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## Application of an enhanced recovery protocol in pancreatic surgery

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**UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE**

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**Application of an enhanced recovery protocol in pancreatic surgery**

THESE

préparée sous la direction du Professeur Martin Hübner  
avec la co-direction du Docteur Didier Roulin

et présentée à la Faculté de biologie et de médecine de  
l'Université de Lausanne pour l'obtention du grade de

DOCTEURE EN MEDECINE

par

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## **Application of an enhanced recovery protocol in pancreatic surgery**

Les protocoles de réadaptation améliorée après chirurgie (ERAS) ont démontré leur sécurité et efficacité dans la réduction du stress chirurgical et de la morbidité postopératoire dans de multiples disciplines chirurgicales. En chirurgie pancréatique, la recherche a toujours été axée sur les duodéno-pancréatectomies (PD).

Le but de cette étude est l'évaluation de la compliance au protocole ERAS pour les pancréatectomies distales (DP), particulièrement dans la période postopératoire, ainsi que l'identification de facteurs prédictifs d'une compliance basse.

Il s'agit d'une étude rétrospective incluant tous les patients opérés de manière élective d'une DP seule ou associée à une splénectomie entre le 1<sup>er</sup> octobre 2012 et le 31 décembre 2018. Les patients ont tous été inclus dans le programme ERAS et opérés dans un hôpital universitaire lausannois. La compliance au programme ERAS a été évaluée en se basant sur les recommandations internationales les plus récentes sur le sujet.




Au total, 83 patients ont été inclus. La compliance globale et détaillée pour chaque item du protocole ERAS a été calculée. La compliance globale était de 71%. Les compliances pré- et peropératoire représentaient respectivement 99 et 94%, tandis que dans la période postopératoire cette valeur chutait à 48%. Dans cette période postopératoire, les items les plus difficiles à respecter étaient la mobilisation précoce, l'administration restreinte de liquides par voie intra-veineuse (iv) et le retrait des sondes urinaires au 2<sup>ème</sup> jour postopératoire (POD). Une compliance globale  $\geq 65\%$  était associée à une réduction de la durée de séjour de 5 jours ( $p = 0.007$ ), un taux réduit de complications (53 vs 87%,  $p = 0.002$ ) et à un *Complication Comprehensive Index* plus bas (13.2 vs 27.7,  $p < 0.001$ ).

La compliance au protocole ERAS  $\geq 65\%$  a été identifiée comme le seul facteur prédictif indépendant de complications réduites. En analyse multivariable, les pertes sanguines peropératoires ont été associées à une probabilité réduite d'administration restreinte de liquides iv (HR 0.996, 95% IC (intervalle de confiance), 0.993 à 0.998,  $p = 0.001$ ) et d'ablation de la sonde urinaire au POD 2 (HR 0.996, 95% IC, 0.994 à 0.999,  $p = 0.030$ ). Les chirurgies réalisées par laparoscopie augmentaient les chances d'ablation de la sonde urinaire dans les délais souhaités (HR 3.64, 95% IC 1.20 à 11.07,  $p = 0.023$ ). Aucun facteur prédictif n'a été identifié pour la mobilisation précoce.

Comme décrit dans d'autres études sur la chirurgie pancréatique, un haut taux compliance dans la période postopératoire est le défi le plus difficile à atteindre, les taux de compliance variant entre 30 et 70%. La compliance postopératoire dans cette étude pour les DP est plus élevée que celle décrite précédemment pour les PD (30%). De manière concordante avec d'autres observations dans d'autres disciplines chirurgicales, la compliance globale au protocole ERAS a le plus grand impact sur la récupération fonctionnelle optimale des patients, avec une réduction des complications après une DP. La réduction des pertes sanguines pourrait potentiellement augmenter la compliance postopératoire, en permettant de respecter une administration équilibrée de liquides iv. La laparoscopie étant associée à des pertes sanguines diminuées et à un retrait précoce de la sonde urinaire, elle devrait être recommandée pour les DP.

La compliance avec le protocole ERAS pour les DP est associée de manière indépendante avec une amélioration des outcomes postopératoires. Les items postopératoires comme la mobilisation précoce, l'administration restreinte de liquides iv ainsi que le retrait de la sonde urinaire sont les plus difficiles à respecter. Les pertes sanguines importantes ont été identifiées comme un déterminant important pour les fluides iv et le retrait de la sonde urinaire. Ces résultats accentuent l'importance de la compliance au protocole ERAS et soulignent son impact dans la récupération fonctionnelle après les DP.

