Introduction: To study whether the implementation of a clinical pathway including some enhanced recovery after surgery (ERAS) items for pancreaticoduodenectomy (PD) in a low volume centre for pancreatic surgery was safe.

Material and methods: Patients undergoing elective PD within a clinical pathway between 1 October 2013 and 30 September 2019 were considered for the study and the outcome was compared between the first and second period of the study. The primary endpoint was the achievement of postoperative key targets of the protocol. Secondary endpoints were complications, mortality and readmissions within 90 days postoperatively, and postoperative hospital stay.

Results: Forty-five patients could be analysed. The two groups were balanced for demographic, clinical and histological variables. In the second period more patients achieved key targets: nasogastric tube removal at postoperative day (PoD) 2, oral fluid at PoD 3, drain removal at PoD 5 and hospital discharge at PoD 9. The rates of postoperative complications, mortality and readmissions were not significantly different between the two groups and were similar to data reported for high volume centres.

Conclusions: Our results show that the implementation of a clinical pathway following PD and including some ERAS items was feasible and safe in a low volume centre for pancreatic surgery.

Key words: pancreaticoduodenectomy, low volume centre, clinical pathway.
A further 8 patients had standard perioperative care at the discretion of the responsible surgeon. Therefore, 45 patients were included in the clinical pathway. The data were retrieved from a prospective database and retrospectively analysed. Patients were followed up for at least 3 months. No patient was lost during follow-up.

Clinical pathway

The items of the ERAS recommendations [12] used and not used in the current study are shown in Table 1. Biliary stenting was performed endoscopically if the total bilirubin level was > 250 µmol/l or if this level would be achieved within a few days without drainage [13]. Preoperative immunonutrition (Oral-Impact) was given for 7 days according to French guidelines [14]. Patient controlled epidural analgesia was routinely used [12]. Alternatively in selected cases (technical reason or not accepted by patients) intravenous (morphine) patient controlled analgesia was used. Allogeneic blood transfusion was given when the haemoglobin level dropped below 8 g/dl and according to haemodynamic tolerance. Intraoperative warming and avoidance of fluid overload were used routinely. Antibiotics were given perioperatively according to French guidelines [15] and in patients with a biliary prosthesis five days of postoperative antimicrobial therapy was given [16]. Bile culture was performed routinely. Patients were monitored in an intermediate care unit for at least 3 days postoperatively and glucose level monitoring and treatment of hyperglycaemia with insulin was used routinely. All patients had thromboprophylaxis with low molecular weight heparin [12]. A somatostatin analogue was not given routinely [12]. A proton-pump inhibitor was given routinely.

Key targets for the postoperative course were derived from the protocol of Robertson et al. in 2012 [17] with some modifications: target for nasogastric tube (NGT) removal postoperative day (PoD) 2, target for solid food PoD 5 because of the pancreaticojejunal anastomosis and target for discharge PoD 8 and are shown in Table 1. Oral nutrition was started at PoD 3 with clear liquids, followed by liquid food at PoD 4 and solid food at PoD 5. Early postoperative enteral nutrition via a percutaneous jejunostomy for postoperative enteral nutrition was placed 30 cm downwards from the gastrojejunal anastomosis. Drainage of the hepaticojejunal and pancreaticojejunal anastomosis was performed with a multitubular silicon drain (Coloplast) [22, 23].

Definitions

Overall complications were defined as any deviation from an uneventful postoperative course within 90 days after surgery. Severity of complications was defined according to the Clavien-Dindo classification [24]. Postoperative pancreatic fistula (POPF) [25], delayed gastric emptying (DGE) [26] and post-pancreatectomy haemorrhage [27] were defined according to the International Study Group of Pancreatic Surgery. Hospital stay was defined as postoperative hospital stay. Undernutrition was defined with the Nutritional Risk Index (NRI) [28]. Comorbidity was defined according to the Charlson Comorbidity index [29].

Endpoints

The primary endpoint was the achievement of postoperative key targets of the pathway. Secondary endpoints were complications and mortality within 90 days postoperatively, readmissions and postoperative hospital stay. The dataset was split in two to compare the outcome between the first 22 patients and the next 23 patients included in the study, in order to analyse changes in protocol compliance and outcome.

