea until two hours prior to planned intubation. For distal pancreatectomy, pancreas enzymes in the drainage fluid were determined on days three and five after surgery. Detailed instructions on how to use an incentive spirometer were given to all patients. Pancreatic enzymes were orally substituted in case of steatorrhea. Glycaemia levels were closely monitored. In the distal pancreatectomy CP, an on-demand insulin scheme was included, whereas the total pancreatectomy CP included a fixed glycaemia-dependent insulin scheme. The designated time of discharge was day ten for distal pancreatectomy and day twelve for total pancreatectomy. Outpatient follow-up appointments were scheduled within 14 days of discharge. Patients were instructed to present at our emergency room in case of clinical abnormalities.

CPs were designed as four-page paper-based documents containing all stipulated treatment steps for the single pre- and postoperative days. They were kept with patients' treatment charts and thus always available for all staff involved in treatment.

## Study Design

The study was designed as a single center retrospective study. A research protocol had been developed before evaluation. The protocol has not been published previously. All patients undergoing elective distal or total pancreatectomy were included. The intervention group (CP group), either distal pancreatectomy (CP-D group) or total pancreatectomy (CP-T group), comprised all consecutive patients operated following the implementation of the CPs in February 2011. The control group (pre-CP group), either distal pancreatectomy (pre-CP-D group) or pancreatectomy (pre-CP-T group), comprised all patients operated in the five years (pre-CP-D) or eight years (pre-CP-T) before CP implementation, respectively. In this retrospective study, there was no formal sample size calculation. Study group sizes were determined in order to obtain equally large groups before and after CP implementation. All necessary data were retrieved by retrospective chart review.

Patients in the CP groups were treated according to the respective CP (see below), whereas the pre-CP groups were treated according to the individual judgment of and decisions taken by the treating surgeons. Although several semiformal standards for selected elements of care (e.g., epidural analgesia, early removal of catheters, early mobilization) had been in place, at that time there was no instrument covering the whole treatment continuum.

The study was approved by the competent ethical committee of the Medical Faculty of Mannheim (2015-863R-MA). Patient consent to review their medical records was not required by the ethical committee because of the retrospective nature of the study without direct patient contact and without any study-related measures which directly affected the patient. Confidentiality of patient data was ensured. The study was conducted in compliance with the Declaration of Helsinki. Neither the individual deidentified participant data, nor the specific data is intended to be shared by the authors. The clinical pathway documents will be accessible indefinitely, as online supplement data. The study has been registered at the German Clinical Trials Register (DRKS 00016749).

## Surgery

In both groups (before and after CP implementation), surgery was performed by dedicated HPB surgeons with an experience of more than four years. All surgeons performed surgery according to the in-house standard. Pancreatectomy and distal pancreatectomy were performed in a uniform fashion. In case of distal pancreatectomy sharp transection was performed with a blade in a "fish-mouth" fashion. The visible main pancreatic duct was occluded by a stich and the pancreatic remnant was secured with minimal sutures.

## Study Outcomes

The preoperative status of patients was assessed using the ASA (American Society of Anesthesiologists) physical status classification system.[26] The study evaluated parameters of both process and outcome quality. Process and outcome quality were defined according to the model proposed by Donabedian.[27,28] Process quality was defined as the adherence to treatment specifications as detailed in the CP. It reflected protocol adherence and was assessed by the following parameters: placement of central venous line and epidural catheter, day of removal of foley catheter and epidural catheter, day of first and second measurement of pancreas enzymes in the drainage fluid, substitution of pancreas enzymes and administration of somatostatin, removal of intraabdominal drainages and nasogastric tube, application of single shot antibiotics, postoperative mobilization and day of resumption of liquid and solid diet.

Outcome quality was measured through the following variables: morbidity, mortality, reoperation, length of stay stratified by the presence or absence of complications, pain levels on a numeric rating scale, day of first postoperative defecation and readmission. Morbidity was assessed according to the Clavien-Dindo classification of postoperative complications.[29] The following complications were specifically assessed: postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and postoperative pancreatic hemorrhage (PPH). For the different degrees of severity, the official definitions of the International Study Group of Pancreatic Surgery (ISGPS) were used.[30–32] Other specific complications included postoperative pancreatitis, hypoglycemia (blood glucose level lower than 60mg/dl), days with at least one measured blood glucose level higher than 200 mg/dl, postoperative diabetes (fasting blood glucose level higher than 126 mg/dl), and exocrine insufficiency (repetitive substitution of pancreas enzymes). Surgical site infections were diagnosed according to the Centers for Disease Control and prevention (CDC) definition.[33] Readmission was only counted as such if it took place within 14 days after initial discharge and was related to a postoperative problem.