# Application of an enhanced recovery after surgery pathway for distal pancreatectomy

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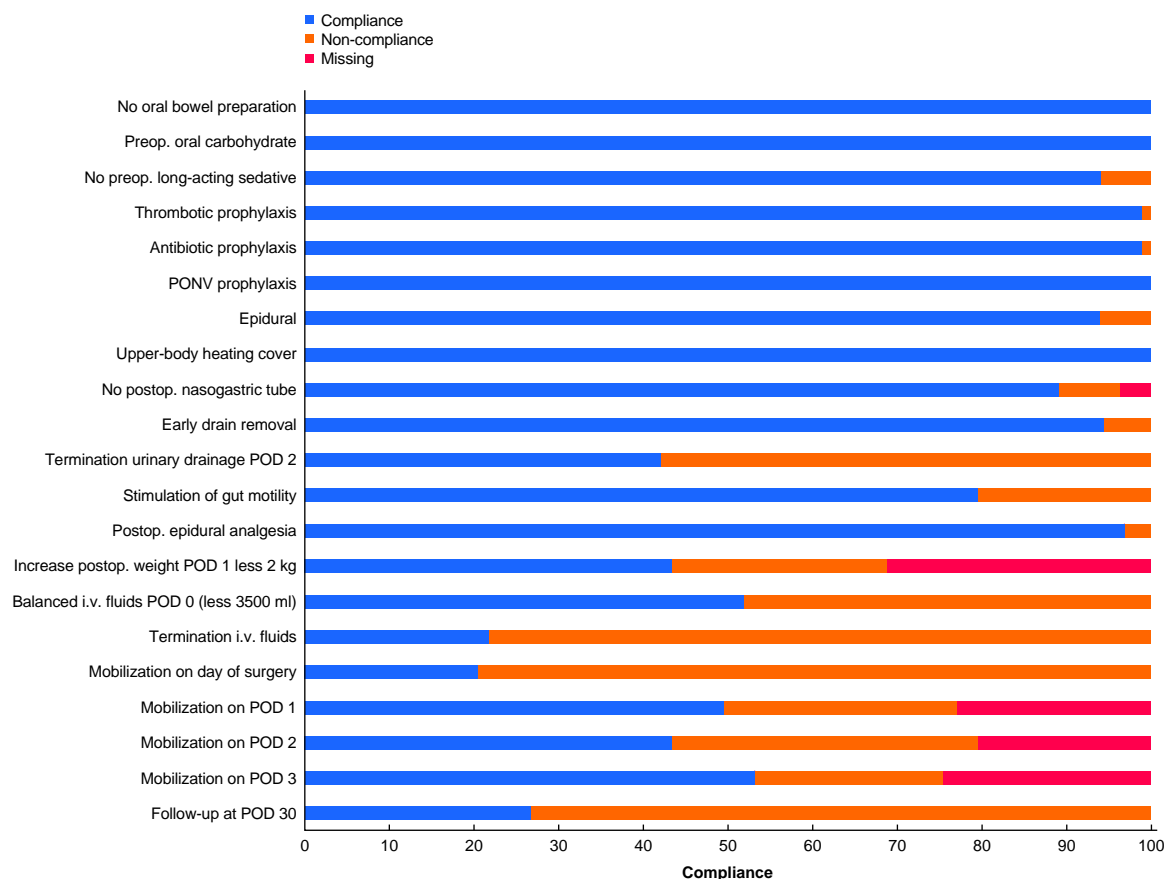
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Dear Editor

Enhanced recovery after surgery (ERAS) pathways have shown safety and efficiency in reducing perioperative surgical stress and postoperative morbidity in various surgical fields. In pancreatic surgery the focus has always been on pancreateo-duodenectomy

(PD)<sup>1</sup>. The present study aimed to assess ERAS compliance for distal pancreatectomy (DP) especially in the postoperative interval, and to identify predictive factors of low compliance.

This is a retrospective analysis of all patients undergoing elective DP with or without *en bloc* splenectomy and enrolled in an ERAS programme in a tertiary referral centre from 1 October



**Fig. 1** Perioperative compliance to enhanced recovery items

PONV, postoperative nausea and vomiting; POD, postoperative day; i.v., intravenous.

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2012 to 31 December 2018. Exclusion criteria were age under 18 years, emergency surgery, and lack of informed consent. Compliance with ERAS guidelines was assessed according to the recommended pathway (Table S1).

Eighty-three patients were included (Table S2). For each ERAS item, the compliance is detailed in Fig. 1. Overall, the mean compliance was 71 per cent. Pre- and intraoperative compliances were 99 per cent and 94 per cent respectively. Postoperative compliance was the lowest (48 per cent). The most challenging postoperative items to fulfil were early mobilization, balanced intravenous (i.v.) fluids administration, and urinary catheter removal on postoperative day (POD) 2. Overall compliance  $\geq 65$  per cent or higher was associated with a 5-day reduction in duration of hospital stay ( $P=0.007$ ), decreased rate of overall complications (53 versus 87 per cent,  $P=0.002$ ), and a lower comprehensive complication index (13.2 versus 27.7,  $P<0.001$ ). A multivariable regression analysis of predictive factors of postoperative outcomes identified overall compliance  $\geq 65$  per cent or higher as the only independent factor of reduced postoperative complications (HR 0.19, 95 per cent c.i. 0.06 to 0.62;  $P=0.006$ ) (Table S3). Multivariable models were run to identify predictors of compliance to the challenging items: blood loss was an important factor associated with a reduced likelihood to comply with i.v. fluid administration (HR 0.996, 95 per cent c.i. 0.993 to 0.998,  $P<0.001$ ) and urinary catheter removal (HR 0.996, 95 per cent c.i. 0.994 to 0.999,  $P=0.030$ ). Laparoscopy increased the chances of urinary catheter removal on POD2 (HR 3.64, 95 per cent c.i. 1.20 to 11.07,  $P=0.023$ ), whereas no predictive factor was identified for early mobilization (Table S4).

