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Research Paper

Evaluation of an enhanced recovery program for outcome improvement after pancreaticoduodenectomy: A retrospective cohort study

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ABSTRACT

Background: The introduction of the Enhanced Recovery After Surgery (ERAS) protocol after pancreaticoduodenectomy (PD) has led to a reduction in hospital stay (LOS) without compromising surgical outcome. The primary endpoint of this study is to evaluate the adherence to postoperative targets of the ERAS protocol, and to describe short-term surgical outcomes. The secondary endpoints are 30-day readmission rate, reoperation rate and mortality.

Materials and methods: This single centre retrospective analysis reviews all data of patients who underwent a PD in our tertiary referral hospital between August 2016 and December 2019. A total of 170 patients were operated of whom 154 patients were enrolled in the ERAS protocol. As per ERAS protocol, epidural analgesia was stopped on postoperative day (POD) 2, nasogastric tube (NGT) removed on POD3, regular food tolerated by POD5. Drains were removed on POD2 and POD3, the soft drain along the pancreatic anastomosis between POD3-10.

Results: Epidural analgesia was removed on POD2 in 26 patients (17.7%), NGT removed on POD3 in 74 patients (49.0%), regular food tolerated by POD5 in 52 patients (34.9%). The lateral drain was removed in 81 patients (52.9%) on POD2, the medial drain in 39 patients (26.2%) on POD3, the soft drain in 95 patients (61.7%) between POD3 and 10. Nine patients (5.8%) had post-pancreatectomy haemorrhage (PPH), 14 (9.1%) postoperative pancreatic fistula grade B or C (POPF), 5 (3.3%) bile leakage, and 44 (28.6%) delayed gastric emptying (DGE). The 30-day readmission rate was 8.4%, reoperation rate 10.4%, and the in-hospital mortality 1.3%.

Conclusions: The adherence to targets of the ERAS protocol was found to be rather low. Biliary leakage, POPF, DGE, and PPH all led to an adapted ERAS protocol with prolonged LOS. Most complications were detected along the ERAS pathway, indicating that also patients at high risk for complications can be safely included in the ERAS protocol.

1. Introduction

Pancreaticoduodenectomy (PD) is a complex surgical procedure with significant morbidity and mortality. The Enhanced Recovery After Surgery (ERAS) protocol is a formalised perioperative care approach that suggest guidelines for the perioperative management of PD. This protocol's main purpose is to optimise patients' hospital course over the entire range of surgical care to reduce the length of stay (LOS) [1–3]. Generalised concepts in the ERAS pathways focus on reducing surgical stress, narcotic-sparing pain control, early ambulation, and promoting early oral diet [3–5].

Previous studies have explored the feasibility and efficacy of the ERAS protocol in PD in terms of LOS, postoperative morbidity, and readmission rate. These studies show that the ERAS protocol was not inferior to the conventional postoperative program with regards to overall operation-related morbidity rates. There was no significant increase in serious adverse events nor in the readmission rates, indicating that patients were not discharged before medically ready [3,6,7]. The implementation of ERAS protocols seems to accelerate perioperative recovery and quality-of-life, thereby reducing the LOS without compromising surgical outcome [6–10], and might lead to significant reduction of in-hospital costs [6,7,10]. The perioperative ERAS pathway has shown to be a safe and a worthy replacement for conventional

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management [2,3,8], but implementation is not always easy. Change of common practice and motivation of all involved personnel can be difficult. Also, other already running protocols concerning pain management might interfere with ERAS, leading to reduced or delayed implementation.

The primary endpoint of this study was to evaluate the adherence to the postoperative targets of the ERAS protocol after PD in a tertiary teaching hospital in Ghent, Belgium, and to describe the short-term surgical outcomes. The secondary endpoints were the 30-day readmission rate, reoperation rate and mortality.

2. Material and methods

2.1. Study population and study design

All data of patients who underwent a pancreaticoduodenectomy between August 2016 and December 2019 were retrospectively reviewed. All patients gave their consent at time of treatment. The Informed consent was approved by the Ethical comity of University Hospital Gent, Belgium on Jun 21, 2019 with EC number: EC/2019–074/sds. This work is fully compliant with the STROCSS criteria [11]. The study was registered in accordance with the declaration of Helsinki at www.researchregistry.com UIN, number researchregistry 5907 (https://www.researchregistry.com/browse-the-registry#home/registrationdetails/5f3566860a19700016db9c63/)

A total of 170 patients were operated of whom 154 were enrolled in the ERAS protocol postoperatively. The decision to exclude patients from the ERAS protocol was made by the operating surgeon pre- or intraoperatively based on the patient's age, comorbidities, and unexpected difficulties during surgery such as soft pancreatic parenchyma or a high risk anastomosis due to a small Wirsung duct diameter, being known risk factors for developing a pancreatic fistula.

