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Somatostatin analogues for the prevention of pancreatic fistula after open pancreatoduodenectomy: A nationwide analysis

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ABSTRACT

Background: Somatostatin analogues (SA) are currently used to prevent postoperative pancreatic fistula (POPF) development. However, its use is controversial. This study investigated the effect of different SA protocols on the incidence of POPF after pancreatoduodenectomy in a nationwide population.
Methods: All patients undergoing elective open pancreatoduodenectomy were included from the Dutch Pancreatic Cancer Audit (2014–2017). Patients were divided into six groups: no SA, octreotide, lanreotide, pasireotide, octreotide only in high-risk (HR) patients and lanreotide only in HR patients. Primary endpoint was POPF grade B/C. The updated alternative Fistula Risk Score was used to compare POPF rates across various risk scenarios.
Results: 1992 patients were included. Overall POPF rate was 13.1%. Lanreotide (10.0%), octreotide-HR (9.4%) and no protocol (12.7%) POPF rates were lower compared to the other protocols (varying from 15.1 to 19.1%, $p = 0.001$) in crude analysis. Sub-analysis in patients with HR of POPF showed a significantly lower rate of POPF when treated with lanreotide (10.0%) compared to no protocol, octreotide and pasireotide protocol (21.6–26.9%, $p = 0.006$). Octreotide-HR and lanreotide-HR protocol POPF rates were comparable to lanreotide protocol, however not significantly different from the other protocols. Multivariable regression analysis demonstrated lanreotide protocol to be positively associated with a low odds-ratio (OR) for POPF (OR 0.387, 95% CI 0.180–0.834, $p = 0.015$). In-hospital mortality rates were not affected.

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Conclusion: Use of lanreotide in all patients undergoing pancreatoduodenectomy has a potential protective effect on POPF development. Protocols for HR patients only might be favorable too. However, future studies are warranted to confirm these findings.

1. Introduction

The most common major complication after pancreatoduodenectomy is leakage of the pancreato-enteric anastomosis which can result in postoperative pancreatic fistula (POPF) development, delayed gastric emptying, postpancreatectomy hemorrhage, and death [1]. Although mortality after pancreatoduodenectomy has decreased to approximately 2% in high-volume centers, the morbidity after these procedures still remains between 30 and 50% mainly due to POPF, of which the incidence varies between 10 and 30% [2–5]. Well-known risk factors of POPF are soft texture of the pancreas without pre-existing fibrosis, small pancreatic duct size, tension on the anastomosis, poor anastomotic perfusion and surgeon's experience with the procedure [6].

Somatostatin is a naturally occurring hormone which has the effect of reducing enteric including pancreatic secretion [7,8]. Among other effects, somatostatin receptor blockers share the ability to inhibit the secretion of pancreatic polypeptides, thus potentially mitigating the detrimental effects of pancreatic fluid leakage in the event of POPF [9]. Somatostatin analogues (SA) are variably used perioperatively for the prevention of POPF and its potentially detrimental effects. However, the benefit of SA for the prevention of POPF has been debated widely [10–16]. In the Netherlands, there is a wide variation of SA use perioperatively as no consensus has been reached yet. The aim of this study was to evaluate the efficacy of the different SA protocols in the Netherlands in preventing POPF, by using nationwide data of the mandatory Dutch Pancreatic Cancer Audit (DPCA).

2. Methods

2.1. Patients

All consecutive patients who underwent a pancreatoduodenectomy for all indications in the Netherlands as registered in the Dutch Pancreatic Cancer Audit (DPCA) from January 2014 until December 2017 were analyzed [17]. Participation in the DPCA is mandatory for all pancreatic surgery centers in the Netherlands, each performing a minimum of 20 pancreatoduodenectomies annually. This specific time frame was chosen to reduce bias as pancreatoduodenectomies were mainly performed by open surgery. After 2017 laparoscopic and robotic surgery was performed more frequently. Data including patient characteristics, tumor characteristics, treatment characteristics, length of hospital stay, postoperative complications and mortality were retrieved. Patients who underwent laparoscopic or robotic pancreatoduodenectomy were excluded.

2.2. SA protocols

The different types of SA used in the Netherlands in the study period are octreotide (Sandostatin, Novartis Pharmaceuticals, Basel, Switzerland), lanreotide (Ipsen, Paris, France) and pasireotide (SOM230, Novartis Pharmaceuticals, Basel, Switzerland). Patients were divided into six groups according to the local protocol for SA use of the hospital at time of surgery and included administration for all patients or only high-risk (HR) patients: no protocol (all patients), octreotide (all patients), lanreotide (all patients), pasireotide (all patients), octreotide-HR (HR patients only) and lanreotide-HR (HR patients only). The different protocols are displayed in Table 1.