## Statistical Analysis

All study outcomes were compared between the respective CP and pre-CP groups. No imputation of missing values was performed, and missing values were not counted in the analyses. Dichotomous variables were evaluated with the chi-square test. Ordinal variables were evaluated with student's *t*-test if normally distributed and the Mann–Whitney-*U*-test if not normally distributed. P-values <0.05 were considered to be significant. There was no adjustment for multiple testing. For all statistical analyses, the software SAS 13.2 was used.

# Results

## Patients' Characteristics

During the study period, 85 patients underwent distal pancreatectomy, of which 43 were in the pre-CP-D and 42 in the CP-D group (Table 1). Thirty-three patients underwent total pancreatectomy, comprising 24 in the pre-CP-T and 19 in the CP-T group. Figure 1 summarizes the patient recruitment and group allocation. There were no relevant differences between the pre-CP and CP groups regarding demographic and clinical characteristics of patients. Likewise, the underlying condition for which resection was performed did not differ between groups for total pancreatectomy. In the CP-D group, the frequency of splenectomy was significantly higher.

## Process Quality

The comparison of measures of process quality is presented in Table 2. Regarding distal pancreatectomy, there was a number of significant differences between the pre-CP-D and CP-D group. The number of patients receiving a central venous catheter decreased after CP implementation. The day of the removal of the central venous catheter, arterial catheter, foley catheter, nasogastric tube and abdominal drainage did not differ for patients treated with and without CP. Likewise, the days of first intake of liquids, liquid nutritional supplement and solids did not change after CP implementation. The postoperative day of first and second determination of pancreas enzymes in drainage liquids differed significantly between groups, with more patients in the CP group receiving enzyme determination on the recommended days. Usage of incentive spirometers increased significantly following CP implementation. All patients in the CP-D group used a spirometer. Lastly, patients were mobilized later in the CP-D group.

For total pancreatectomy, there were fewer differences between the pre-CP-T and CP-T group. The only significant finding was that patients in the CP-T group used significantly more often an incentive spirometer than those in the pre-CP-T group. In the CP-T group, all but one patient used a spirometer. Foley catheters were removed later in the CP-T than the pre-CP-T group, and the finding showed a trend towards statistical significance.

## Outcome Quality

The results regarding outcome quality are outlined in Table 3. The causes of mortality are well-known complications after total pancreatectomy. In the pre-CP-T group, one patient each died due to septic multi-organ failure, post-pancreatectomy hemorrhage and an unknown cause. One patient with septic multi-organ failure suffered from a bowel leakage, the other patient from a severe atypical pneumonia and the third patient from liver failure of unknown cause. The patient with post-pancreatectomy hemorrhage had a leakage of the duodenojejunostomy, with septic bleeding from the aorta. In the CP-T group, two patients died due to multi-organ failure: one caused by postoperative hemorrhage from the portal vein and the other one caused by necrotizing pancreatitis and severe pneumonia. One patient in the CP-T group died due to liver failure caused by postoperative occlusion of the hepatic artery. After distal pancreatectomy, one patient in each group died due to septic multi-organ failure, caused by severe pneumonia. One of these patients suffered from severe COPD, the other one had POPF Grade C.

There were several significant differences in patients undergoing distal pancreatectomy. After CP implementation, the median number of days with glycaemia >200 mg/dl was reduced from 2.5 to 0, and the incidence of postoperative diabetes mellitus was lower. The incidence of postoperative exocrine insufficiency was lower in the CP-D compared to the pre-CP-D group. The number of days with a relevant pain level was higher in the CP-D than the pre-CP-D group, but the difference was only borderline significant. It was not reflected by a higher number of requests for additional analgesics. Regarding postoperative morbidity and mortality, there were no differences between groups, neither for the summary measures, nor for specific complications. Length of stay did not relevantly differ between patients treated with and without CP, and the discharge goal stipulated in the CP was not met.