2.2. ERAS protocol

A standardized pancreaticoduodenectomy was performed in all cases. The surgical approach was subcategorized as PD with antrectomy, pylorus-preserving pancreaticoduodenectomy (PPPD), both with or without vascular reconstruction. The gastrojejunal anastomosis was performed in an antegrade fashion in all cases. Two abdominal drains and a soft, flexible rubber (penrose) drain were routinely used. The medial and penrose drain were located anterior and posterior of the pancreaticojejunostomy (PJ) respectively, and the lateral drain was located posteriorly of the bile duct anastomosis. As per ERAS protocol (Table 1) the nasogastric tube (NGT) was removed on POD3. The patient started drinking at POD2, an oral liquid diet (yogurt, tea, and soup) was started on POD3, followed by lightly digestible food on POD4, and resuming regular diet on POD5. The epidural catheter was removed on POD2, followed by the removal of the urinary catheter. If no signs of bile were present, the lateral drain was removed on POD2. The medial drain was removed on POD3 and the penrose drain was, in the absence of a postoperative pancreatic fistula (POPF), mobilised on POD3, monitored by the drain lipase level and drain output on POD3. No precise definition was used to evaluate a pancreatic fistula. High lipase level and suspicious aspect of the drain fluid were criteria used to define POPF. It was the decision of the operating surgeon to remove the medial drain and start the mobilisation of the penrose drain based on these criteria. The patients were all mobilised on POD1.

2.3. Outcome variables

Our primary outcome was to evaluate the adherence to the different targets of the ERAS protocol postoperatively, and to describe short-term surgical outcomes, including the overall pancreatic surgery specific morbidities. The secondary endpoints were the 30-day readmission rate, reoperation rates and mortality.

2.4. Patient characteristics

Sex, BMI, age at time of pancreatic surgery, medical history (cardiac, vascular, respiratory, endocrinologic, neurologic, psychiatric, orthopaedic, and urogenital comorbidities), preoperative biliary stenting, and intraoperative factors (duration of surgery, use of somatostatin) were variables chosen for analysis based on their clinical relevance in regard to the pancreatic surgery. All patients were planned for surgery after adequate preoperative optimisation and were subcategorised following the American Society of Anesthesiology (ASA) classification in 1, 2 or 3.

The pathologic indication was grouped into pancreatic adenocarcinoma (e.g. pancreaticobiliary type, intestinal type), benign (e.g. pancreatitis, intraductal papillary mucinous neoplasia, cystadenoma), and non-adenocarcinoma malignancy (e.g. cholangiocarcinoma, neuroendocrine tumour [NET], sarcoma). Neoadjuvant radiation and chemotherapy were aggregated into a single variable if a patient received neoadjuvant therapy.

Postoperative morbidity was measured according to the Clavien-Dindo Classification [12]. Morbidity was defined as any postoperative non-surgical (systemic) or surgical (local) complication that occurred in the same admission or within 30 days of surgery. Non-surgical complications included respiratory events (e.g. pneumonia), cardiac events (e.g. atrial fibrillation), cerebrovascular events (e.g. delirium), or renal problems. Surgical complications included pancreatic surgery specific complications and general surgical complications (eg. surgical site infection (SSI), intra-abdominal abscess, and chyle leakage). Pancreatic surgery specific complications were defined according the International Study Group on pancreatic Surgery (ISGPS) for postoperative pancreatic fistula (POPF), post-pancreatectomy haemorrhage (PPH), delayed gastric emptying (DGE), and biliary fistula [4]. The POPF were classified in grade A, B, and C. Grade A was a biochemical leak; Grade B and C were true POPF, when a prolonged presence of drains or a radiological or surgical intervention was deemed necessary [13]. The classification of DGE is based on the duration of nasogastric intubation, the inability to consume solid food by certain postoperative days, the presence of vomiting, and the usage of prokinetic drugs [14]. Postoperative mortality was defined as death within 30 days after surgery. Patients were discharged when criteria for adequate pain control on oral analgesia, adequate solid diet and sufficient mobilisation were met and no morbidity was present at the time of discharge. Removal of the penrose drain was not considered mandatory before discharge.

2.5. Statistical analysis

A descriptive analysis was performed on the different targets of the ERAS protocol, and on patientrelated factors i.e. age, BMI, comorbidities, preoperative biliary stenting, neo-adjuvant therapy, postoperative complications, and LOS. Statistical analysis was performed using SPSS (version 25.0) software. Data were presented as means (standard deviation) for continuous variables. Categorical data were presented as numbers (percentages) of the total sample in the group.

Table 1
ERAS protocol.

Perioperative day	Perioperative protocol
Preoperative outpatient visit	- Pre-admission counseling - Patient information
Day before surgery	- Normal oral nutrition until midnight - Clear fluids until 2 h before induction of anaesthesia - No preanaesthetic medication
Day of surgery	- Preoperative antimicrobial prophylaxis - Mid-thoracic epidural anaesthesia - Short-acting IV anaesthetic agent - Warm IV- fluids and upper and lower body bear hugger - Patient sent to recovery ward (ICU setting) - Start antithrombotic prophylaxis
POD 1 patient sent to surgical ward	- Patient mobilises in bed - Continue portable epidural analgesia-Antiemetic if necessary
POD 2	- 10 cm retraction of NGT - Free drinking up to 1.5 L - Remove epidural analgesia - Remove urinary catheter - Start NSAID's based on pain score - Remove lateral drain - Continue mobilisation
POD 3	- Remove NGT - Start oral liquid diet - Remove medial drain and start mobilisation of the penrose drain regarding the drain lipase level and output - Continue analgesics based on pain score - Continue mobilisation
POD 4	- Start lightly digestible food - Continue analgesics based on pain score - Continue mobilisation
POD 5-10	- Start regular diet - Continue analgesics based on pain score - Continue mobilisation - Discharge from hospital

ICU, intensive care unit; NGT, nasogastric tube; NSAID, nonsteroidal anti-inflammatory drugs; POD, postoperative day.