As described in other studies on pancreatic surgery, compliance in the postoperative interval is one of the most challenging tasks, with compliance rates ranging from 30 to 70 per cent<sup>2-4</sup>. The postoperative compliance observed in the present study on DP was higher (48 per cent) than previously described for PD (30 per cent)<sup>2</sup>. Consistent with observations in other surgical fields<sup>4</sup>, the overall compliance had the greatest impact on optimal recovery and was the most significant predictor of improved outcome, with a significant reduction in complications after DP. Interestingly, increasing blood loss was identified as a predictive factor of failure of balanced i.v. fluids administration on the day of surgery. Reducing blood loss could potentially increase postoperative compliance. Laparoscopy was associated with decreased median blood loss in the DIPLOMA study<sup>5</sup> and was also associated with early urinary catheter removal in this study. Thus, laparoscopy for DP should be recommended. Further data on larger multicentric cohort should be analysed to confirm these findings.

Compliance with the ERAS protocol for DP was independently associated with improved postoperative outcomes. Postoperative items such as early mobilization, balanced fluids administration,

and urinary catheter removal represented the most challenging items. Increased blood loss was identified as an important determinant of compliance for i.v. fluid management and urinary catheter removal. These results emphasize the importance of compliance with the ERAS protocol and highlight its impact on recovery after DP.

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## Disclosure

MH is appointed officer of the ERAS® Society. ND is member of the executive committee of the ERAS® Society.

## Supplementary material

Supplementary material is available at BJS Open online.

## Data sharing

Data are available upon request from the corresponding author.

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# **Application of an enhanced recovery after surgery pathway for distal pancreatectomy**

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Informed consent was obtained from all individual participants included in the study.

## **Abstract**

### Objective :

Enhanced recovery (ERAS) pathways demonstrated safety and efficiency for numerous major surgeries, including pancreatic surgery but with a focus on pancreato-duodenectomy. Therewith, data for distal pancreatectomy (DP) remain scant. The present study aimed to assess how ERAS is applicable to DP by analyzing compliance and to investigate whether compliance may impact outcomes.

### Methods :

Retrospective analysis of consecutive adult patients undergoing elective DP with or without splenectomy at Lausanne University Hospital between October 2012 and December 2018.

### Results :

A total of 83 patients were included. Spleno-pancreatectomy was performed in 63 (76%) and spleen-preserving DP in 20 (24%) patients. Mean overall compliance was 71%, with pre-, intra- and post-operative compliance of 99%, 94% and 48%, respectively. A compliance  $\geq 65\%$  was associated with reduction of hospital length of stay (LOS) of 5 days ( $p = 0.007$ ), decreased rate of overall complications (53 vs 87%,  $p$  value = 0.002) with lower Comprehensive Complication Index (13.2 vs 27.7,  $p < 0.001$ ). Compliance  $\geq 65\%$  was identified as an independent predictive factor for reduced postoperative complications (HR 0.19: 95% CI 0.06-0.62;  $p = 0.006$ ).

### Conclusion :

Application of an ERAS pathway for distal pancreatectomy is feasible, showing a high compliance for pre- and intra-operative items. A threshold of 65% of overall compliance was identified and independently associated with reduced postoperative complications.



## Introduction

Enhanced Recovery After Surgery (ERAS) pathways have shown safety and efficiency in reducing perioperative surgical stress and postoperative morbidity in a large panel of different surgical specialties (1-10). Regarding the specific area of pancreatic surgery, the implementation of ERAS principles was supported by the ERAS Society guidelines for pancreatoduodenectomy (PD) (11), updated in 2019 (12). The implementation of ERAS principles to pancreatic cancer surgery was associated with a significant reduction in postoperative morbidity, a lower rate of delayed gastric emptying and a shorter length of stay (13). The most important predictor of a successful ERAS pathway is compliance, which is the overall percentage of ERAS items applied to the patients. In a multicenter study on patients undergoing PD a compliance  $\geq 70\%$  was associated with lower complications and shorter length of stay (14). However, the current ERAS guidelines and most of the studies assessing ERAS for pancreatic surgery are focusing on PD. Therefore, specific data on ERAS compliance and relation with outcome for DP are scarce.

The present study aimed to assess ERAS compliance for DP, and to identify predictive factors of postoperative complications and LOS.