2.3. Outcome measures and definitions

Primary outcome was a clinically relevant POPF, i.e. grade B or C, defined according to the International Study Group on Pancreatic Surgery 2005 and 2016 definitions (2016 was only available for patients operated in 2017) [1,18]. Secondary outcome was other postoperative morbidity and was divided into surgical complications (post-pancreatectomy hemorrhage (ISGPS grade B/C) [19], delayed gastric emptying (ISGPS grade B/C) [20], wound infection, medical complications (pulmonary, cardiac) and re-interventions (endoscopic, radiological or surgical). In addition, length of hospital stay, in-hospital mortality and re-admission within 30-days were analyzed.

2.4. Updated alternative fistula risk score

The updated-alternative Fistula Risk Score (ua-FRS) is an externally validated online tool to predict POPF after both minimal invasive and open pancreatoduodenectomy [21]. It uses body mass index (BMI), male sex, pancreatic duct size and pancreatic texture. The ua-FRS was used to assess the effect of the different protocols across various risk scenarios. Patients were divided into two groups according to the calculated ua-FRS for the risk of ISGPS grade B/C POPF: low-intermediate risk (<20%) and high risk (≥20%).

2.5. Statistical analysis

Baseline characteristics and outcomes were assessed using descriptive statistics. Symmetric continuous variables were reported as mean with standard deviation (SD) and skewed continuous variables as median with interquartile range (IQR). Differences between groups were analyzed with the Pearson Chi-square test or Fisher's exact test, when appropriate, in case of dichotomous data. The ANOVA test was used to compare continuous variables between groups. Patient and tumor characteristics were assessed with univariable analysis as potential risk factors for POPF, as well as known risk factors from literature. Variables tested were male sex, BMI >25 kg/m^2, a pancreatic duct smaller than 3 mm, ASA score III/IV, intraoperative drain placement, hospital volume (<40 and >40 pancreatic resections annually, based on the median annual volume in Dutch centers), type of pancreato-jejunal anastomosis and pathology (neuroendocrine tumor). Intraoperative blood loss could not be analyzed as this was not registered in the national database and impossible to collect retrospectively due to the anonymous aspect of the registry. Variables with $p \leq 0.10$ were subsequently selected for multivariable logistic regression analysis and reported as odds ratio (OR) with corresponding 95% confidence interval (CI). A subgroup analysis was performed for ua-FRS groups. All p-values were based on a two-sided test. A p-value ≤ 0.05 was considered statistically significant. Statistical analyses were performed in SPSS statistics version 26.

3. Results

3.1. Study population

In total, all 1992 consecutive patients who underwent elective, open pancreatoduodenectomy between 2014 and 2017 at all 16 Dutch centers for pancreatic surgery were included. Patient, tumor, and treatment characteristics are detailed in Table 2. Overall, 236 patients were treated according to a no SA-protocol (two hospitals), 303 patients according to an octreotide protocol (three hospitals), 750 patients according to a lanreotide protocol (seven hospitals), 199 patients according to a pasireotide protocol (one hospital), 160 patients according to an octreotide-HR protocol (one hospital) and 344 patients according to a lanreotide-HR protocol (two hospitals). Fig. 1 displays the patient and hospital distribution amongst the different SA protocols. Age, BMI, intraoperative drain placement and adenocarcinoma pathology were comparable between these six groups. Significant differences between the groups were observed for male sex, ASA grade III/IV, diameter of the pancreatic duct, soft pancreatic tissue, type of procedure c.q. Whipple or pylorus preserving pancreatoduodenectomy (PPPD), neuroendocrine tumor and high ua-FRS.

3.2. Pancreatic fistula

Postoperative outcomes are detailed in Table 3. The incidence of POPF was significantly different between the groups: POPF occurred less often in patients treated according to lanreotide protocol ($n = 75$, 10.0%) and octreotide-HR ($n = 15$, 9.4%) and no SA protocol ($n = 30$, 12.7%), compared to a higher incidence in hospitals with lanreotide-HR ($n = 52$, 15.1%), octreotide ($n = 54$, 17.8%) and pasireotide protocol ($n = 35$, 19.1%). The rate of grade C POPF did not differ significantly ($p = 0.358$) between hospitals with octreotide-HR protocol ($n = 4$, 2.5%), lanreotide-HR protocol ($n = 23$, 2.9%), no protocol ($n = 7$, 3.0%), lanreotide ($n = 23$, 3.1%), octreotide ($n = 12$, 4.0%), and pasireotide protocol ($n = 12$, 6.0%).