**Table 1** Characteristics Of The Study Groups

| Patient Characteristic | Distal Pancreatectomy | | p-value | Total Pancreatectomy | | p-value |
|---|---|---|---|---|---|---|
| | January 2006 -February 2015 | | | August 2003 -February 2015 | | |
| | Pre-CP-D Group (n=43) % | CP-D-Group (n=42) % | | Pre-CP-T Group (n=24) % | CP-T-Group (n=19) % | |
| Mean age (years) | 63.79 | 62.12 | 0.595 | 66.04 | 66.68 | 0.853 |
| Sex | | | 0.933 | | | 0.342 |
| Male | 16 (37.2) | 16 (38.1) | | 13 (54.2) | 13 (68.4) | |
| Female | 27 (62.8) | 26 (61.9) | | 11 (45.8) | 6 (31.6) | |
| Mean BMI | 28.00 | 26.18 | 0.241 | 24.75 | 25.25 | 0.691 |
| ASA-Score | | | 0.709 | | | 0.868 |
| I | 3 (6.9) | 2 (4.7) | | 1 (4.2) | 1 (5.3) | |
| II | 17 (39.5) | 22 (52.4) | | 7 (29.2) | 9 (47.4) | |
| III | 11 (25.5) | 18 (42.9) | | 4 (16.6) | 7 (36.8) | |
| IV | 0 | 0 | | 0 | 2 (10.5) | |
| X | 12 (28.0) | 0 | | 12 (50.0) | 0 | |
| Underlying condition | | | | | | |
| Adenocarcinoma | 13 (30.2) | 10 (23.8) | | 20 (83.3) | 10 (52.6) | |
| Others | 8 (18.6) | 15 (35.7) | | 0 | 4 (21.1) | |
| NET | 5 (11.6) | 4 (9.5) | | 0 | 0 | |
| IPMN | 11 (25.6) | 7 (16.7) | | 3 (12.5) | 3 (15.8) | |
| Chronic pancreatitis | 6 (14.0) | 6 (14.4) | | 1 (4.2) | 2 (10.5) | |
| UICC$^{+}$ | | | 0.092 | | | 0.593 |
| IA | 0 | 1 (2.4) | | 0 | 1 (5.3) | |
| IB | 1 (2.3) | 0 | | 1 (4.2) | 0 | |
| IIA | 4 (9.3) | 3 (7.1) | | 4 (16.7) | 2 (10.5) | |
| IIB | 6 (14.0) | 5 (11.9) | | 11 (45.8) | 6 (31.6) | |
| III | 0 | 1 (2.4) | | 1 (4.2) | 1 (5.3) | |
| IV | 2 (4.7) | 0 | | 2 (8.3) | 0 | |
| X | 0 | 0 | | 1 (44.2) | 0 | |
| No carcinoma | 28 (65.1) | 32 (76.2) | | 4 (16.7) | 9 (47.3) | |
| Mean albumin (g/l) | 36.2 | 36.0 | 0.877 | 34.52 | 32.4 | 0.371 |
| Mean hemoglobin g/dl) | 12.74 | 12.75 | 0.971 | 12.58 | 12.59 | 0.978 |
| Median glucose (mg/dl) [range] | 100 [46–251] | 110.5 [9–460] | 0.651 | 115 [74–339] | 117 [69–232] | 0.864 |
| Mean operation time (min) | 245.86 | 244.17 | 0.913 | 406.92 | 439.63 | 0.354 |
| Splenectomy | 27 (62.8) | 35 (83.3) | 0.033* | 7 (29.1) | 6 (31.6) | 0.864 |
| Median number of resected lymph node [range] | 12 [1–35] | 9 [0–33] | 0.202 | 17.5 [2–39] | 16.5 [6–44] | 0.796 |
| Median number transfused blood products [range] | 0 [0–6] | 0 [0–8] | 0.295 | 1.5 [0–53] | 1 [0–27] | 0.372 |

**Notes:** Underlying condition others Pre-CP-D Group= in declining order three cystadenomas, two non-Hodgkin lymphomas, and one pancreatic adenosquamous carcinoma, perforated pancreatic cyst, biliary fistula each; dignity others CP-D Group= in declining order seven cystadenomas; and one non Hodgkin lymphoma, liposarcoma, infiltrating urothelial carcinoma; metastasis of renal cell carcinoma, pseudocyst; metastasis of bronchial carcinoma, pancreas retention cyst, intrapancreatic splenic heterotopia each; dignity others CP-T Group= in declining order two undifferentiated pancreas carcinomas, and one metastasis of liposarcoma, metastasis of renal cell carcinoma each; *p-value ≤ 0.05; $^{+}$for patients with pancreatic adenocarcinoma; X=missing data.

**Abbreviations:** BMI, Body-Mass-Index; ASA, American Society of Anesthesiology; UICC, Union Internationale Contre le Cancer; Pre-CP-D Group, Pre-Clinical pathway-Distal pancreatectomy Group; CP-D Group, Clinical pathway-Distal pancreatectomy Group; Pre-CP-T Group, Pre-Clinical pathway-Total pancreatectomy Group; CP-T Group, Clinical pathway-Total pancreatectomy Group; g/l, gram/liter; g/dl, gram/deciliter.