## Methods

Retrospective analysis of consecutive patients undergoing elective distal pancreatic resection within an enhanced recovery pathway in Lausanne University Hospital (CHUV), Switzerland. Distal pancreatic resection included pancreas tail resection with or without splenectomy, performed by open or laparoscopic approach.

A prospective database was created and data about demographics, surgical details, outcomes and compliance to ERAS protocol were filled. Follow-up of selected patients began the day of surgery and extended until the 30<sup>th</sup> postoperative day (POD 30).

Period of data collection extended from October 1<sup>st</sup> 2012, date of implementation of an enhanced recovery protocol for pancreatic surgery in our center, to December 31<sup>th</sup> 2018. Exclusion criteria were patients under 18 years old, emergency surgery and the lack of consent form. The research protocol was accepted by the local ethical committee (# **2017-01169**) and patients gave informed consent. The manuscript and analysis were reported according to the STROBE guideline (15) and RECOVER checklist (16).

Data were encoded and anonymized in an online database, the ERAS Interactive Audit System ([www.eras.society.org](http://www.eras.society.org)). An extraction of data was performed in December 2019 for statistical analyses. Compliance to ERAS guidelines for PD was assessed for pre-, intra- and postoperative items and was reported as compliant, non-compliant or missing. Overall compliance was defined as the rate of compliant items out of the twenty-one perioperative items according to the 2012 ERAS guidelines (11). The definition for each item was the same as previously published for PD (14).

Primary length of stay was defined as the number of nights from the day of surgery until the hospital discharge, whereas total length of stay was the number of nights from readmission or until POD 30 added to the primary length of stay.

Postoperative complications until POD 30 were reported and graded using the Clavien classification (17) and the Comprehensive Classification Index (CCI) (18).

Minor complications included grade I and II, and major complications grade IIIa to IVb.

Pancreatic specific complications (pancreatic fistula, delayed gastric emptying and post-pancreatectomy hemorrhage) were graded using the International Study Group for Pancreatic Specific Complications classification (ISGPS) (19-21).

Continuous variables were shown as median with interquartile range (IQR) or as mean with standard deviations (SD), according to their distribution. Likewise, they were compared with Student's t-test or Mann-Whitney U test. Categorical data were shown as frequencies with percentages and compared with  $\chi^2$  or Fisher's exact test. Receiver operating curve allowed calculating area under the curve (AUC) of compliance. Cut-off was determined to obtain equal sensitivity and specificity. Multivariable analyses were performed by logistic regression, integrating confounding factors. Statistical significance was defined as a p-value  $<0.05$ . IBM SPSS Statistics 27.0 was used to perform all analyses.

## Results

During the study period, a total of eighty-six consecutive patients underwent elective DP within an ERAS pathway. Three patients did not consent to the use of their data and were excluded. Therefore, eighty-three patients could be included in the present study. Patients' characteristics and operative details are summarized in **Table 1**. The rate of minimally-invasive surgery was 51%. The main indication for surgery was malignant tumor in 56 patients (67%).

The median primary length of stay was 8 days (IQR 6-13) with a 23% readmission rate. Overall complications were reported in 54 (65%) of patients, and 24 (29%) of them had major complications. There was no 30 days postoperative mortality. The following specific pancreatic surgery complications were reported: delayed gastric emptying (7%), clinically relevant pancreatic fistula (18%), and post-pancreatectomy hemorrhage (5%).

### Compliance

For each ERAS item, the compliance was detailed on **Figure 1**. Overall, the mean compliance was 71%. Pre- and intra-operative compliances were 99% and 94%, and the postoperative compliance reached 48%. The mean rate of missing values for compliance items was 4.9%. Particularly difficult items in the postoperative period were termination of intravenous fluid on POD2 and mobilization on day of surgery, achieving a reduced compliance (22% and 21%, respectively). A ROC curve analysis of overall compliance and the occurrence of overall complications was performed and the

optimal cut-off for compliance was determined at 65%, with 52% specificity and 53% of positive predictive value (PPV).

According to the above determined threshold of 65% compliance, postoperative outcomes between patients with an ERAS compliance  $\geq 65\%$  was compared to those with lower compliance (**Table 2**). Patients with a  $\geq 65\%$  compliance showed improved postoperative outcome, with a reduction by 5 days of the median primary length of stay, and with 39% reduction of overall complications and 62 % reduction of major complications. There was no difference in the occurrence of specific related pancreatic surgery complications.

### **Compliance is an independent predictor of overall postoperative complications**

A uni- and multi-variable regression analysis of potential predictive factors of postoperative outcome, including patient's characteristics, intraoperative variables and the identified threshold of  $\geq 65\%$  compliance was performed as detailed on **Table 3**. When adjusted for potential confounding factors such as patient's comorbidity, surgical approach and intraoperative blood loss, an overall compliance  $\geq 65\%$  was the only independent factor associated with reduced postoperative complications (HR 0.19: 95% CI 0.06-0.62;  $p = 0.006$ ).