Statistical analysis

Continuous variables were reported as median with interquartile range (IQR) and compared with the non-parametric Mann-Whitney U test. Dichotomous variables were reported as n (%) and compared with the Pearson χ² or Fisher’s exact test, as appropriate. All statistical tests were two-sided, and p < 0.050 was considered significant.

Results

The first 22 patients were operated on between 1 October 2013 and January 2017, the next 23 patients between January 2017 and 30 September 2019.

Baseline characteristics of all 45 patients are shown in Table 2. Undernutrition defined by an NRI < 97.5 was registered in 26 patients (57.7%) and preoperative anaemia (haemoglobin level < 12.5 g/dl) in 25 patients (55.5%). Preoperative biliary drainage was required in 23 patients (51.1%) with a preoperative bilirubin level over or near 250 µmol/l. The median total bilirubin level before stenting is given in Table 2. The intraoperative variables were not different between the two groups and are shown in Table 3. Forty patients (88.9%) were operated on for malignancy. Nine patients (20%) had portal or superior mesenteric vein resection. Two patients had a pancreatocojugal anastomosis, one because of a previous gastrectomy and the other because of a difficult mobilisation of the pancreatic tail. The variables impacting POPF, as determined
Table 1. Clinical pathway for pancreaticoduodenectomy

| ERAS items [12]                                      | Current study                                                                                                                                 |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Preoperative counselling                             | Applied routinely                                                                                                                                 |
| Perioperative biliary drainage                       | Drainage if bilirubin > 250 µmol/l [13]                                                                                                                                 |
| Preoperative smoking and alcohol consumption         | Was attempted                                                                                                                                 |
| Preoperative nutrition                               | In malnourished patients: oral supplements                                                                                                                                 |
| Perioperative oral immunonutrition                   | Routinely used for 7 day preoperatively                                                                                                                                 |
| Oral bowel preparation                                | Bowel preparation not used                                                                                                                                 |
| Preoperative fasting and                            | Solid food until 12 p.m. the day before the operation, clear fluid up to 2 h before operation                                                |
| Preoperative treatment with carbohydrates           | Oral carbohydrate loading not used                                                                                                                                 |
| Pre-anaesthetic medication                           | No long acting premedication used                                                                                                                                 |
| Anti-thrombotic prophylaxis                          | Low molecular weight heparin and compression routinely used for 4 weeks                                                                                                                                 |
| Antimicrobial prophylaxis                            | Routinely used [15], in patients with biliary drainage 5 days treatment [16]                                                                 |
| Skin preparation                                     | Routinely used                                                                                                                                 |
| Epidural analgesia                                   | Peridural anaesthesia routinely used, removed PoD 3                                                                                                                                 |
| Intravenous analgesia                                | PCA used alternatively, removed PoD 3                                                                                                                                 |
| Wound catheters and TAP block                       | Not used                                                                                                                                 |
| Postoperative nausea and vomiting                    | Pharmacological intervention routinely used                                                                                                                                 |
| Incision                                             | Subcostal incision with upper midline extension                                                                                                                                 |
| Avoiding hypothermia                                 | Intraoperative cutaneous warming routinely used                                                                                                                                 |
| Postoperative glycaemic control                     | Monitoring of glucose levels and insulin treatment used routinely                                                                                                                                 |
| Nasogastric intubation                              | Nasogastric tubes routinely used for 24–48 h                                                                                                                                 |
| Fluid balance                                        | Fluid and salt overload was avoided, transoesophageal Doppler not used                                                                                                                                 |
| Perianastomotic drain                                | Drain removal at PoD 5 according to drain amylase level                                                                                                                                 |
| Somatostatin analogues                               | Not used routinely                                                                                                                                 |
| Urinary drainage                                     | Transurethral catheterisation removed PoD 3                                                                                                                                 |
| Delayed gastric emptying                             | No prevention strategy                                                                                                                                 |
| Stimulation of bowel movement                       | Oral laxatives and chewing gum not used routinely                                                                                                                                 |
| Postoperative artificial nutrition                   | Routine enteral nutrition starting PoD1, oral nutrition: PoD 3 liquids, PoD 5 solid food                                                                                                                                 |
| Early and scheduled mobilization                     | Active mobilization starting PoD 1                                                                                                                                 |
| Audit                                                | Current study                                                                                                                                 |