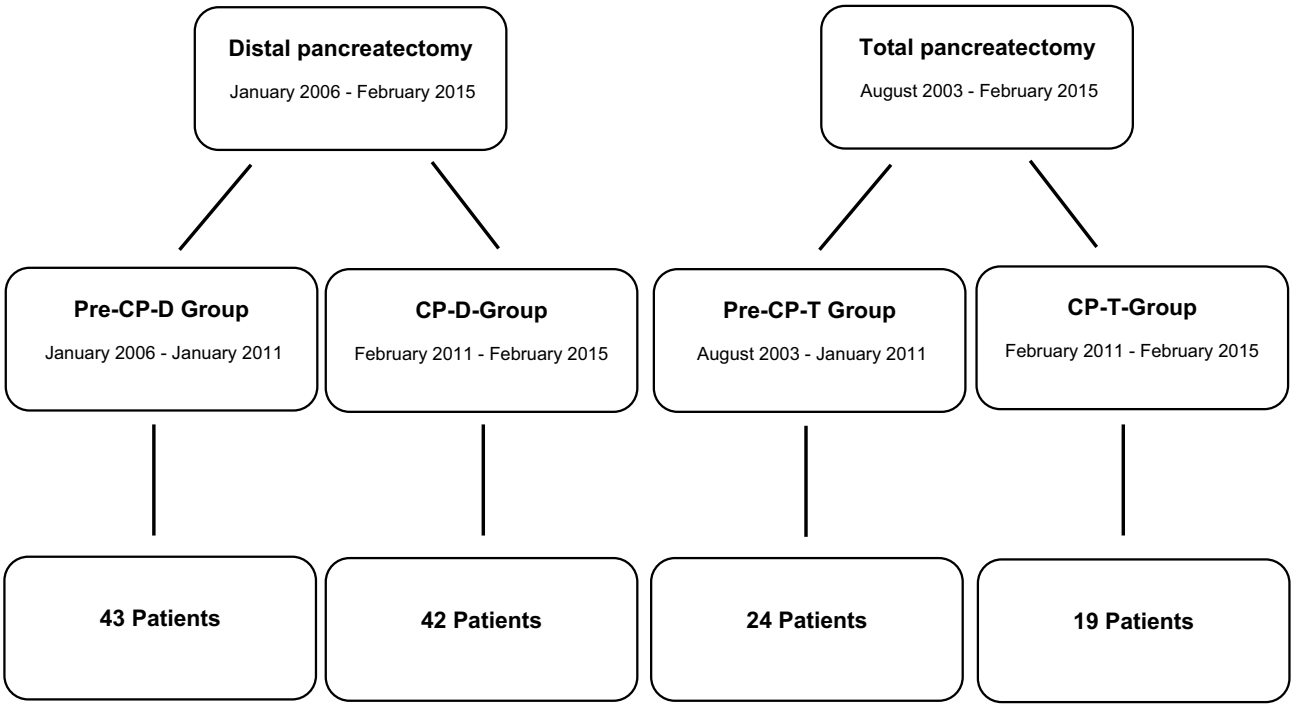


**Figure 1** Flowchart of patient recruitment. The four groups comprised all patients consecutively operated during the respective study period.
**Abbreviations:** Pre-CP-D Group, Pre-Clinical pathway-Distal pancreatectomy Group; CP-D Group, Clinical pathway-Distal pancreatectomy Group; Pre-CP-T Group, Pre-Clinical pathway-Total pancreatectomy Group; CP-T Group, Clinical pathway-Total pancreatectomy Group.

For total pancreatectomy only one significant difference was found. The number of days with a relevant pain level (higher than 3) increased from one in the pre-CP-T group to three in CP-T group. No difference was observed regarding additional analgesic requests. For all other measures of outcome quality, there were no relevant differences between patients treated with and without CP. In both groups, length of stay was generally longer than foreseen in the CP.

## Discussion

This study evaluated the effect of CP implementation for distal and total pancreatectomy on various parameters of perioperative process and outcome quality. Pancreatic surgery is complex and should only be performed by experienced and specialized surgeons. In the last decades, perioperative mortality has dropped, but morbidity remains high.[34–37] This might partly be explained by the fact that older patients with significant comorbidities or locally advanced tumors are resected, but a lack of standardization of perioperative treatment might contribute to high morbidity.[38–40] Therefore, the principal aim of this study was to evaluate if CP implementation led to standardization of perioperative treatment patterns and therefore to an amelioration of process and outcome quality of patients undergoing distal and total pancreatectomy.