## Discussion

In this single center retrospective study, high compliance for pre- and intraoperative items was obtained. Global compliance  $\geq 65\%$  was associated with improved postoperative outcome, such as decreased length of stay and morbidity and was identified as an independent factor associated with decreased overall complications and with a reduction in respiratory complications.

Regarding postoperative outcome, the present results are comparable to previous studies on enhanced recovery after distal pancreatectomy (22, 23) and in the range of established benchmarks for pancreatic surgery (24). Our overall morbidity rate was 65%, with pancreatic fistula present in 18%, post-pancreatectomy hemorrhage in 5% and delayed gastric emptying in 7%. Median length of stay was 8 days and readmission rate was 23%. In 44 consecutive patients undergoing distal pancreatectomy within an enhanced recovery program, Aoyama et al found major complication rate of 29%, mortality of 0% and with pancreatic fistula being the most frequent specific complication with a 18% rate. However, they reported a median LOS of 14 days (22). This difference of LOS can be explained by the fact that the enhanced recovery protocol in their institution included the abdominal drains ablation at POD7, preventing medical team to allow an earlier discharge.

A recent retrospective study from Pecorelli et al including 376 patients with distal pancreatectomy within ERAS reported a similar overall morbidity but less major complications (17.3%). Specific pancreatic complications were similar for post-pancreatectomy hemorrhage, more frequent for pancreatic fistula (46.3%) and less

frequently reported for delayed gastric emptying (3.4%), in a high-volume center specialized in pancreatic surgery (23).

Compliance is an important factor in ERAS protocols, as it has been demonstrated to be associated with improved postoperative outcomes. A dose-response effect of compliance to ERAS in colorectal surgery was initially identified by Gustafson and al in 2011 with a reduction of postoperative complications (OR 0.73, CI 0.55-0.98) (25). Similar results were found in pancreatic surgery. Roulin et al showed in a multicenter retrospective international study including 404 patients undergoing PD that a compliance  $\geq 70\%$  was associated with reduction in complications ( $p = 0.029$ ) and LOS ( $p < 0.001$ ) (14).

Respiratory complications are frequent after major abdominal surgery. They are also influenced by compliance to ERAS protocols, as shown by Jurt and al (26) who described that 9.8% patients undergoing colorectal surgery developed respiratory complications and that a high compliance  $\geq 70\%$  was a protective factor against these complications (OR 0.53; 95% CI 0.30-0.94). In the present study, a similar result was reported, with a significant decrease in pulmonary complications among patients undergoing DP and reaching  $> 65\%$  compliance.

Comparing compliance rate with other studies is difficult, because there is a large heterogeneity in applied ERAS protocols and there are until now no available specific guidelines recommendations for DP. Our institutional protocol was based on the 2012 guidelines of the ERAS Society for PD (12) and included 21 items. Of note, an updated ERAS protocol for pancreas surgery has been published in 2020 and will be used for further studies (12).

In the present study, while pre- and perioperative compliance were high, (99% and 94% respectively), postoperative compliance was low (48%). The most difficult postoperative ERAS items were with mobilization on the day of surgery and termination of IV fluid administration at POD 2. This is with a known phenomenon, as described in other studies with postoperative compliance rates varying from 30 to 70% (14, 23, 27). However, the postoperative compliance observed after the present study was higher (48%) than previously described for PD (30%) (14). Moreover, the very low compliance observed during follow-up at 30 POD was mainly explained by the very restrictive criterion for achieving compliance, as the follow-up needed to be performed strictly within a range of 3 days around the 30 POD. In our center, most patients were seen for follow-up between the fourth and sixth postoperative week, thus are not compliant. The development of early complications, i.e delay gastric emptying or urinary retention, could prevent patients to follow the recommended postoperative elements of the ERAS protocol. Data from a previous study from Roulin et al described that non-respect of the protocol during postoperative period in 55%, 78% of the cases was medically justified. Only in 26%, the deviation of the protocol recommendations was due to the patients themselves (27). For DP, only very few data on compliance to ERAS protocol were reported. Aoyama et al (22) described 12 ERAS elements and reported that most of them were achieved in more than 90%, with low compliance obtained for removal of epidural catheter at day 3 (31%), removal of urinary catheter at day 3 (35%), and removal of abdominal drain at day 7(23%). Pecorelli et al (23) achieved an overall 71% of compliance for 16 items, with comparable preoperative (78%) and intraoperative (83%) compliance, and higher postoperative compliance (70%). However, some items such as early drain removal were not accounted in the compliance.



Some limitations of the present study need to be addressed. This is a retrospective monocentric study with limited number of patients. This could have influenced statistical analyzes, including specificity of ROC curve analysis. The small sample size also precluded to thoroughly analyze the impact of compliance to each ERAS item on outcomes. Due to a lack of consensus guidelines for enhanced recovery protocols in DP, generalization of our findings may be challenged. It can also be hypothesized that if a specific ERAS pathway was tailored for DP, the mean compliance and the threshold could be higher. As in any retrospective study, a potential selection bias could be present despite the fact that all consecutive patients without any selection were included.

