



## Original Research

# Level of pancreatic division and postoperative pancreatic fistula after distal pancreatectomy: A retrospective case-control study of 157 patients with non-pancreatic ductal adenocarcinoma lesions

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## ABSTRACT

**Background:** Several studies have suggested that the level of pancreatic division during distal pancreatectomy (DP) has an impact on postoperative pancreatic fistula (POPF) occurrence. The purpose of this study was thus to investigate the level of pancreatic division as a potential risk factor for POPF after DP for non-pancreatic ductal adenocarcinoma lesions (non-PDAC) in the era of parenchyma-sparing resection.

**Methods:** Data from 217 patients requiring DP were collected in a prospectively maintained database from January 1997 to December 2017 and analyzed retrospectively. Only data from patients who underwent DP using a linear stapler for non-PDAC lesions were analyzed. The outcomes of DP with body/tail division (Body-Tail group) were compared to DP with neck division (Neck group). The primary outcome was POPF according to the 2016 ISGPF.

**Results:** Data from 157 patients who underwent DP using a linear stapler for non-PDAC lesions were included for analysis. Body-Tail (n = 53) and Neck (n = 104) groups were comparable concerning demographic data, period of treatment, BMI, ASA score, comorbidities, type of lesion, median lesion size, laparoscopic or open approach and spleen preservation rate. No differences were found in POPF (5.5 and 12.5%,  $p = 0.388$ ) and new-onset pancreatogenic diabetes mellitus (22.5 vs. 20%;  $p = 0.439$ ) in Body-Tail and Neck groups respectively.

**Conclusion:** Clinically relevant POPF and postoperative diabetes do not appear to be affected by pancreatic division level. The intention to prevent POPF or pancreatogenic diabetes should not influence the decision on level of pancreatic division during DP.

## 1. Introduction

Distal pancreatectomy is pancreatic resection at the left of the mesentericoportal axis and is used to treat both benign and malignant diseases of the body and tail of the pancreas. Postoperative pancreatic fistula (POPF) remains the leading cause of morbidity after distal pancreatectomy, frequency being between 13% and 64% [1–4]. The definition of POPF was updated by the International Study Group for Pancreatic Fistula (ISGPF) in 2016: 1. Biochemical leak (BL) applying to pancreatic fluid leakage without clinically relevant consequences (POPF grade A according to the former definition) is no longer defined as POPF [5]. 2. A drain in situ at discharge is only scored now as POPF

grade B when the surgical drain remains in place for more than 21 days after surgery. 3. Intensive care admission for POPF grade C criteria has changed to patient requirement of relaparotomy and/or admission to intensive care unit due to organ failure, and/or pancreatic fistula, leading to death.

The factors predisposing to POPF after distal pancreatectomy remain poorly recognized. The recent meta-analysis by Peng et al. including 20 studies, with a total of 2070 patients (ranging from 33 to 352 patients per study), indicates that soft pancreatic texture, higher BMI, blood transfusion, massive intraoperative blood loss and prolonged operative time were associated with increased POPF incidence [6]. Many groups have attempted different pancreatic stump closure

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and/or transection techniques, but unfortunately the data does not show a clear consensus regarding the optimal technique for gland closure.

In current practice, radical anterior modular pancreaticosplenectomy (RAMPS) remains the standard procedure for patients with distal pancreatic ductal adenocarcinoma (PDAC). Personalized parenchyma-sparing distal pancreatectomy should be favored when feasible for benign or borderline lesions in order to prevent new-onset pancreatogenic diabetes mellitus (5%–42% frequency after distal pancreatectomy) and exocrine insufficiency [7].

The uncertainty concerning the level of pancreatic division is highlighted in this former case in which the compromise between quality of resection, parenchyma-sparing and complication risk is a major concern. Several studies have suggested that the level of pancreatic division has an impact on POPF risk, especially for the cases of body or tail division [8,9]. To date, very little attention has been addressed to the possibility that the level of pancreatic division during distal pancreatectomy could be a risk factor for POPF occurrence.

Therefore, the aim of this study was to investigate if the level of division (Neck versus Body-Tail) during distal pancreatectomy influenced POPF occurrence in a homogeneous cohort of pancreatectomies for non-pancreatic ductal adenocarcinoma lesions (non-PDAC) in the era of parenchyma-sparing resection.