Parameters of process quality were regarded as key performance indicators to measure protocol adherence. We observed an improvement for a few parameters of process quality, while others remained unchanged or even deteriorated after CP implementation. The frequency of incentive spirometer usage increased significantly for both procedures so that all but one patient in the CP groups used the device. Incentive spirometers are a valuable means to lower the risk of pneumonia and therefore their increased use is an important step towards prevention of this common postoperative complication.[41] For distal pancreatectomy, the timing of pancreas enzyme measurement in drainage fluid was standardized after CP implementation. This measurement is important for a timely diagnosis of a possible postoperative pancreatic fistula, the most frequent complication after distal pancreatectomy. At the same time, the risk of drain-related ascending infection or enteral fistula increases with the time of drain indwelling, so that timely drain removal is recommended once drain fluid shows no increased enzyme levels.[42–44]

In contrast to these encouraging findings, process quality regarding some other parameters deteriorated after CP

**Table 2** Parameters Of Process Quality

| Patient Characteristic | Distal Pancreatectomy | | p-value | Total Pancreatectomy | | p-value |
|---|---|---|---|---|---|---|
| | January 2006 -February 2015 | | | August 2003 -February 2015 | | |
| | Pre-CP-D Group (n=43) % | CP-D Group (n=42) % | | Pre-CP-T Group (n=24) % | CP-T Group (n=19) % | |
| Somatostatin administration (at least once) | 37 (86.1) | 32 (78.1) | 0.339 | 2 (8.3) | 3 (15.8) | 0.64 |
| Pancreas enzyme substitution (at least once) | 17 (39.5) | 5 (11.9) | 0.004* | 24 (100) | 19 (100) | 1.0 |
| Antibiotic prophylaxis | 38 (90.5) | 41 (97.6) | 0.36 | 19 (90.5) | 19 (100) | 0.489 |
| Peridural analgesia | 38 (90.5) | 37 (88.1) | 1.0 | 20 (83.3) | 19 (100) | 0.614 |
| Central venous catheter | 38 (90.5) | 29 (69.1) | 0.015* | 23 (95.8) | 19 (100) | |
| Arterial catheter | 39 (92.9) | 36 (85.7) | 0.483 | 23 (100) | 19 (100) | |
| Usage of incentive spirometer | 35 (83.3) | 42 (100) | 0.012* | 14 (58.3) | 18 (94.7) | 0.012* |
| Mean day of PDA removement | 5.24 | 3.9 | 0.132 | 4.89 | 5.93 | 0.429 |
| Median day of central venous catheter removement [range] | 5 [1–16] | 4 [0–19] | 0.64 | 6 [4–52] | 9 [4–74] | 0.137 |
| Median day of arterial catheter removement [range] | 1 [0–9] | 1 [0–6] | 0.725 | 3 [0–6] | 2 [2–23] | 0.449 |
| Median day of foley catheter removal [range] | 3 [1–11] | 3 [1–23] | 0.805 | 5 [2–20] | 6.5 [3–48] | 0.066 |
| Mean day of nasogastric tube removal | 2.43 | 4.33 | 0.39 | 3.78 | 12.4 | 0.347 |
| Median day of drain removal [range] | 7 [5–56] | 6 [4–47] | 0.243 | 7 [4–53] | 6 [2–49] | 0.357 |
| Median day of first measurement of pancreas enzymes | 1 [0–3] | 3 [1–5] | <0.0001* | | | |
| Median day of second measurement of pancreas enzymes [range] | 3 [1–8] | 5 [2–14] | <0.0001* | | | |
| Median day of first intake of liquids [range] | 0 [0–2] | 0 [0–2] | 0.42 | 1 [0–7] | 1 [0–23] | 1.0 |
| Mean day of first intake of liquid nutritional supplement | 1.72 | 1.75 | 0.939 | 3.96 | 5.17 | 0.475 |
| Median day of first intake of food [range] | 3 [0–10] | 2 [1–26] | 0.266 | 5 [2–13] | 5 [4–44] | 0.787 |
| Median day of first mobilization to edge of the bed [range] | 1 [0–2] | 1 [0–16] | 0.062 | 1 [1–3] | 1 [1–26] | 0.839 |
| Median day of full mobilization [range] | 3 [0–5] | 3 [1–17] | 0.034* | 3 [1–12] | 3 [1–49] | 0.863 |