3. Results

3.1. Patients' characteristics

Between August 2016 and December 2019, 201 patients presented for a pancreaticoduodenectomy (PD). Thirty-four of them were inoperable (16.9%); in 21 patients the tumour was considered locally advanced, and in 13 patients hepatic or peritoneal metastasis were confirmed intraoperatively. Of those 34 patients, 3 patients received neoadjuvant treatment and were still operated on in the period of this study. A total of 170 patients underwent a PD operation of whom 154 (90.6%) patients were enrolled in the ERAS protocol (Fig. 1).

Therefore, the population for analysis included 154 patients (94 male; 60 female patients). The mean age of the study group was 65.0 +- 10.5 years. The demographics, preoperative, operative and pathologic data of the ERAS group, and the non-ERAS group are stated in Table 2. In the ERAS group 50 patients (32.5%) had 3 or more comorbidities, and 60 patients (39.0%) were classified as ASA Class III. The ASA class is known as a risk factor for surgical complications [13]. Preoperative biliary stenting was done in 38 patients (24.7%), and 14 patients (9.1%) received neoadjuvant therapy. One hundred and twenty-seven patients (82.5%) underwent a pylorus preserving pancreaticoduodenectomy. In 11 patients (7.1%) a vascular reconstruction was indicated. Somatostatin was used intraoperatively, and continued postoperatively in 87 patients (56.5%). Final pathological diagnosis showed pancreatic adenocarcinoma in 113 patients (73.4%), non-adenocarcinoma malignancy in 20 patients (13.0%), and benign pathology in 21 patients (13.6%).

3.2. Study outcomes

The primary endpoint was to evaluate the adherence to the ERAS protocol postoperatively. The nine targets of the ERAS protocol selected for evaluation are listed in Fig. 2.

As per ERAS protocol, the NGT has to be removed on POD3, a liquid diet started on POD3, lightly digestible food on POD4, and a regular diet on POD5. Seventy-four patients (49.0%) had their NGT removed on POD3 (mean POD 4.6 ± SD 3.3). Eighty-three patients (54.3%) tolerated liquid diet on POD3, and 73 patients (48.0%) tolerated lightly digestible food on POD4. We were able to start a regular diet by the fifth postoperative day in 52 patients (34.9%) (mean POD 8.0 ± SD 4.6). The NGT needed to be replaced in 11 patients (7.1%) of whom 3 patients were re-operated on with replacement of the NGT in the operating theatre. Delayed gastric emptying was diagnosed in 44 patients (28.6%); 26 patients had ISGPS Grade A, 8 patients had a grade B and 10 had a grade C DGE.

In 26 patients (17.7%) the epidural analgesia was removed on POD2 according to the ERAS protocol (mean POD 3.97 ± SD 1.77), followed by the removal of the urinary catheter on POD2 in 22 patients (15.6%) (mean POD 4.4 ± SD 3.7). In 7 patients (4.6%) (6 male; 1 female patient) the urinary catheter needed to be replaced; 2 needed to be re-operated for other reasons; 2 had postoperative haematuria, 1 was preoperatively diagnosed with benign prostatic hyperplasia, and 2 had no previous urological history.

The lateral abdominal drain was removed in 81 patients (52.9%) on POD2 (mean POD 3.2 ± SD 3.2) in line with the ERAS protocol. In total 5 patients (3.3%) had a biliary leakage, of whom 4 of them had a suspicious aspect of the drain fluid in the lateral drain on POD2. Three of them were re-operated immediately on POD2; in 1 patient the diagnosis of bile leakage was initially unclear, and re-operation was performed on POD4. In one patient the lateral drain was removed on POD2 without signs of bile. Re-operation was performed for a bleeding of the gastroduodenal artery and intraoperative a dehiscence of the bile duct anastomosis was detected; a T-tube drain was inserted.

According to the ERAS protocol, the medial drain has to be removed on POD3 and the penrose drain between POD3 and 10. In 39 patients (26.2%) the medial drain was removed on POD3 (mean POD 5.2 ± SD 3.1), and in 95 patients (61.7%) the penrose drain was removed between POD 3 and 10. In total 19 patients (12.3%) were discharged with penrose drain in place; 7 patients had lymphatic leakage, 11 patients were diagnosed with a POPF grade B, and 4 patients with a POPF grade C as per ISGPS definition. Seventy patients (46.1%) were discharged between POD5 and 10. Overall, the average LOS was 13.2 ± 6.6 days.

The adherence to the different targets of the ERAS protocol in percentages is demonstrated in Fig. 2. In line with these results, the number of targets every patient achieved was calculated going from 0 to 9 targets maximum (Fig. 3). A correlation between the number of targets achieved, and the LOS is demonstrated in Fig. 3. In regard to the LOS, the ERAS group was divided in 2 groups; 70 patients had a LOS $\leq$10 days, and 82 patients a LOS >10 days. The adherence to the different targets of the ERAS protocol was analysed for the group of patients with a LOS >10 days. The last achieved target in every patient in postoperative days, and therefore a predictor for a LOS >10 days, was calculated. In Fig. 4 the number of the last achieved targets was presented in percentages of patients with a LOS >10 days.

The pancreatic surgery specific complications, the surgical complications, and non-surgical complications are listed in Table 3.