## 2. Patients and methods

### 2.1. Study design and population

From January 1998 to December 2017, data from all consecutive patients requiring distal pancreatectomy in our public tertiary hospital were prospectively collected and analyzed retrospectively. Since 1998, the laparoscopic approach has been routinely proposed for distal pancreatectomy, initially for selected patients with non-PDAC lesions, and then later also for PDAC. We aimed to generate an adequate sample of patients in which the level of pancreatic division was defined preoperatively by the surgeon according to the localization of the lesion. Therefore, patients with pancreatic ductal adenocarcinoma were excluded, and only patients with pancreatic division using a linear stapler were included in this case-control comparative study. Anatomic determination between neck and body/tail is illustrated in Fig. 1. Outcome of patients who underwent either distal pancreatectomy using a body-tail division without neck dissection (Body-Tail group) or neck dissection and division above the mesentericoportal axis (Neck group) were compared (Fig. 2). The decision on when to perform a distal pancreatectomy was taken by expert senior surgeons and was discussed in the context of a multidisciplinary institutional meeting.

Our primary outcome was POPF occurrence, defined and classified according to the 2016 ISGPF definition [5]. The secondary outcomes were 90-days postoperative outcomes and new-onset pancreatogenic diabetes mellitus (PDM) occurrence at 6 months after surgery.

The Institutional Review Board approved this study. Data has been reported in line with STROCSS criteria [10].

### 2.2. Surgical procedure

More than 60 pancreatic resections are performed each year on average in our department. All distal pancreatectomies were done by experienced pancreatic surgeons with significant experience in laparoscopic distal pancreatectomy, as previously described [11,12]. Spleen preservation was planned whenever possible. Splenic vessels were conserved as described by Kimura et al. [13]. Splenic conservation while sacrificing the splenic vessels (Warshaw technique [14]) was not performed in this patient cohort.

In the case of non-PDAC lesion, the level of pancreatic division was planned before the procedure and confirmed by intraoperative ultrasound for medial lesions. Regarding pancreatic sparing strategy, we

decided whenever possible not to dissect the neck of the pancreas and to begin the dissection by deporting on the left of the mesenteric root. In all patients, the pancreas was transected with an Endo-GIA™ stapler (Covidien, Medtronic), without staple line reinforcement. The distal transected pancreas was gently lifted and a medial-to-lateral dissection started. In the case of spleen preservation, the splenic vein and artery were skeletonized toward the hilum of the spleen. This allowed both a lymphadenectomy and a step-by-step division of all the branches coming from the splenic vessels. For distal pancreatectomy with splenectomy, first the splenic artery, and then the vein, were divided after pancreatic transection. This was followed by a medial-to-lateral en bloc dissection posterior to the splenic vein along the retroperitoneal plane. A closed non-aspirating drain was placed at the end of the procedure.

### 2.3. Outcome and data source

Demographic, clinical and surgical data (including neck dissection/no neck dissection), were collected using a standardized case report form for pancreatic surgery and analyzed retrospectively. Main pancreatic duct diameter at the level of transection was measured on preoperative imaging and pancreatic texture was defined by the surgeon during the specimen examination. Operation duration was defined as the time between incision and closure. After surgery, a physician examined all patients daily until hospital discharge. Thoraco-abdomino-pelvic computed tomography (CT scan) with intravenous contrast injection was performed selectively in patients with suspected abdominal or thoracic complications.

POPF was defined and classified according to the 2016 update of ISGPF [5]. Drain amylase values were systematically measured at postoperative day 3, and the drain was removed for cases of negative values. All patients with amylase-rich drain fluid after postoperative day 3 received octreotide (standardized post-distal pancreatectomy pathway) regardless of POPF severity. Only clinically relevant grade B/C leak was considered as POPF. A fluid collection was identified through CT scan or ultrasound (fluid presence > 5 cm in diameter) with or without clinical relevance. Early postoperative hemorrhage was defined according to the ISGPS [15].

Patients were followed at 1 month, and then every 3 months, with systematic clinical and blood examinations (standardized post-distal pancreatectomy pathway, including assessment of fasting plasma glucose and hemoglobin A1c (HbA1c) levels). Postoperative complications were stratified according to Clavien-Dindo (CD) classification, defining major complications by a score of III or above [16]. Complications, readmissions and operative mortality were considered as those occurring within 90 days of surgery [17].

New-onset PDM was defined according to diagnosis and classification by the American Diabetes Association [18]: (a) fasting plasma glucose level of 126 mg/dL or greater, (b) hemoglobin A1c (HbA1c) of 6.5% or higher at 6 months after surgery for patients without history of diabetes or use of antidiabetic drugs [7,19].