**Notes:** *=p-value ≤ 0.05.

**Abbreviations:** Pre-CP-D Group, Pre-Clinical pathway-Distal pancreatectomy Group; CP-D Group, Clinical pathway-Distal pancreatectomy Group; Pre-CP-T Group, Pre-Clinical pathway-Total pancreatectomy Group; CP-T Group, Clinical pathway-Total pancreatectomy Group; PDA, peridural anesthesia.

implementation. Most importantly, mobilization after distal pancreatectomy took place significantly later in patients treated with a CP compared to those treated without. The results show that the median day of first mobilization does not differ between the two groups, but that the difference originates from a high number of outliers in the CP-D group in whom mobilization took place exceedingly late. The reasons for this finding are not fully understood. Probably, late mobilization can be at least partially explained by complications. However, the incidence of complications was the same among the two groups, and thus it remains unclear why many patients treated with the CP were mobilized late. Mobilization of patients in a limited physical status, with drains and catheters in place, is cumbersome and requires intensive efforts by staff and the patient as well as sufficient time to perform these efforts. Therefore, it is conceivable that in spite of the recommendations being clearly stated in the CP, these could not be realized due to a lack of sufficient resources. Another possible reason for delayed mobilization could be insufficient pain control. The number of days with a relevant pain level was in fact higher in the CP groups. This finding is rather surprising, because the CP contained a dedicated analgesia scheme according to recent recommendations. It included epidural catheter placement, which was carried out in the overwhelming majority of patients. Additional oral analgesics were administered in a stepwise, pain-adjusted manner, so that there is no obvious explanation for higher pain levels in patients treated according to the CP. Additional analgesic requests by patients also occurred with the same frequency as in patients treated without CP. One potential explanation, although merely hypothetical, could be that nursing staff had increased awareness for possible postoperative pain after CP implementation and tended to assess patients more meticulously regarding their pain, inciting a higher reported pain level. This would be a form of ascertainment bias. Delayed mobilization and insufficient pain control can have relevant consequences for the patient, because of an increased risk of postoperative morbidity especially with regard to pulmonary complications.[45] Moreover, some studies found a significant correlation between delayed mobilization and increased length of stay.[46]

Regarding outcome quality, several differences between patients treated with and without CP were observed. In patients undergoing distal pancreatectomy, the number of days with at least one measurement of blood glucose higher than 200 mg/dl was significantly lower in the CP group. These findings are indicative for a much-improved glucose management by using a CP which contains a detailed and aggressive insulin scheme aiming at early postoperative normoglycemia. The safety of this scheme was demonstrated by the absence of hypoglycemia. Tight glycemic control after pancreatic surgery is crucial to prevent infectious complications.[47] For total pancreatectomy, glycemic control was not different between pre-CP and CP patients. This shows that already prior to CP implementation, glycemic control had been in the focus of treatment after total pancreatectomy. Beyond improved glycemic control, the incidence of postoperative diabetes, defined as elevated fasting glucose, was also lower after CP implementation in patients undergoing distal pancreatectomy. This finding can obviously not be explained as a consequence of improved glucose management and the exact reasons remain unclear. It is possible that the surgical approach changed from one surgeon to the other and that surgeons operating after CP implementation performed less radical distal pancreatectomies, thus leaving more endocrine pancreatic tissue in situ. The same might be a potential explanation for the observed lower incidence of exocrine pancreatic failure.

of Regarding the incidence of postoperative complications and mortality, the analyses did not show a difference between patients treated before and after CP implementation. While mortality after distal pancreatectomy was in the range of what is reported from comparable series,[48,49] mortality after total pancreatectomy was higher than benchmark rates found in the literature.[1,50] Since the overall number of patients comprised in the present analysis is rather low, the found mortality rates are sensitive to random fluctuation and might overestimate the true mortality in our setting. Yet, the relatively low overall volume of pancreatectomy cases during the study period might have contributed to an increased mortality, as there is a well-known volume-outcome relationship for total pancreatectomy.[50] Compared to other studies, also the overall postoperative complication rate in our patients seems high.[1] A possible reason is the use of the Clavien-Dindo classification for postoperative complications. This classification counts every deviation from the normal postoperative process as complication, while many studies reporting complications have not used a dedicated classification or lack a detailed definition of complications.[29,51] The incidence of specific complications has also not changed significantly after implementation of the CPs. The most frequent complication after distal pancreatectomy is postoperative pancreatic fistula. It is virtually impossible to influence its incidence postoperatively.