The present study suggests that the application of ERAS protocol for DP is feasible and safe and should be recommended. Compliance is an essential component in ERAS pathway, and a compliance > 65% was independently associated with improved postoperative outcome. The need for specific DP ERAS guidelines remains debated, it could allow a common world-wide reference, with better comparison and improvement of ERAS for DP.

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**Table 1** Patient's characteristics and operative details.

<b>Variables</b>	<b>N =83</b>	<b>(%)</b>
<i>Male gender</i>	42	51
<i>Age, mean (SD), years</i>	61.8 (12)	
<i>ASA score I-II</i>	77	93
<i>BMI, mean (SD), kg/m<sup>2</sup></i>	26.6 (5)	
<i>Preoperative WHO status performance</i>		
0	31	37
1-3	52	63
<i>Recent immunosuppressive treatment</i>	3	4
<i>Neoadjuvant chemotherapy</i>	1	1
 <i>Comorbidites</i>		
<i>Diabetes mellitus</i>	15	18
<i>Severe cardiac disease</i>	4	5
<i>Smoker</i>	32	39
<i>Alcohol usage</i>	8	10
 <i>Procedure type</i>		
<i>Splenopancreatectomy</i>	63	76
<i>Distal pancreatectomy (DP)</i>	20	24
 <i>Surgical approach</i>		
<i>Open/converted</i>	41	49
<i>Laparoscopic</i>	42	51
 <u><i>Diagnosis</i></u>		
<i>Primary adenocarcinoma</i>	47	57
<i>Other primary malignancy</i>	5	6
<i>Metastasis or recurrence of any malignancy disease</i>	4	5
<i>Benign tumor/disease</i>	21	25
<i>Chronic pancreatitis</i>	6	7

Corresponds to a number of patients in percentage. BMI: body mass index, ASA: American society of anesthesiology, WHO: world health organization.

**Table 2** Postoperative outcomes according to overall ERAS compliance of patients undergoing distal pancreatectomy

<b>Variables</b>	<b>Compliance ≥65% (n=53)</b>	<b>Compliance &lt;65% (n=30)</b>	<b>p-value</b>
<i>Primary LOS, median (IQR), nights</i>	9,8 (± 9,3)	14,8 (± 9,3)	0.020
<i>Readmission, n (%)</i>	10 (19)	9 (30)	0.266
<i>Total LOS, median (IQR), nights</i>	10,9 (± 9,5)	17,3 (± 10,8)	0.007
<i>Overall complications, n (%)</i>	28 (53)	26 (87)	0.002
<i>Major complications (Clavien III-IV), n (%)</i>	10 (19)	15 (50)	0.003
<i>Mortality, n(%)</i>	0	0	1
<i>CCI, mean (+/- SD)</i>	13.20 (±15.26)	27.70 (±18.62)	<0.001
<i>Pancreatic fistula (grade B-C), n (%)</i>	9 (17)	9 (30)	0.167
<i>Delayed gastric emptying, n(%)</i>	3 (6)	4 (13)	0.227
<i>Postpancreatectomy hemorrhage, n(%)</i>	2 (4)	2 (7)	0.554
<i>Respiratory complications, n (%)</i>	3 (6)	7 (23)	0.017

N: number of patients, LOS: Length of Stay, IQR: interquartile range, CCI: comprehension complication index, SD standard deviation.