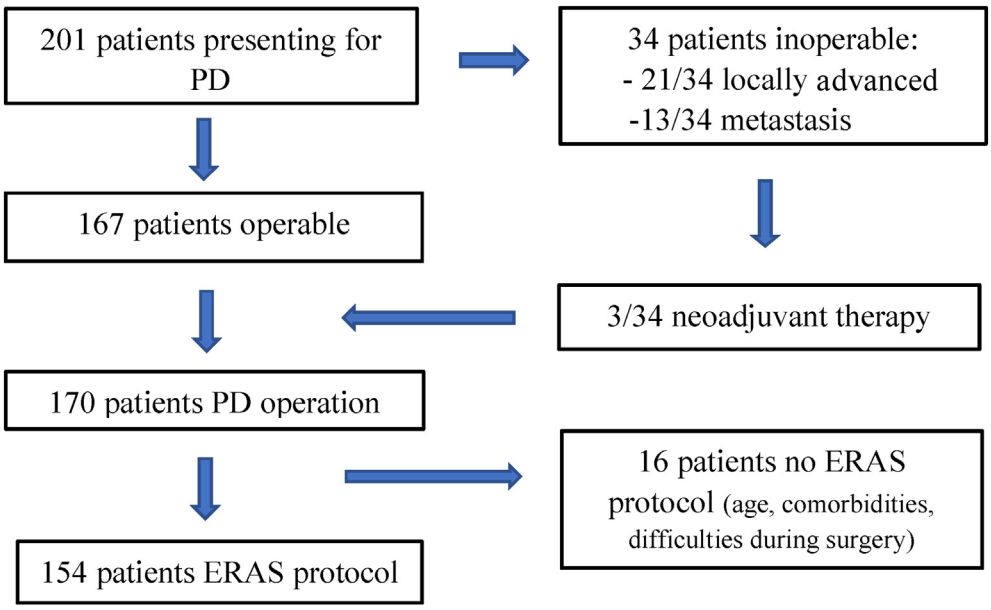

Fig. 1. Flow chart patient selection.

Table 2
The demographics, preoperative, operative, and pathologic data of the ERAS group and the non-ERAS group.

			ERAS protocol ($n = 154$)	Non-ERAS protocol ($n = 16$)
Patient characteristics	Age at time PD		65.0 ± 10.52	66.4 ± 15.9
	Sex, n (%)	Male	94 (61.0)	7 (43.75)
		Female	60 (39.0)	9 (56.3)
Clinical characteristics	BMI kg/m^2		24.1 ± 4.6	26.8 ± 3.4
	Comorbidities, n (%)	0	42 (27.3)	5 (31.3)
		1	29 (18.8)	2 (12.5)
		2	33 (21.4)	3 (18.8)
		3	33 (21.4)	4 (25.0)
		≥4	17 (11.0)	2 (12.5)
	ASA, n (%)	I	18 (11.7)	1 (6.3)
		II	76 (49.4)	9 (56.3)
		III	60 (39.0)	6 (37.5)
Preoperative data	Pathologic diagnosis, n (%)	Malignant	132 (85.7)	13 (81.3)
		Benign	22 (14.3)	3 (18.8)
	Biliary stenting, n (%)		38 (24.7)	4 (25.0)
	Neoadjuvant therapy, n (%)		14 (9.1)	1 (6.3)
Intraoperative data	Operation procedure	PD, n (%)	27 (17.5)	3 (18.8)
		PPPD, n (%)	127 (82.5)	13 (81.3)
		Vascular reconstruction, n (%)	11 (7.1)	0 (0)
	OR time, min		434.6 ± 106.1	457.8 ± 89.6
	Use of somatostatin, n (%)		87 (56.5)	13 (81.3)
Pathological results	Malignant cases	R0 Resection, n (%)	93 (70.5)	13 (100)
	(ERAS $n = 132$, non-ERAS $n = 13$)	Tumour diameter, cm	2.6 ± 1.1	2.2 ± 1.2
	Anatomopathological result	Pancreatic adenocarcinoma, n (%)	113 (73.4)	7 (43.8)
		Benign, n (%)	21 (13.6)	3 (18.8)
		Non-adenocarcinoma malignancy, n (%)	20 (13.0)	6 (37.5)

Continuous variables are expressed with means + - standard deviations; ERAS, enhanced recovery after surgery; PD, Pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; SD, standard deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status classification; OR, operating room.

The in-hospital mortality was 2 (1.2%) within 30 days of surgery. One patient died due to PPH and multiple organ failure, and another patient died due to respiratory failure. A third patient died due to PPH on POD38 and was therefore not calculated in the in-hospital mortality within 30 days of surgery.

Re-operation within one month of surgery occurred in 21 patients (12.4%) (of whom 16 patients in the ERAS group [10.4%] and 5 in the non-ERAS group [31.3%]). The data are shown in Table 4. In total 16 patients in the ERAS group were re-operated within one month of surgery. In 12 patients the indication for surgery was detected following the ERAS protocol; 4 patients on the other hand re-admitted after discharge with a postoperative complication that needed re-operation. Of those 4 patients one had an intra-abdominal abscess and 3 patients presented with a PPH. Eighteen