### 2.4. Statistical analysis

Baseline characteristics followed by clinical outcomes were analyzed using standard univariate analysis. The median with range is reported for continuous variables, whereas absolute/relative frequencies are reported for categorical variables. Continuous variables were compared using non-parametric tests (Mann-Whitney U). Categorical data were compared with Chi-square tests or Fisher's exact tests depending on size. A P value < 0.05 was considered as statistically significant. Statistical analyses were performed using SPSS Statistics (Version 20.0) for Macintosh (IBM Corp, Armonk, NY) and SAS software (SAS Institute, Cary, North Carolina).

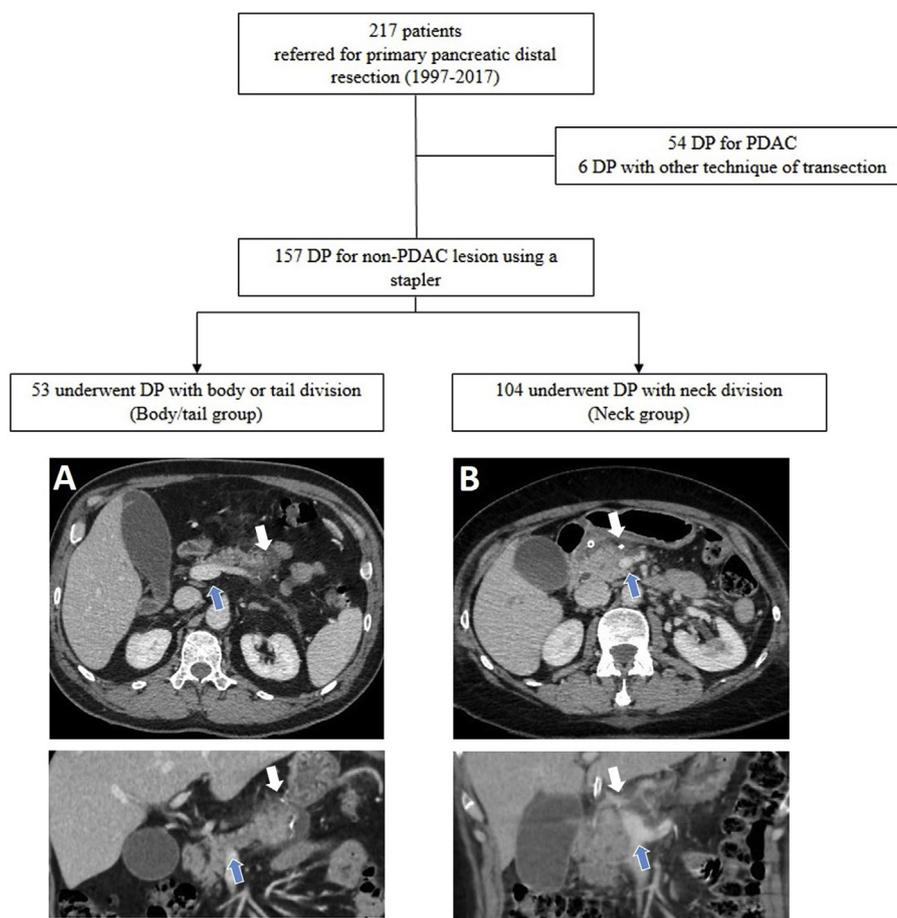


Fig. 1. Anatomic determination between neck and body/tail for pancreatic level of division. PV, portal vein; SMV, superior mesenteric vein; CT, celiac trunk; SMA, Superior mesenteric artery.

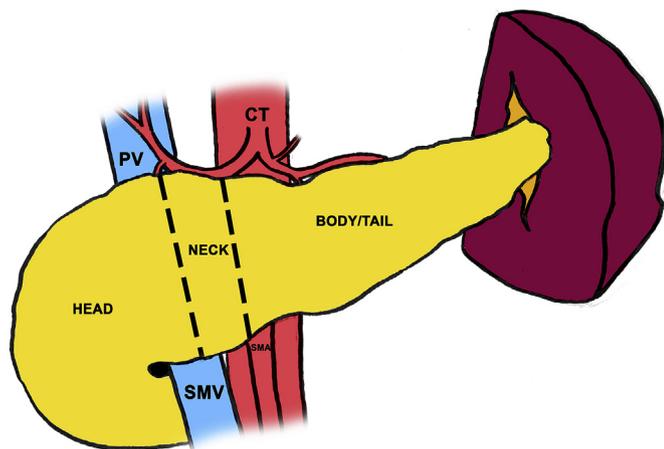


Fig. 2. Study schema illustrated by postoperative CT scan at 7th postoperative day of 2 patients who underwent (A) DP with tail division (Body/tail group) and (B) DP with neck division above the mesentericoportal axis (Neck group). Blue arrow: mesentericoportal vein axis; white arrow: level of pancreatic division. DP: distal pancreatectomy; PDAC: pancreatic ductal adenocarcinoma. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