**Table 3** Parameters Of Outcome Quality

| Patient Characteristic | Distal Pancreatectomy | | p-value | Total Pancreatectomy | | p-value |
|---|---|---|---|---|---|---|
| | January 2006 -February 2015 | | | August 2003 -February 2015 | | |
| | Pre- CP-D Group (n=43) % | CP-D-Group (n=42) % | | Pre-CP-T Group (n=24) % | CP-T Group (n=19) % | |
| Readmission | 10 (23.3) | 6 (14.3) | 0.339 | 3 (12.5) | 2 (10.5) | 1.0 |
| Mortality | 1 (2.4) | 1 (2.5) | 1.0 | 5 (20.8) | 3 (15.8) | 1.0 |
| Morbidity according to Clavien-Dindo classification | | | 0.688 | | | 0.808 |
| 0 | 11 (25.6) | 12 (28.6) | | 4 (16.7) | 1 (5.3) | |
| I | 13 (30.2) | 13 (30.9) | | 4 (16.7) | 4 (21.0) | |
| II | 11 (25.6) | 9 (21.4) | | 5 (20.8) | 5 (26.3) | |
| IIIA | 3 (7.0) | 6 (14.3) | | 2 (8.3) | 2 (10.5) | |
| IIIB | 4 (9.3) | 1 (2.4) | | 3 (12.5) | 3 (15.8) | |
| IVA | 0 | 0 | | 0 | 1 (5.3) | |
| IVB | 0 | 0 | | 1 (4.2) | 0 | |
| V | 1 (2.4) | 1 (2.5) | | 5 (20.8) | 3 (15.8) | |
| POPF | | | 0.357 | | | |
| Grade A | 5 (11.6) | 8 (19.1) | | | | |
| Grade B | 10 (23.3) | 7 (16.7) | | | | |
| Grade C | 1 (2.3) | 4 (9.5) | | | | |
| DGE | | | 0.112 | | | 0.962 |
| Grade A | 11 (25.6) | 5 (11.9) | | 4 (16.7) | 2 (10.5) | |
| Grade B | 1 (2.3) | 4 (9.5) | | 3 (12.5) | 3 (15.8) | |
| Grade C | 0 | 2 (4.8) | | 3 (12.5) | 2 (10.5) | |
| PPH | | | 0.202 | | | 0.881 |
| Grade A | 1 (2.3) | 0 | | 1 (4.2) | 2 (10.5) | |
| Grade B | 0 | 0 | | 1 (4.2 | 1 (5.3) | |
| Grade C | 1 (2.3) | 0 | | 1 (4.2) | 0 | |
| Postoperative pancreatitis | 2 (4.7) | 1 (2.4) | 1.0 | | | |
| Insulin administration (at least once) | 23 (56.1) | 21 (50.0) | 0.578 | 24 (100) | 19 (100) | 0.209 |
| Postoperative diabetes | 12 (27.9) | 3 (7.1) | 0.012* | 24 (100) | 19 (100) | |
| Hypoglycemia | 0 | 0 | | 0 | 0 | |
| Median [range] number of days with blood glucose ≥200 mg/dl | 2.5 [0–24] | 0 [0–13] | 0.006* | 10 [3–21] | 11.5 [0–29] | 0.443 |
| Exocrine insufficiency | 16 (37.2) | 5 (11.9) | 0.007* | 24 (100) | 19 (100) | 1.0 |
| Revisional surgery | 6 (14.0) | 3 (7.1) | 0.36 | 9 (37.5) | 7 (36.8) | 0.965 |
| Median [range] number of days with highest pain level > 3 | 1 [0–11] | 2 [0–16] | 0.079 | 1 [0–6] | 3 [0–9] | 0.012* |
| Analgesics requested (Mean number of doses during hospital stay) | 0.81 | 0.89 | 0.481 | 0.52 | 0.47 | 0.87 |
| Mean day of first defecation | 3.74 | 3.88 | 0.72 | 4.29 | 4.88 | 0.473 |
| Discharge | | | 1 | | | 1 |
| Home | 39 (90.7) | 38 (90.5) | | 15 (62.5) | 12 (63.2) | |

(*Continued*)

**Table 3** (Continued).

| Patient Characteristic | Distal Pancreatectomy | | p-value | Total Pancreatectomy | | p-value |
|---|---|---|---|---|---|---|
| | January 2006 -February 2015 | | | August 2003 -February 2015 | | |
| | Pre- CP-D Group (n=43) % | CP-D-Group (n=42) % | | Pre-CP-T Group (n=24) % | CP-T Group (n=19) % | |
| Other hospital<br>Rehabilitation | 1 (2.3)<br>2 (4.7) | 1 (2.4)<br>2 (4.8) | | 1 (4.2)<br>3 (12.5) | 1 (5.3)<br>3 (15.8) | |
| Median [range] length of stay on ICU | 1 [1–11] | 1.5 [1–20] | 0.91 | 6 [2–71] | 6 [2–68] | 0.432 |
| Median [range] length of stay | 16 [8–66] | 14 [5–77] | 0.162 | 20 [14–75] | 28 [12–140] | 0.274 |
| Median [range] length of stay postoperative | 13 [7–65] | 13 [4–76] | 0.41 | 16 [13–60] | 22 [11–139] | 0.162 |