3.3. Other complications

Post-pancreatectomy hemorrhage (42.7% vs 16.2–34%, $p < 0.0001$), wound infection (23.4% vs 2.9–8.3%, $p < 0.000$) and re-intervention rate (39.9% vs 20.1–30.7%, $p < 0.001$) was significantly higher in patients treated according to a pasireotide protocol. The various complication rates between the octreotide-HR and the lanreotide-HR group were comparable, except for the endoscopic re-intervention rate (1.3% vs 6.7%, $p = 0.020$) and post-pancreatectomy hemorrhage rate (16.2% vs 31.1%, $p = 0.001$), which were significantly lower in the octreotide-HR group. There were no significant differences in pneumonia, length of hospital stay, re-admission within 30-days and in in-hospital mortality between the groups.

3.4. Multivariable regression

Factors associated with POPF in univariable analysis were: type of SA protocol, male sex, BMI, soft pancreatic tissue, pancreatic duct size <3 mm, neuroendocrine tumor pathology, ASA III/IV score and hospital volume. Multivariable analysis, correcting for these factors, showed lanreotide protocol to be associated with a low OR for POPF development (OR 0.387; 95% CI 0.180–0.834, $p = 0.015$) compared to other protocols (Table 4). For hospitals using octreotide-HR or lanreotide-HR, a low OR was observed, however not statistically significant (OR 0.666; 95% CI 0.280–1.58, $p = 0.356$ and OR 0.887; 95%CI 0.369–2.082, $p = 0.766$ respectively). For octreotide and pasireotide this effect was also not observed (OR 1.742; 95%CI 0.770–3.940, $p = 0.132$ and OR 1.267; 95%CI 0.578–2.780, $p = 0.555$ respectively).

3.5. Sub-analysis according to ua-FRS

Sub-analysis of the effect of the different SA protocols for patients with low-intermediate or high ua-FRS is summarized in Table 5. Data on ua-FRS were available in 1017 patients. In patients with low-intermediate risk, POPF rates were comparable between the six groups ($p = 0.298$). In patients with high POPF risk, the POPF rate was significantly lower in patients treated according to lanreotide protocol compared to no protocol, octreotide and pasireotide protocols (21.6%, 26.9%, 26.9%, respectively, $p = 0.005$). Octreotide-HR and lanreotide-HR protocol (16.7% and 19.4% respectively) were non-inferior to lanreotide protocol, however did not significantly differ from the none, octreotide and pasireotide protocols.

4. Discussion

This nationwide analysis suggests that administration of lanreotide in all patients undergoing open pancreatoduodenectomy is associated with a reduced rate of POPF (OR 0.387; 95% CI 0.180–0.834, $p = 0.015$) compared to other protocols. Furthermore, sub-analysis in patients with a high-risk of POPF according to the ua-FRS, lanreotide protocol significantly had the lowest POPF rate. Use of octreotide-HR and lanreotide-HR protocol was comparable to the lanreotide protocol, however not significantly different from the other protocols. SA use did not significantly affect mortality.

Available meta-analyses show conflicting results on the beneficial effects of SA for the prevention of POPF. A recent meta-analysis of 15 studies involving 2221 patients, showed that SA prophylaxis reduced the incidence of POPF after all types of pancreatic resections. There was no evidence of reduced mortality [16]. Another recent meta-analysis, including 12 randomized studies involving 1615 patients after pancreatoduodenectomy, concluded that SA did not significantly reduce the incidence of POPF (OR 0.48 [95% CI, 0.22–1.06, $p = 0.07$) [2]. The conflicting results of previous studies have led to many different protocols for SA use, shown both by this study as well as previous studies. In a questionnaire among German pancreatic surgeons, just under two third of the respondents had a protocol for SA use, with great variation between centers for type of SA and protocol [10]. In the current study, some participating centers administered octreotide or lanreotide when an anastomosis was clinically assessed as having a high risk of leakage (octreotide-HR and lanreotide-HR groups) based on the diameter of the PD and/or the texture of the pancreas. Although these factors were identified as two important risk factors by multivariable analysis, the distribution of patients in the octreotide-HR and lanreotide-HR groups over the risk-group stratification by the ua-FRS was not significantly different between the other groups. This suggests that clinical determination of high-risk patients is currently not performed using a tool like the ua-FRS (available via www.pancreascalculator.com).