Deviations from ERAS recommendation are in bold

PoD Postoperative key targets (underlined) for the clinical pathway

1. NGT removed if volume < 500 ml/24 h, start enteral nutrition: 10 ml/h, sit for 2 × 30 min
2. NGT removed, enteral nutrition 20 ml/h, sit for 2 × 1 h
3. Epidurals and urinary catheter removed, oral liquids, enteral nutrition 30 ml/h, sit for 2 × 1 h, short walk, discharge of intermediate care unit
4. Tolerating liquid oral diet, enteral nutrition 40 ml/h
5. Drainage removed if amylase < 150 U/l, tolerating solid oral diet, walking in ward
6. STOP l.v. fluids
7. STOP enteral nutrition, normal diet
8. Discharge home or to rehabilitation facility

With oral proton-pump inhibitor, oral nutritional complements if indicated (undernutrition), 3 weeks of thromboprophylaxis with low-molecular-weight heparin

ERAS = enhanced recovery after surgery, NGT = nasogastric tube, PoD = postoperative day, TAP = transversus abdominis plane
analysed lymph nodes, intraoperative blood loss, peripera-

tive specimen are shown in Table 4. The number of resected and

by the “fistula risk score” [30], were not different between

Table 2. Baseline characteristics of 45 patients undergoing pancreaticoduodenectomy in a clinical pathway

| Number | First period | Second period | p   |
|--------|--------------|---------------|-----|
| n = 22 | n = 23       |               |     |
| Female gender | 5 | 6 | 1   |
| Age in years | 64 (56–70) | 72 (64–75) | 0.040* |
| Charlson comorbidity index | 3 (2–4) | 3 (2–4) | 0.682* |
| COLD | 2 | 2 | 1   |
| Ischemic heart disease | 4 | 4 | 1   |
| Cerebrovascular disease | 2 | 1 | 0.608 |
| Diabetes | 9 | 8 | 0.763 |
| History of other cancer | 3 | 6 | 0.459 |
| Haemoglobin level < 12.5 g/dl | 14 | 11 | 0.372 |
| ASA score ≥ 3 | 12 | 15 | 0.549 |
| Weight loss > 10% | 12 | 11 | 0.768 |
| NRI < 97.5 | 13 | 13 | 1   |
| Biliary drainage | 14 | 9 | 0.189 |
| Total bilirubin level (before stenting in µmol/l) | 274 (222–385) | 381 (300–406) | 0.332* |
| Neoadjuvant chemotherapy | 0 | 2 | 0.489 |

ASA – American Society of Anesthesiologists, COLD – chronic obstructive lung disease, NRI – nutritional risk index

Continuous variables are reported as median and interquartile range. Dichoto-

mous variables were compared using Fisher’s exact test.

Table 3. Perioperative data for pancreaticoduodenectomy in 45 patients in a clinical pathway

| Number of patients | Group A | Group B | p   |
|--------------------|---------|---------|-----|
| n = 22 | n = 23   |         |     |
| Pancreatogastric anastomosis | 22 | 21 | 0.489 |
| Feeding jejunostomy | 22 | 22 | 1   |
| “Hard” consistency of pancreas | 9 | 7 | 0.542 |
| Pancreatic duct size [mm] | 5 (3–5) | 4 (3–5) | 0.484 |
| Peri-operative transfusion | 8 | 5 | 0.336 |
| Duration of surgery in [min] | 407 (390–438) | 395 (372–420) | 0.190 |
| SMV or portal vein resection | 4 | 1 | 1   |
| Estimated blood loss in [ml] | 375 (212–500) | 300 (250–325) | 0.267 |
| Fistula risk score ≥ 3 | 13 | 9 | 0.238 |

SMV – superior mesenteric vein

Continuous variables are reported as median and interquartile range. Dichoto-

mous variables were compared using the Mann-Whitney U test. Dichoto-

mous variables were compared using Fisher’s exact test. Fistula risk score [30]: 0–2: no/low risk; ≥ 3 moderate/high risk.