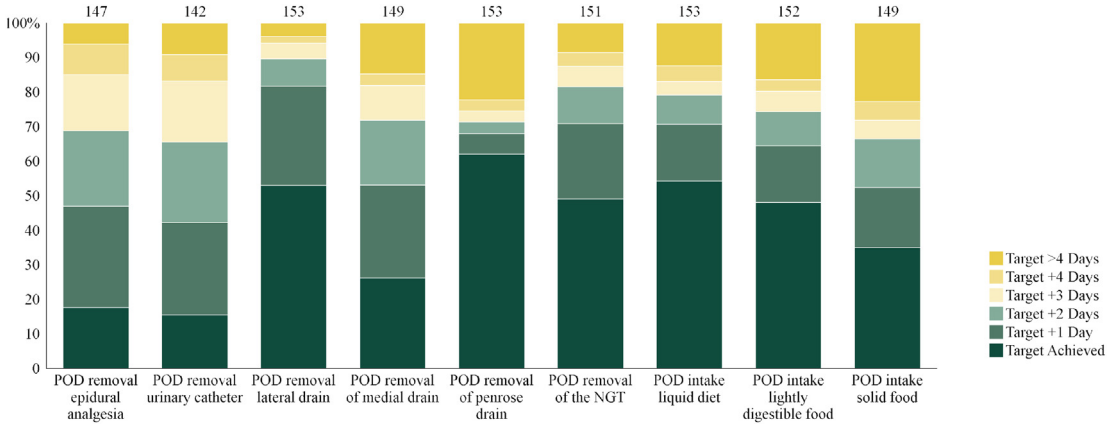

Fig. 2. The relative adherence to the different targets of the ERAS protocol is listed per target. The different colours indicate the distribution of the target in postoperative days. Dark green shows the percentage of patients who achieved the target on time. POD = postoperative day.

patients (10.6%) (of whom 13 patients in the ERAS group and 5 in the non-ERAS group) were re-admitted within one month of surgery after discharge (Table 5).

4. Discussion

Pancreaticoduodenectomy is one of the most complex abdominal operations with high morbidity and mortality rates, even in high-volume centres. Because of the major postoperative complications, surgeons often prefer a more conservative approach what might lead to an increase in LOS. The perioperative ERAS pathway has shown to be a safe and a worthy replacement for conventional management [2,3,8], but implementation is not always easy. In this study the primary endpoint was to evaluate the adherence to the different targets of the ERAS protocol postoperatively and to describe the short-term surgical outcome.

_underThe adherence to the targets was found to be rather low. Only a limited amount of studies, evaluating the adherence to the different targets in the ERAS protocol, can be found in literature. In a single centre study of Mahendran et al. (2018), the ERAS protocol was evaluated in 50 patients with an adherence to the different targets ranging from 82% to 90% [15]. A recently published study of Zhang et al. (2019) evaluated the implementation of the ERAS protocol for 176 patients. The NGT was removed in 80.1% of the patients on POD2 and solid food was tolerated on POD4 in 59.7% of the patients. The epidural catheter was removed within 36 h in 100% of the patients, followed by the removal of the urinary catheter in 71.6% of the patients [16]. In a Japanese study of Takagi et al. (2018) the adherence to the targets was evaluated for 74 patients. They described a protocol compliance of 30% for all postoperative targets [8].

The adherence to the different postoperative targets in our analysis was lower in comparison to the study of Zhang et al. [16] or Mahendran et al. [15]. A possible explanation might be the relatively higher morbidity rates and reoperation rates reported in our analysis. In the study of Mahendran, only 6% of the patients experienced DGE and no patients with PPH or POPF were described [15]. In the study of Zhang et al. more POPF grade B (16.0% vs 6.5%), more DGE grade B (8.5% vs 5.2%), but less DGE grade C (5.1% vs 6.5%) and less PPH (2.8% vs 5.8%) were reported, and less patients were re-operated within 1 month of surgery (4.5% vs 10.4%). The difference in postoperative morbidity and reoperation rate might be related to a higher preoperative ASA score of the patients reported in this study in comparison to the study of Zhang et al. (38.96% vs 25%). The ASA score is a known risk factor for postoperative complications [16]. If a patient develops a postoperative complication a more individual postoperative course is followed maintaining the NGT or drainage longer than planned according to the ERAS

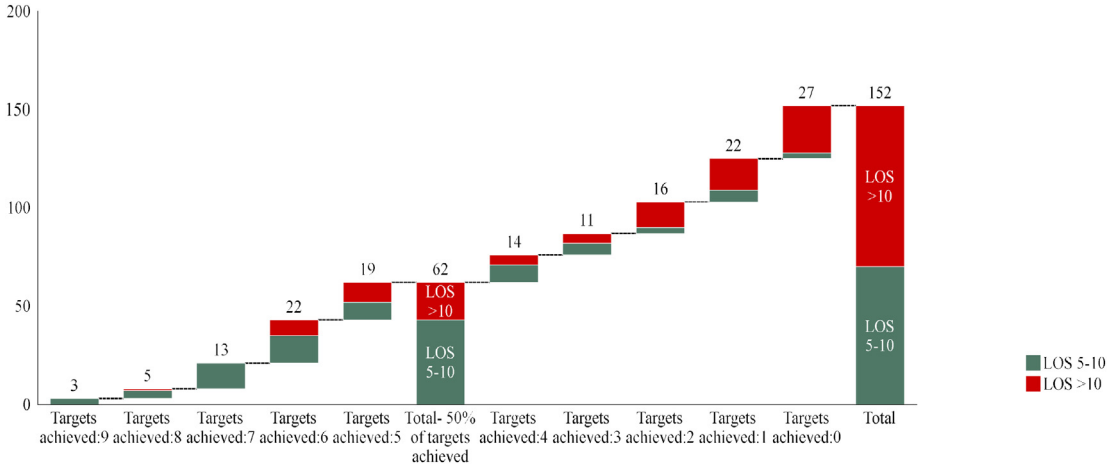

Fig. 3. The number of targets a patient achieved going from the maximum (= 9 targets) to the minimum (= 0 targets) is plotted. The length of hospital stay (LOS) in correlation to the number of targets achieved is indicated in colour.