**Notes:** Postoperative diabetes= fasting blood glucose level higher than 126 mg/dl; Rehab=Rehabilitation; *=p-value ≤ 0.05.
**Abbreviations:** Pre-CP-D Group, Pre-Clinical pathway-Distal pancreatectomy Group; CP-D Group, Clinical pathway-Distal pancreatectomy Group; Pre-CP-T Group, Pre-Clinical pathway-Total pancreatectomy Group; CP-T Group, Clinical pathway-Total pancreatectomy Group; POPF, Postoperative pancreatic fistula; DGE, Delayed gastric emptying; PPH, Postoperative pancreatic hemorrhage.

However, potentially hazardous sequelae can be mitigated by dedicated drain management,[52] which was realized more frequently after CP implementation.

One of the aims of CP implementation is to avoid unnecessarily long hospital stays without a clear medical reason by means of streamlining perioperative processes. In this study, length of stay did not decrease after CP implementation, and still showed a relevant variation between single patients. However, length of stay in larger series in the literature was rather in the range of what we observed before and after CP implementation than in the range of the goals of the CP.[49,53] Moreover, the analyses comprised all consecutive patients including those with relevant complications, which explains the large variation and exceedingly long hospital stay in some patients.

The study has a number of methodological limitations. It is retrospective and relied on chart review for data collection. Therefore, the validity of data could be inferior to prospectively collected data. Moreover, for some variables values for single patients were not documented and not used for the analyses. This might bias the results, although there is no reason to assume that variables were selectively not recorded. During the development and implementation of the CPs, a crossover respectively contamination bias could have been occurred. Likewise, caregivers who were part of the development team could have used their knowledge of CP content prior to implementation in February 2011. To counteract these points, we carried out the actual design and implementation of CPs over a short time period of approximately three months. Therefore, a third group covering only the transition period would have been too small for meaningful analyses. Obviously, surgical technique and the skills and experience of the single surgeon do affect perioperative outcomes.[35] During the study period, a number of different surgeons operated on patients and surgical performance bias cannot be excluded. Most of these limitations would have been overcome by designing the study as randomized controlled trial, which is however hardly feasible to conduct when evaluating clinical pathway usage.[36]

The methodological strength of our study was that patients were included according to the "intention-to-treat" principle. All consecutive patients undergoing distal or total pancreatectomy before and after CP implementation were included. Even if certain goals of the CP such as drain removal or mobilization were not met, patients were not taken "off the pathway". Moreover, patients were analyzed regardless of possible complications. Consequently, selection bias can virtually be ruled out. We believe this approach to be the only valid way for evaluating the true clinical impact of CPs because it represents clinical reality, where CPs are meant to be a tool for treating the entirety of patients with a specific intervention or condition.

## Conclusion

In conclusion, this study showed that CPs for distal and total pancreatectomy can affect several aspects of perioperative treatment. CP usage fulfilled the expectations regarding a high degree of process standardization. Drain management and the uptake of respiratory training as well

as glycemic control were improved. Other expected improvements, such as earlier mobilization, better pain control, and shorter length of stay, were not realized after CP implementation. Outcome parameters such as morbidity and mortality did not differ between patients treated with and without CP. CPs in pancreatic surgery can be used to facilitate some perioperative processes, but their utility must be weighed against the expected cost and efforts of implementation. The results of this study can serve to further refine and adapt the two used CPs in our given setting, but also to inform the design of future studies assessing CPs for pancreatic surgery.

## Author contributions

P. Téoule and U. Ronellenfitsch participated in the conception and design of the study. L. Römling and P. Téoule performed data collection, analyzed the data and drafted the manuscript. P. Téoule, U. Ronellenfitsch, L. Römling, M. Schwarzbach, E. Birgin, F. Rückert, TJ. Wilhelm, M. Niedergethmann, S. Post, NN. Rahbari and C. Reißfelder participated in the analysis and interpretation of data, revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Disclosure

The authors report no proprietary or commercial interests in any products mentioned or concept discussed in this article.

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