Table 4. Histological data for pancreaticoduodenectomy specimen in 45 patients in a clinical pathway

| Number of patients | Group A | Group B | p   |
|--------------------|---------|---------|-----|
| n = 22 | n = 23   |         |     |
| Ductal adenocarcinoma | 12 | 14 | 0.767 |
| Distal bile duct carcinoma | 3 | 0 | 0.108 |
| Ampullary carcinoma | 2 | 3 | 1   |
| Other cancer (IPMN, endocrine, duodenal) | 4 | 2 | 0.414 |
| Benign disease | 1 | 4 | 0.346 |
| R1 resection (+ arterial margin) | 8 | 5 | 0.337 |
| Median number of resected lymph nodes | 20 (14–25) | 23 (15–29) | 0.418 |
| TNM stage pN+ | 10 | 13 | 0.556 |
| TNM stage pT ≥ 3 | 14 | 9 | 0.139 |
| Perineural invasion | 14 | 10 | 0.236 |
| Perivascular invasion | 4 | 8 | 0.314 |
| Lymphatic invasion | 4 | 6 | 0.722 |

IPMN – intraductal papillary mucinous neoplasm, TNM – tumour, node, metastasis classification

Continuous variables are reported as median and interquartile range. Dichoto-

mous variables are reported as N.

Continuous variables were compared using the Mann-Whitney U test. Dichoto-

mous variables were compared using Fisher’s exact test.

Complications were recorded in 29 patients (64.4%). Post-pancreatectomy haemorrhage was registered in 6 patients (13.3%) and 5 patients (11.1%) needed reoperations: 3 for early haemorrhage (within 24 h) and 2 for late haemorrhage. Three reoperated patients needed further procedures: 2 patients an arterial embolisation and one patient a second re-operation.

Pancreatic fistula was registered in 10 patients (22.2%) and clinically relevant grade B/C fistula in 9 patients (20%). The fistula risk score [30] was predictive for pancreatic fistu-

la: no and low risk group (score 0–2): 4.3% fistula (1 out of 23), moderate and high risk group (score ≥ 3): 40.9% fistula (9 out of 22) (p = 0.004).

Post-pancreatectomy haemorrhage was reported in 4 out of 10 patients (40%) with POPF versus 2 out of 35 patients (5.7%) without a pancreatic fistula (p = 0.016).

Delayed gastric emptying was registered in 13 patients (28.8%) and grade B/C in 4 patients (8.9%). Major compli-

cations (Clavien-Dindo ≥ 3) were registered in 7 patients (15.5%).

Two patients (4.4%) died within 90 days. In both pa-

tients post-pancreatectomy haemorrhage caused by POPF was the cause. In the remaining 43 patients median fol-

low-up was 23 months (range 4–62).

After hospital discharge 37 patients (82.2%) went home and 8 (17.7%) were transferred to a rehabilitation facility.
Median length of stay was 11 days (IQR: 8–14) and mean length of stay was 12.5 days for all 45 patients. Median length of stay was 9 days in 35 patients without POPF versus 16.5 days in 10 patients with a pancreatic fistula ($p = 0.019$).

Seven patients (15.5%) were readmitted within 31 days to the hospital for a median of 9 days (IQR: 3.5–18 days). No further readmission was registered after 31 days. Causes of readmissions were: bleeding complications in 3 patients requiring reoperation (2 patients) and arterial embolisation of aneurysm (1 patient), undernutrition requiring treatment (1 patient) and non-specific abdominal pain (2 patients). No significant differences for complications, mortality and readmissions were observed between the first and the second period of the study (Table 5).

### Postoperative key targets

The nasogastric tube was removed by PoD 2 in 28 patients (Table 6), and by PoD 6 in 41 patients. Clear liquids were given at PoD 3 in 38 patients and solid food at PoD 5 in 18. Oral nutrition was impacted by DGE, which manifested with nausea and vomiting at median PoD 4 (range 3–6 days). A total of 13 patients (29%) had a pancreatic fistula and in those patients the drainage was removed at median PoD 14.

Drain amylase level was measured at PoD 1, 2 and 3 and drains were removed by PoD 5 in 28 patients (Table 6). Ten patients had a pancreatic fistula and in those patients the drainage was removed at median PoD 14.