### 3. Results

#### 3.1. Patients and surgical data

Out of the 983 pancreatectomies performed in our center, 217

patients required a distal pancreatectomy. According to inclusion/exclusion criteria (PDAC (n = 54), technique of division other than stapler (n = 6)), we analyzed data from 157 patients who underwent distal pancreatectomy for non-PDAC lesions (F: 91/M: 66). In particular, 53 patients underwent distal pancreatectomy with body-tail division (Body-Tail group), and 104 with neck division (Neck group). Body-Tail and Neck groups were comparable concerning demographic data, period of treatment, BMI, ASA score, comorbidities, type of lesion, median lesion size, pancreatic characteristics, laparoscopic or open approach and spleen conservation indications. Table 1 summarizes the clinicopathologic characteristics of the two groups.

The median length of surgery was similar for both different strategies: 180 min for Body-Tail group and 196 min for Neck group ( $p = 0.625$ ). No difference was found concerning operative time regarding spleen conservation between Body-Tail and Neck groups. The surgical approach did not differ in the two groups with similar rates of laparoscopy (43 vs. 51%, *ref*), robot assisted laparoscopy (8 vs. 7%,  $p = 0.189$ ) and laparotomy (49 vs. 42%,  $p = 0.388$ ). Conversion rates to open procedure were similar in both groups (4 vs. 3%,  $p = 1.000$ ). Spleen preservation was planned and feasible in 29/29 patients and 51/51 patients in Body-Tail and Neck groups respectively ( $p = 0.501$ ). Median intraoperative blood loss was 95 ml (50–480 ml) in Body-Tail group and 110 ml (50–2700 ml) in Neck group ( $p = 0.334$ ). Intraoperative transfusion was not necessary in Body-Tail group, contrary to the Neck group (0 vs. 7%;  $p = 0.096$ ). Surgical data are detailed in Table 2.

**Table 1**  
Clinicopathologic characteristics of patients.

	Body-Tail division, n (%)	Neck division, n (%)	p value
Patients	53	104	
Gender			
Female	23 (43.3)	68 (65.4)	–
Male	30 (56.7)	36 (34.6)	0.283
Period			
1997–2007	19 (35.8)	33 (31.7)	–
2008–2017	34 (64.2)	71 (68.2)	0.604
Age, years	median (range)	60 (21–87)	0.125
BMI, kg/m <sup>2</sup>	24 (4)	25 (4)	0.317
ASA score			
Grade I	21 (39.6)	33 (31.7)	–
Grade II	29 (54.7)	64 (61.5)	0.638
Grade III	2 (3.7)	6 (5.8)	0.698
Grade IV	1 (2)	1 (1)	0.415
Comorbidities			
DM	2 (3.8)	7 (6.7)	0.719
Chronic obstructive pulmonary disease	2 (3.8)	8 (7.7)	0.496
Cardiovascular disease	5 (9.4)	9 (8.7)	0.941
Renal insufficiency	2 (3.8)	4 (3.8)	1.000
Previous upper abdominal surgery	15 (28.6)	19 (18)	0.291
Main pancreatic duct (mm)			
< 3	28 (52)	58 (55.8)	–
≥ 3	25 (48)	46 (44.2)	0.726
Pancreatic texture			
soft	41 (77.4)	76 (73)	–
hard	12 (22.6)	28 (27)	0.698
Tumor size on histopathology (mm), median (range)	25 (11–102)	28 (12–290)	0.401
Final histology			
Endocrine tumor	19 (35.8)	36 (33.5)	0.878
Non-malignant IPMN	5 (9.5)	12 (11)	0.688
Metastasis	6 (11)	6 (5.5)	0.215
Mucinous cystic neoplasm	5 (9.5)	13 (19)	0.568
Serous cystic neoplasm	3 (5.6)	12 (11)	0.389
Others	15 (28.6)	21 (20)	0.830

BMI: body mass index; DM: diabetes mellitus; IPMN:intraductal papillary mucinous neoplasia.