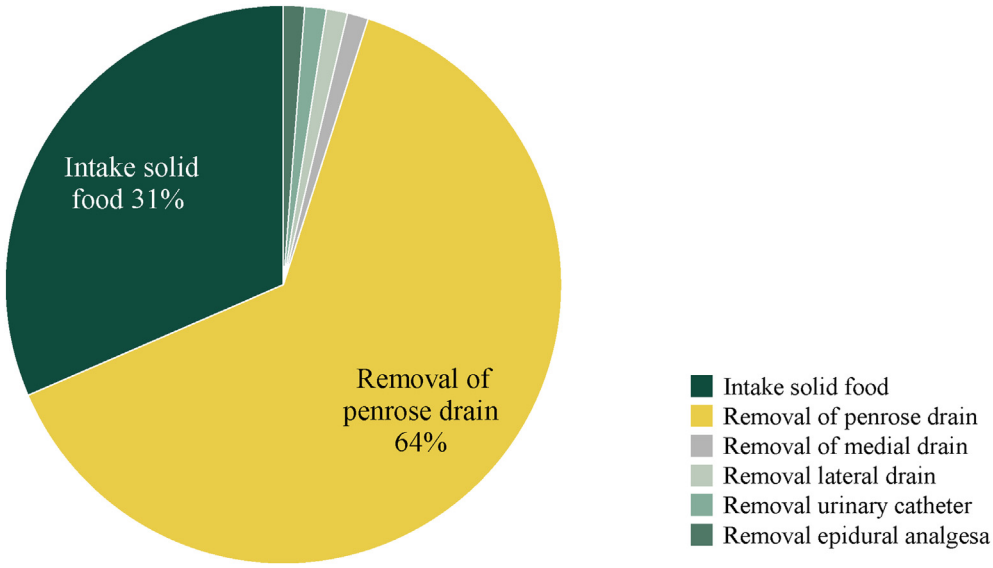

Fig. 4. The number of the last achieved targets of the ERAS protocol (in percentages) for the group of patients with a LOS >10 days.

Table 3
Postoperative morbidities.

			ERAS protocol ($N = 154$)	Non-ERAS protocol ($N = 16$)
Pancreatic surgery specific complications	POPF	Grade A, n (%)	20 (13.0)	4 (25.0)
		Grade B, n (%)	10 (6.5)	1 (6.3)
		Grade C, n (%)	4 (2.6)	0 (0)
	PPH, n (%)		9 (5.8)	2 (12.5)
	DGE	A, n (%)	26 (16.9)	9 (56.3)
		B, n (%)	8 (5.2)	2 (12.5)
		C, n (%)	10 (6.5)	2 (12.5)
	Biliary leakage, n (%)		5 (3.3)	2 (12.5)
Surgical complications	SSI, n (%)		11 (7.1)	1 (6.3)
	Intra-abdominal abcess, n (%)		9 (5.8)	5 (31.3)
	Stenosis	Bile duct anastomosis, n (%)	2 (1.3)	0 (0)
	Chyle leakage, n (%)		7 (4.6)	2 (12.5)
Non-surgical complications	Cardiac, n (%)		15 (9.7)	4 (25.0)
	Respiratory, n (%)		14 (9.1)	0 (0)
	Neurological, n (%)		15 (9.7)	3 (18.8)
	Renal, n (%)		10 (6.5)	1 (6.3)
	Diabetes de novo, n (%)		4 (2.6)	1 (6.3)
Complication grade, n (%)	Clavien-Dindo Classification	0	71 (46.1)	1 (6.3)
		I	16 (10.4)	1 (6.3)
		II	49 (31.8)	9 (56.3)
		III A	2 (1.3)	1 (6.3)
		III B	10 (6.5)	4 (25.0)
		IV A	2 (1.3)	0 (0)
		IV B	1 (0.7)	0 (0)
		V	3 (2.0)	0 (0)
Readmission < 30 days after PD, n (%)			13 (8.4)	5 (31.3)
Reoperation < 30 days after PD, n (%)			16 (10.4)	5 (31.3)
Mortality < 30 days after PD, n (%)			2 (1.3)	0 (0)

ERAS, enhanced recovery after surgery; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy haemorrhage; DGE, delayed gastric emptying; SSI, surgical site infection; PD, pancreaticoduodenectomy; BD anastomosis, bile duct anastomosis.

protocol. Another explanation for the lower adherence to the postoperative targets might be the setting of a tertiary teaching hospital with an important rotation of surgical trainees, fellows, anaesthetic trainees, physiotherapist, and nurses, who might not be routinely informed about the ERAS protocol. The entire team must work in an united way to achieve the targets of the ERAS protocol on time. Fig. 2 illustrates that many targets are achieved with a 1 or 2 day delay. This implies that also for surgeons the protocol is rather new, and surgeons still tend to be careful in regard to drain removal and oral food intake. In order to improve the adherence to the protocol, multidisciplinary staff meetings might be organised to facilitate the communication and evaluate the different targets on a daily basis.

Three drains are routinely placed in our department to evaluate common pancreatic surgery related complications postoperatively. In the ERAS group, 5 patients had biliary leakage, of whom 4 were diagnosed early because of bile in the drain. In total, 10 grade B POPF, 4 grade C POPF were reported, and 19 patients were discharged with a penrose drain (12 POPF; 7 lymphatic leakage). In literature the use of drainage is still controversial. In this study 4/5

Table 4
Re-operation within one month of surgery.