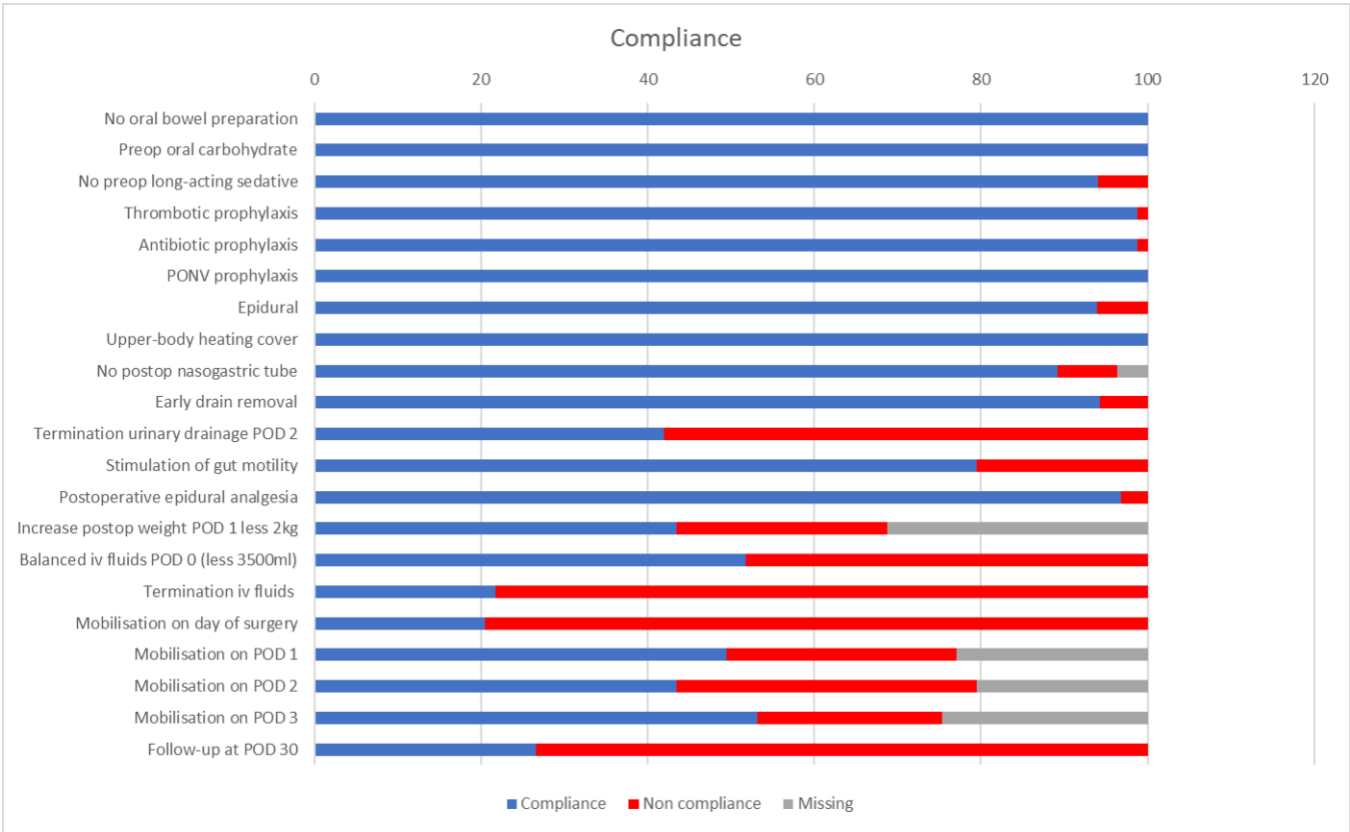
**Table 3** Multivariable analysis of predictors of overall postoperative complications

<b>Variables</b>	<b>Univariable</b>		<b>Multivariable</b>	
	HR (95% CI)	p-value	HR (95% CI)	p-value
<i>Age (years)</i>	0.97 (0.93-1.01)	0.104		
<i>Gender (female)</i>	0.87 (0.35-2.14)	0.756		
<i>ASA (III-IV)</i>	4.28 (0.89-20.49)	0.069	3.55 (0.7-18)	0.127
<i>BMI (kg/m<sup>2</sup>)</i>	1.05 (0.96-1.15)	0.265		
<i>Smoking (n)</i>	0.69 (0.32-1.48)	0.343		
<i>Associated splenectomy (n)</i>	1.10 (0.78-1.56)	0.587		
<i>Laparoscopy (n)</i>	1.47 (0.63-3.43)	0.369		
<i>Blood loss (ml)</i>	1.00 (1.00-1.00)	0.406		
<i>Compliance &gt;65%</i>	0.17 (0.05-0.56)	0.004	0.19 (0.06-0.62)	0.006

ASA: American Society of Anesthesiologist, BMI: Body mass index.



**Figure 1** Compliance to ERAS items



Compliance to each ERAS items for distal pancreatectomy, according to the ERAS guidelines for patients undergoing pancreateo-duodenectomy. Compliance is expressed in percentage, with compliant patients in blue and non-compliant patients in red. Percentage of missing data are represented in grey.  
 POD: postoperative days.

**Supplementary Table 1** Definitions of enhanced recovery after surgery (ERAS) elements used for compliance calculation.

<i>ERAS elements</i>	<i>Compliance definition</i>
Oral bowel preparation	No bowel preparation
Preoperative oral carbohydrate	Carbohydrate drink until 2 hours before surgery.
No preoperative long-acting sedative medication	No preoperative long-acting sedatives on day of surgery
Thrombotic prophylaxis	Preoperative low-molecular-weight heparin + sequential compression device
Antibiotic prophylaxis	Antibiotic prophylaxis before skin incision
PONV prophylaxis	PONV prophylaxis if two or more risk factors (female, non-smoker, previous PONV/motion sickness)
Epidural	Thoracic epidural only for open surgery
Upper-body heating cover	Use of upper-body forced-air heating cover intraoperatively
No postop nasogastric tube	Removal of nasogastric tube before end of surgery
Early abdominal drain removal	Early drain removal on POD3 if low risk
Termination urinary drainage POD 2	Transurethral catheter removal on POD 2
Stimulation of gut motility	Oral laxatives and/or chewing gum given postoperatively
Increase weight POD 1	Increase of weight of less than 2kg
Balanced IV fluids POD 0	Less than 3500ml IV fluid on day of surgery
Termination IV fluids	Termination of intravenous infusion less than 2 postoperative nights
Mobilisation on day of surgery	Any mobilisation (to walk, to sit on a chair or rising from bed)
Mobilisation on POD 1	Mobilisation in total for more than 4 hours
Follow-up on POD 30	Clinical follow-up at POD 30