**Table 2**  
Operative features.

	Body-Tail division n (%)	Neck division n (%)	p value
Surgical approach			
laparoscopy	23(43)	53 (51)	ref
robot-assisted laparoscopy	4 (8)	7 (7)	0.732
laparotomy	26(49)	44 (42)	0.387
Duration of surgery (min), median (range)	180 (97–382)	196 (110–315)	0.625
Spleen preservation	29 (54)	51 (49)	0.501
Intraoperative blood loss (ml), median (range)	95 (50–480)	110 (50–2700)	0.334
Intraoperative transfusion	0 (0)	7 (6.7)	0.096

### 3.2. Comparison of postoperative outcome

Median follow-up of patients was 49 months (range 3–216). **Table 3** details postoperative results for both groups. A clinically relevant POPF was diagnosed in 5.5 and 12.5% ( $p = 0.388$ ) in Body-Tail and Neck groups respectively.

Median postoperative hospital stay was similar in both groups (9 vs. 10 days,  $p = 0.741$ ). A complicated postoperative course occurred in 17% of Body-Tail group and in 30% of Neck group ( $p = 0.505$ ). The rate of complication grade  $\geq$  III was significantly lower in Body-Tail group than in Neck group (0 vs. 10.5%;  $p = 0.016$ ). Complication

**Table 3**  
Postoperative results.

	Body-Tail division n (%)	Neck division n (%)	p value
<b>Primary outcome</b>			
No biochemical leak or POPF	37 (70)	75 (72)	ref
Biochemical leaks	13 (24.5)	16 (15.5)	0.189
POPF (grade B/C) <sup>a</sup>	3 (5.5)	13 (12.5)	0.388
grade B	3 (5.5)	11 (10.5)	
grade C	0 (0)	2 (1.9)	
<b>Secondary outcomes</b>			
New onset diabetes mellitus	12 (22.5)	21 (20)	0.439
<b>Other outcome</b>			
Fluid collection	6 (11)	25 (24)	0.165
Postoperative hemorrhage	1 (0)	2 (1.9)	0.549
Postoperative transfusion	0 (0)	5 (4.8)	0.322
Splenic infarction	0 (0)	0 (0)	1.000
Respiratory complications	3 (5.5)	8 (7.5)	1.000
Postoperative confusion	1 (1.8)	6 (5.8)	0.676
Reoperation	0 (0)	3 (3)	0.551
90-days readmission	3 (5.5)	11 (10.5)	0.387
90-days postoperative complications	9 (17)	31 (30)	0.083
Major complications (Clavien-Dindo $\geq$ 3)	0 (0)	11 (10.5)	0.016
90-days postoperative mortality	0 (0)	2 (1.9)	0.549
Duration of hospitalization (days), median (range)	9 (5–29)	10 (5–90)	0.741

<sup>a</sup> According to the 2016 ISGPF classification.

grade  $\geq$  III ( $n = 11/104$ ) in Neck group was related to (i) POPF grade B (6 percutaneous drainage, of which 2 required general anesthesia), (ii) POPF grade C (reoperations with intensive care unit transfer ( $n = 2$ )) and (iii) other causes (colic fistula requiring a colostomy ( $n = 1$ ) and death ( $n = 2$ ) related to an acute ischemic stroke and a pulmonary embolism without arguments of underlying POPF).

There were no significant differences in peripancreatic fluid collection rates, postoperative transfusion rates, splenic infarction rates, pulmonary complication rates, reoperation rates and readmission rates between the Body-Tail and Neck groups. There was no significant difference in new-onset PDM 6 months after surgery between the two groups (22.5 vs. 20%;  $p = 0.439$ ).

## 4. Discussion

Several studies have suggested that the body/tail level for pancreatic division has an impact on POPF occurrence that remains a major concern for pancreatic surgeons. In the era of minimally invasive and parenchyma-sparing pancreatectomy for patients with non-PDAC lesions, the purpose of this study was to investigate the impact of pancreatic division level on POPF after distal pancreatectomy. To our knowledge, this is the first study focusing on pancreatic division level in a homogeneous cohort of 157 consecutive distal pancreatectomies for non-PDAC lesions using a linear stapler. Overall, we did not find a higher risk of POPF with division at the body-tail level compared to the neck level. Despite similar POPF rates, we found different patterns of POPF between the two groups. The rate of major complications after pancreatic division at the neck was significantly higher. In parallel, our present study confronts previous results published on postoperative diabetes occurrence, finding no difference in new-onset PDM rates between Body-Tail division and Neck division groups.