	ERAS protocol	Reason of re-operation	Readmission	Management	Mortality <(30 days)	LOS
1	Yes	Hypovolemic shock (GDA)	No	Interventional radiology	No	16
2	Yes	1) Intestinal leakage 2) Hypovolemic shock (CHA)	Yes	1) Surgery 2) Interventional radiology	No	25
3	No	Biliary leakage	No	Surgery	No	37
4	Yes	Biliary leakage	No	Surgery	No	24
5	Yes	Haemorrhage (GDA)	No	Interventional radiology + Surgery	Yes	/
6	Yes	Intestinal ischemia	No	Surgery x5	No	56
7	Yes	Biliary leakage x2	Yes	Surgery x2	No	20
8	No	Biliary leakage	No	Surgery	No	15
9	No	Haemorrhage (GDA)	Yes	Interventional radiology	No	20
10	Yes	Haemorrhage (LGA)	No	Interventional radiology	No	17
11	Yes	1) Stenosis BD anastomosis 2) hypovolemic shock (GDA)	Yes	1) Surgery 2) Interventional radiology	No	20
12	Yes	Intra abdominal abscess	Yes	Interventional radiology	No	13
13	Yes	Stenosis BD anastomosis	No	Surgery	No	22
14	No	Haemorrhage (PJ anastomosis)	Yes	Surgery + interventional radiology	No	14
15	No	Incarcerated umbilical hernia	No	Surgery	No	13
16	Yes	Biliary leakage	No	Surgery	No	14
17	Yes	Haemorrhage (BD anastomosis)	Yes	Surgery	No	8
18	Yes	Hypovolemic shock (GDA) + Biliary leakage	No	Surgery	Yes	Death POD 38
19	Yes	Hypovolemic shock (PJ anastomosis)	No	Surgery	No	19
20	Yes	Biliary leakage	No	Surgery	No	20
21	Yes	Haemorrhage (GJ anastomosis)	No	Endoscopy	No	17

ERAS, enhanced recovery after surgery; LOS, Length of hospital stay; GDA, gastroduodenal artery; CHA, common hepatic artery; LGA, left gastric artery; BD anastomosis, bile duct anastomosis; PJ anastomosis, pancreaticojejunostomy anastomosis; POD, postoperative day: GJ anastomosis, gastrojejunal anastomosis.

Table 5
Readmission within one month of surgery after discharge.

	ERAS protocol	Date of discharge	Reason of readmission	Management
1	Yes	25	Hematemesis + melena	Interventional radiology (CHA)
2	Yes	20	Woundinfection	Conservative
3	No	20	Hypovolemic shock	Interventional radiology (GDA)
4	Yes	20	Hypovolemic shock	Interventional radiology (GDA)
5	Yes	13	Intra-abdominal abscess	Interventional radiology
6	Yes	17	Woundinfection	Conservative
7	No	14	Hypovolemic shock	Surgery + interventional radiology
8	Yes	9	Diarrhea	Conservative
9	Yes	8	Hypovolemic shock	Surgery (BD anastomosis)
10	Yes	20	Change aspect drain fluid	Conservative
11	Yes	9	Intra-abdominal collection (POPF B)	Conservative
12	Yes	15	Fever of unknown origin	Conservative
13	No	14	Vomiting	Conservative
14	No	12	Intra-abdominal collection	Conservative
15	No	12	Intra-abdominal collection	Conservative
16	Yes	9	Anemia + anorexia	Blood transfusion
17	Yes	9	Anorexia	TPN
18	Yes	12	Diarrhea + anorexia	TPN

ERAS, enhanced recovery after surgery; CHA, common hepatic artery; GDA, gastroduodenal artery; BD anastomosis, bile duct anastomosis; TPN, total parenteral nutrition.

patients (80%) with biliary leakage, and 13/14 patients (92,9%) with POPF were detected immediately, thanks to the routine drain placement. The present results are in line with a previous report of Addison et al. where routine placement of drains is supported in order to decrease serious morbidity. However the length of drainage is associated with an increase of morbidity thus stimulating an early drain removal policy [17]. Patients with drains have a prolonged LOS, a higher incidence of DGE, and pancreatic fistula [1,18,19]. In contrast, the 30-day mortality seems higher in the group of patients without drains [19]. A prospective multi-centre trial of Van Buren et al. was stopped early because mortality increased from 3% to 12% in the group without intraperitoneal drainage [20]. In this study most of the postoperative complications regarding POPF, chyle leakage or bile leakage were detected following the ERAS protocol. Based on these results the inclusion of all the patients in the ERAS protocol was preferred, even for patients at high risk for postoperative complications. In case of a postoperative complication, the ERAS protocol was automatically adapted with prolonged drainage or reoperation if necessary. Delayed postpancreatectomy haemorrhage (>24 h postoperatively) is not routinely monitored in the ERAS protocol and associated with a high morbidity and mortality [21,22]. Nine patients of the ERAS group presented with a hypovolemic shock caused by a delayed bleeding postoperatively. Of these 9 patients, three were already discharged. In the literature pancreatic fistulas are considered to play a crucial role in the pathogenesis of PPH [21–23]. In this study 4/11 (36.4%) patients with a POPF developed a PPH. Patients with a known POPF should be more closely monitored after discharge.