In the second period of the study more patients achieved key targets: NGT removal PoD 2, oral fluids PoD 3 and drainage removed at PoD 5. The medium number of key targets achieved (out of 7) was 3 for the first 22 patients versus 5 for the next 23 patients, reflecting better compliance with the protocol. The median postoperative hospital stay was reduced in the second period and more patients were discharged at PoD 9.

### Discussion

The aim of the present study was to report the short-term outcome after implementation of a clinical pathway for PD including some ERAS items in a low volume centre for pancreatic surgery. The hypothesis was that pathway implementation would be safe in this setting.

Outcome data of the present study showed accordance with data reported for PD in French academic centres: complications 64.4% versus 54.4% [33], mortality: 4.4% versus 3.8% [33], reoperation 11.1% versus 11.7% [33], respectively. Ninety day mortality of 4.4% in the present study was similar to data reported by high volume centres in the Netherlands: 4.3% [6] and England: 5.3% [7].

Over 80% of patients in the present study were discharged home. The readmission rate was 15.5% and similar to 15.6% [34] reported by Boteon et al. for the Birmingham group.

The number of resected lymph nodes, intraoperative blood loss, perioperative transfusion rate and duration of surgery were in accordance with recommendations for quality control in pancreatic surgery [31, 32]. The rather high rate of arterial margin involvement (46%, 12 out of 26) in ductal adenocarcinoma in the current study was
Outcome after implementation of a clinical pathway for pancreaticoduodenectomy in a low volume centre

Adherence to the clinical pathway was higher in the second study period (since January 2017), probably reflecting a learning curve, and resulting in a reduced median hospital stay, but without affecting the complication and readmission rates.

The main limitation of the present study was the absence of a control group. In the authors’ opinion, the number of patients (n = 8) undergoing elective “standard” pancreaticoduodenectomy was too small to serve as a control group. These 8 patients were managed outside the pathway because one surgeon started the clinical pathway in September 2013 and the other surgeon followed several months later. A comparison with a “historic” control group (before October 2013) was not done as this long time interval would have included further significant bias.

The small number of patients included per year and the resulting long study period are explained by the setting of a low volume centre. However, no significant changes in the perioperative management were observed during the study period for the included patients. Seventeen patients (27%, 17 out of 62) were managed outside the pathway either because of an emergency, associated procedures, total PD or surgeon preferences. Similar findings were reported by Delpero et al., in a French multicentre study [35].

In 2016 a randomised study reported a mortality rate of 12.7% after PD with enteral nutrition via a naso-jejunal feeding tube [38]. Although in our experience a similar mortality rate was not observed, the benefit of routine enteral nutrition should be questioned. There is evidence that early oral feeding with “on demand” enteral nutrition is better than routine enteral nutrition [39].

Another challenge was the avoidance of routine drainage and early drain removal if amylase levels were below a predefined value. In our institution drain amylase levels were recorded at PoD 1, 2 and 3 and further on if increased values (> 3x upper normal serum value at PoD 3) were registered. The fistula risk score [30] was predictive for POPF in the current study and may be useful for selective drain management in the future.

The major reason for a longer hospital stay in the present study was a pancreatic fistula. The median length of stay (a surrogate marker for a successful ERAS pathway) was 9 days in 35 patients without POPF versus 16.5 days in 10 patients with POPF (p = 0.019). In two patients a pancreatic fistula was diagnosed during the re-admission at PoD 11 and 16, after an initial uneventful hospital stay of 8 and 12 days respectively, with normal drain amylase levels at PoD 3 and a fistula risk score of 3 (moderate risk). This raises the question whether a target of discharge at PoD 8 was safe in these patients, as both patients had to be re-operated on for bleeding complications. However, we presume that it is rather unlikely that a longer initial hospital stay would have led to different management of complications. With these experiences in mind, particular care should be taken in identifying pancreatic fistula during the initial hospital stay, as it was the main risk factor for mortality, bleeding complications and a longer hospital stay.

Conclusions

Our results show that implementation of a clinical pathway including some ERAS recommendations for elective PD in selected patients was feasible and safe in a low volume centre for pancreatic surgery.

The authors declare no conflict of interest.

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