PONV, postoperative nausea and vomiting; POD, postoperative day; IV, intravenous

**Supplementary Table 2** Patient's characteristics and operative details.

<b>Variables</b>	<b>N =83</b>
<b>Male gender (%)</b>	42 (51)
<b>Age, mean (SD), years</b>	61.8 (12)
<b>ASA score I-II (%)</b>	77 (93)
<b>BMI, mean (SD), kg/m<sup>2</sup></b>	26.6 (5)
<b>Preoperative WHO status performance (%)</b>	
0	31 (37)
1-3	52 (63)
<b>Recent immunosuppressive treatment (%)</b>	3 (4)
<b>Neoadjuvant chemotherapy (%)</b>	1 (1)
<b>Comorbidities (%)</b>	
Diabetes mellitus	15 (18)
Severe cardiac disease	4 (5)
Smoker	32 (39)
Alcohol usage	8 (10)
<b>Procedure type (%)</b>	
Distal pancreatectomy with splenectomy	63 (76)
Spleen preserving distal pancreatectomy	20 (24)
<b>Surgical approach (%)</b>	
Open/converted	41 (49)
Laparoscopic	42 (51)
<b>Diagnosis (%)</b>	
Primary adenocarcinoma	47 (57)
Other primary malignancy	5 (6)
Metastasis or recurrence of any malignancy disease	4 (5)
Benign tumour/disease	21 (25)
Chronic pancreatitis	6 (7)

BMI: body mass index, ASA: American society of anaesthesiology, WHO: world health organization.

**Supplementary Table 3** Multivariable analysis of predictors of overall postoperative complications after distal pancreatectomy

Variables	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	0.97 (0.93-1.01)	0.104		
Gender (female)	0.87 (0.35-2.14)	0.756		
ASA (III-IV)	4.28 (0.89-20.49)	0.069	3.55 (0.70-18.00)	0.127
BMI (kg/m <sup>2</sup> )	1.05 (0.96-1.15)	0.265		
Smoking	0.69 (0.32-1.48)	0.343		
En-bloc splenectomy	1.10 (0.78-1.56)	0.587		
Laparoscopy	1.47 (0.63-3.43)	0.369		
Blood loss (ml)	1.00 (1.00-1.00)	0.406		
Compliance >65%	0.17 (0.05-0.56)	0.004	0.19 (0.06-0.62)	0.006

HR: hazard ratio; CI: confidence interval; ASA: American Society of Anesthesiologist; BMI: body mass index.

**Table S4** Multivariable analysis of predictors of overall compliance and compliance to specific elements of enhanced recovery after distal pancreatectomy

Variables	Univariable			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
<b>Mobilisation on POD 1</b>						
Age (years)	0.992	0.948-1.038	0.732			
Gender (female)	0.792	0.285-2.202	0.654			
ASA (III-IV)	0.617	0.166-2.301	0.472			
BMI (kg/m <sup>2</sup> )	0.991	0.905-1.085	0.847			
Smoking	1.269	0.497-3.241	0.619			
Associated -						
splenectomy	1.107	0.757-1.618	0.600			
Laparoscopy	0.833	0.288-2.413	0.737			
Blood loss (mL)	0.999	0.997-1.000	0.164			
<b>Intravenous fluid less than 3500ml the first 24 hours</b>						
Age (years)	1.021	0.983-1.061	0,288			
Gender (female)	1.400	0.589-3.325	0,446			
ASA (III-IV)	1.900	0.609-5.932	0,269			
BMI (kg/m <sup>2</sup> )	0.979	0.902-1.063	0,614			
Smoking	1.012	0.484-2.115	0,975			
Associated -						
splenectomy	0.794	0.564-1.117	0,185			
Laparoscopy	1.510	0.679-3.358	0,312			
Blood loss (mL)	0.996	0.993-0.998	<0.001	0.996	0.993-0.998	<b>&lt;0.001</b>
<b>Urinary catheter removal on POD 2</b>						
Age (years)	0.988	0.951-1.026	0.521			
Gender (female)	1.043	0.432-2.522	0.925			
ASA (III-IV)	0.905	0.289-2.836	0.864			
BMI (kg/m <sup>2</sup> )	0.955	0.876-1.043	0.307			
Smoking	0.664	0.304-1.452	0.305			
Associated -						
splenectomy	0.577	0.393-0.849	0.005	0.644	0.409-1.015	0.058
Laparoscopy	4.700	1.742-12.677	0.002	3.640	1.197-11.068	<b>0.023</b>
Blood loss (mL)	0.996	0.994-0.998	0.001	0.996	0.994-0.999	<b>0.003</b>

HR: hazard ratio; CI: confidence interval; POD: postoperative day; ASA: American Society of Anesthesiologist; BMI: Body Mass Index.