The secondary endpoints were the readmission rate, the reoperation rate, and mortality within 30 days of surgery. The readmission rate within 30 days of surgery for patients in the ERAS group (8.4%) was lower than that reported in the study of Zhang et al. (10.2%). In the study of Zhang et al., patients with a POPF grade B or DGE grade B, or C were more likely to be re-admitted within 30 days of surgery ($P < 0.001$) [16]. In this study the reasons for readmission were more diverse; only 3/13 patients presented with DGE, and 4/13 presented with a POPF grade B or C. In total 4/13 patients (30.8%) who re-admitted needed endovascular or surgical

treatment. This implies that only 4 of the 154 patients (2.6%) who followed the ERAS protocol were discharged with a postoperative complication not detected following the ERAS protocol. Lessing et al. (2019) investigated the impact on morbidity, mortality, and long-term survival after early re-operation following PD. The most common indications for reoperation were anastomotic leaks, followed by PPH, and wound complications [24]. In this study similar results were found. The most common indication for re-operation is PPH (11/21), followed by bile leakage (7/21). The mortality within 30 days after reoperation is 4.8%. This is much lower than the mortality rate (18.7%) reported in the study of Lessing et al. [24].

In the literature LOS is often the primary endpoint to evaluate the implementation of the ERAS protocol. In this study, the ERAS protocol was evaluated according to the adherence to the different targets. Interestingly, of the 62 patients who achieved 5 or more targets still 31% had a LOS of more than 10 days. This implies that the LOS is influenced by multiple factors, and is therefore not a good parameter to evaluate the implementation of an ERAS protocol. Not only patient recovery, but also the healthcare system contribute to the timing of discharge. Healthcare systems differ a lot among countries. In Asian countries (e.g. Japanese, Korean, Chinese) hospitals usually provide not only postoperative care, but also subsequent rehabilitation [1,2,7,8]. On the contrary, in the UK it is common practice to discharge patients from the hospital early, and continue care in the community. Furthermore the medical insurance differs between countries, contributing to a higher heterogeneity regarding LOS [8]. The overall trend after starting the ERAS protocol tends towards a shorter LOS [1,7–10,15]. In this study a similar trend has been found regarding LOS. The better the adherence to the ERAS protocol, the shorter the LOS. In the study of Zhang et al., patients with a POPF grade B or DGE grade B or C were significantly correlated with a longer LOS ($p < 0.001$). The failure to remove the NGT on POD2 ($p = 0.036$) or tolerate liquid diet on POD3 ($p = 0.014$) were predictors for a longer LOS, and therefore considered 'failure' to the ERAS protocol [16]. In our study the presence of a penrose drain and the inability to tolerate solid food were 2 targets associated with a LOS >10 days. These results confirm that DGE and POPF are important causes of a prolonged LOS as stated by others [9,16,25,26]. Despite the fact that a postoperative pancreatic fistula was less frequently present than DGE, as the presence of a postoperative pancreatic fistula has been reported being the most important predictor of DGE [26,27], DGE on itself is frequent in our population (28.6%) and might be due to a very high percentage of pylorus preserving pancreaticoduodenectomy (82.5%), but DGE has also been associated with age $\geq$ 75 years old, male gender, or a prolonged operating time [27]. In this study the mean LOS was 13.2 +- 6.6 days, with a median of 11 days. This is shorter than observed in most Japanese or Chinese high-volume hospitals, but much longer than seen in the US.

This study had certain limitations. First of all this study has a retrospective design. Therefore we could not control for whether patients were in an ERAS or fast-track perioperative care protocol. It was a decision made by the two main operating surgeons at the hospital, but no clear definition was used to exclude patients. Although the ISGPS criteria for POPF were evaluated in all patients, the decision to maintain the drains was surgeon-dependent. This limits the external validity and applicability to compare results to other health care centres. This study used a modified ERAS protocol that was feasible to be implemented in the hospital setting, instead of using all 27 recommendations of the ERAS guidelines. In other centres, modified ERAS protocols have been applied following the elements that were practically possible. It is therefore difficult to compare the adherence of the ERAS targets, especially regarding the postoperative LOS, one of the most frequently chosen primary outcomes.

5. Conclusion

Pancreaticoduodenectomy remains a complex surgical procedure with significant morbidity. The ERAS protocol is a formalised perioperative care approach that improves the postoperative course without compromising surgical outcome and leads to earlier detection of postoperative complications. Only a limited amount of studies, evaluating the adherence to the different targets in the ERAS protocol, can be found in the literature. Considering the adherence to the targets of the ERAS protocol, efficient implementation requires strict follow-up of all included ERAS elements, but should not be restricted to low-risk patients. In this study most complications were detected along the ERAS pathway, indicating that also patients at high-risk for complications could be included in the ERAS-group. Delayed gastric emptying and postoperative pancreatic fistula are predictors for a prolonged LOS. Length of hospital stay is influenced by multiple factors and therefore not a good parameter to evaluate implementation of an ERAS protocol.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

All patients given their consent at time of treatment. The informed consent was approved by the Ethical comity of UZ Gent. Last approved ICF version was: "*AHHK informed consent volwassene NL versie 3.0*" approved on 21 June 2019 with EC number: **EC/2019-074/sds**. All standard pseudonymized data was stored in the (by Ethical comity of UZ Gent approved) database on REDCap with EC Number **BC-08135**.

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Author contribution

Prof. Dr. Frederik Berrevoet: study design and writing;
Hufkens Ann-Sophie: data analysis and writing;
Stijn van Cleven: contributor and data analysis;
Luis Abreu de Carvalho: contributor and critical evaluation of the manuscript;
Ande Vanlander: design of study and contributor.

Conflict of interest statement

None.

Guarantor

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Research registration number

1. Name of the registry: Researchregistry.com.
2. Unique Identifying number or registration ID: 5907.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/register-now#home/registrationdetails/5f3566860a19700016db9c63/.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijso.2020.11.025.

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