Our results highlight that distal pancreatectomy is a major surgical procedure, associated with an overall postoperative morbidity rate of 1.9% and a clinically relevant pancreatic fistula rate of 10%. Major complications defined according to the Clavien-Dindo (CD) classification  $\geq$  III accounted for 7% of cases. Given that all the procedures were performed for benign or borderline neoplasms, a soft pancreatic texture and a systematic drainage close to the pancreatic stump could have critically contributed to POPF rate. In terms of major

complications and clinically relevant POPF, our results are comparable with previous studies reporting a major complication rate of 11%, and a clinically relevant POPF rate of 10% [20]. In the present study, the rate of major complications after neck division was significantly higher, but CD complication  $\geq$  III was not systematically related to POPF. However these results could suggest that pancreatic fistula, when it occurs, tends to be more severe at this division level in close contact with the mesentericoportal and coeliac axis vascular sutures and collaterals. A peripancreatic fluid collection at this level could be more complex to drain using a conservative approach.

Pannegeon et al. found that division of the pancreas at the body rather than the neck level was a risk factor for POPF [8]. Hashimoto et al. suggested that a larger residual gland might generate a greater intraductal pressure, and this increased pressure could overcome the duct/gland ligation [16].

Sell et al. were the first team to explore a potential correlation between the level of pancreatic division and the development of pancreatic fistula. They compared distal pancreatectomy with neck versus body-tail division, however without any focus on new-onset post-operative diabetes [9]. This study concluded that POPF occurs more often when the body-tail is transected, although the majority were biochemical leaks and of minimal clinical significance. Grade B/C pancreatic fistula occurred at equivalent rates regardless of transection site. Nevertheless, 2 major confounding factors were present; inclusion of pancreatic ductal adenocarcinoma and no uniform technique for gland transection over the study period. Obviously, they did not defend that all distal pancreatectomies had to be performed with neck division over the superior mesenteric vein axis given that the majority of pancreatic fistula developed were biochemical leaks and did not change clinical management or outcomes. The authors suggested that transection site should be considered as a variable in future studies of POPF. In addition, and in line with our findings, Malleo et al. reported that specimen length was not related to POPF [21].

Surprisingly, our analysis from a non-PDAC cohort of patients did not find any difference in new-onset PDM rates between Body/Tail and Neck groups. The overall new-onset PDM rate at 6 months was 21%. It is likely that the rate of new-onset PDM after pancreatic resection is frequently underestimated as retrospective reviews have reported variable PDM rates of between 5% and 42% after distal pancreatectomy [7]. On the other hand, rates may be inflated in studies that rarely consider the incidence of preexisting diabetes before pancreatectomy, with all procedures and neoplasms confounded [19,22]. In studies dedicated to distal pancreatectomy, a resection of more than 25–44% of the pancreatic volume in non-diabetic patients was shown to be an independent risk factor for new-onset PDM 3 months after distal pancreatectomy [23,24].

Despite the interesting outcomes of this present study, and the fact that the findings were obtained from a homogeneous cohort of consecutive patients, reflecting real life in a minimally invasive pancreatic surgery team, there are several study limitations. Firstly, its design was retrospective. Secondly, the relatively limited sample size and thus potential inherent risk of type II errors should be considered. Sample size calculation was difficult due to the lack of data available on the impact of pancreatic division level on POPF rate. Nevertheless, this present study remains useful in the design of further prospective studies.

In conclusion, this study suggests that POPF and new-onset pancreatogenic diabetes mellitus occur at equivalent rates regardless of the level of pancreatic division during distal pancreatectomy in homogeneous patient cohorts. The intention to prevent POPF or diabetes should not influence the surgeon's decision on pancreatic transection site. We recommend a personalized distal pancreatectomy for patients with non-PDAC lesions, mixing laparoscopic approach [25,26], spleen conservation [4,27–29] and pancreatic parenchyma-sparing with body/tail division when feasible. Further comprehensive studies are needed to explore the potential correlations between the level of pancreatic

transection, volume of remnant/resected pancreas, pancreatic blood supply and risks of POPF/new-onset PDM.

### Ethical approval

For retrospective studies in France, no Ethical Approval is systematically required. In the department, all patients signed a nonopposition form for the use of their specimen/clinical data. The database was anonymized.

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### Author contribution

All authors declare that has participated sufficiently in the work to take public responsibility for appropriate portions of the content, as defined in to the guidelines of the International Committee of Medical Journal Editors (ICMJE).

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### Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

### Research registration number

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### Guarantor

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### Provenance and peer review

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijso.2019.03.020>.

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