Several randomized trials have studied the role of SA for the prevention of POPF with conflicting results [22–27]. However, as the occurrence of POPF is multifactorial and perioperative management varies widely between centers, the external validity of these RCT results is hampered. It is believed that the results of this study, based on the data from a nationwide, mandatory prospective audit, overcomes several of these limitations, due to its nationwide character, the analogy of the reported outcome and its high number of participating centers and total inclusions.

A possible reason for the efficacy of lanreotide in this study lays in the pharmacodynamic- and binding profile of lanreotide, as it differs from that of pasireotide and octreotide. Primary somatostatin-receptor subtypes (SSRS) in the pancreas are SSRS 1,

2, 3 and 5. The half-life of octreotide is less than 2 h. It binds primarily to SSRS 2 and 5 [28–31]. Pasireotide has a half-life of 11 h approximately and binds to SSRS 1,2,3 and 5 with a higher affinity than octreotide [32–34]. Lanreotide primarily binds with high affinity to SSRS 2 and 5 and is available in long-acting preparation which lasts between 10 and 14 days after a single injection [35,36]. Since this leads to a more consistent and longer bioavailability during both the postoperative phase before and after the occurrence of POPF compared to the other SA's, it is possible that lanreotide is more effective at reducing pancreatic exocrine secretions and thus at preventing pancreatic leak.

The number needed to treat to prevent one POPF in high-risk patients treated with lanreotide is 10, according to this study. In the Netherlands, the average costs of one lanreotide injection are €1666. Thus, the cumulative costs to prevent one POPF in HR patients treated with lanreotide are €16.666 (i.e. 10 patients injected once with lanreotide). The median total hospital costs for a single patient with POPF are €53.760, more than three times the total hospital costs of a patient without complications and the costs to prevent one fistula [37]. Therefore, it can be concluded that it could be cost-effective to use lanreotide to prevent POPF.

This study fails to support the prophylactic role of octreotide and pasireotide use in all patients in reducing the development of POPF. However, the results of this study should be viewed in the light of several limitations. First, the dosing regimens clearly varied between centers. Different durations of administration (five days before surgery; until discharge – 7 days postoperatively) were used. Second, in the DPCA it is not registered if patients actually received the drug, therefore only a per protocol analysis could be performed, limiting conclusions on the true effect of the drug. Due to the anonymous aspect of the national registry, this data could not be collected retrospectively. Third, several data required to determine the ua-FRS were missing and in the low-intermediate group, incidence of POPF was very low. If these data would have been available or if the incidence or sample size would have been higher, the role of prophylactic SA in patients who are considered low-intermediate or high risk according to ua-FRS could have been assessed more precisely. However, sub-analysis still involved 1017 patients, which is still considered an appropriate sample size.

Despite these limitations, the accumulated evidence through this present, nationwide cohort study suggests that use of lanreotide in all patients undergoing pancreatoduodenectomy might have a potential protective effect on POPF development, however, in-hospital mortality was not affected. Protocols for HR patients only might be favorable too. These findings should be confirmed in future trials where the limitations of this study can be taken into account and be improved.

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Appendix

Table 1
The six SA protocols that are used in the Netherlands

Type of protocol	Explanation
None	All patients undergoing pancreatoduodenectomy: - No SA administered
Octreotide	All patients undergoing pancreatoduodenectomy: - 100 μg Sandostatin® subcutaneous injection three times a day for seven days, starting the day before surgery
Lanreotide	All patients undergoing pancreatoduodenectomy: - 120 mg Somatuline® subcutaneous injection at home a few days before surgery
Pasireotide	All patients undergoing pancreatoduodenectomy: - 900ug of subcutaneous pasireotide twice daily beginning preoperatively on the morning of the operation and continuing for 7 days (14 doses).
Octreotide-HR	Only administered in patients undergoing pancreatoduodenectomy deemed as being high-risk* - 100 μg Sandostatin® subcutaneous injection three times a day for five-seven days, starting the day before surgery or on the first postoperative day
Lanreotide-HR	Only administered in patients undergoing pancreatoduodenectomy deemed as being high-risk*: - 120 mg Somatuline® subcutaneous injection at home a few days before surgery or on the first postoperative day.

HR = high-risk; * = pancreatic duct <3 mm on computed tomography scan and/or soft pancreatic tissue intraoperatively.

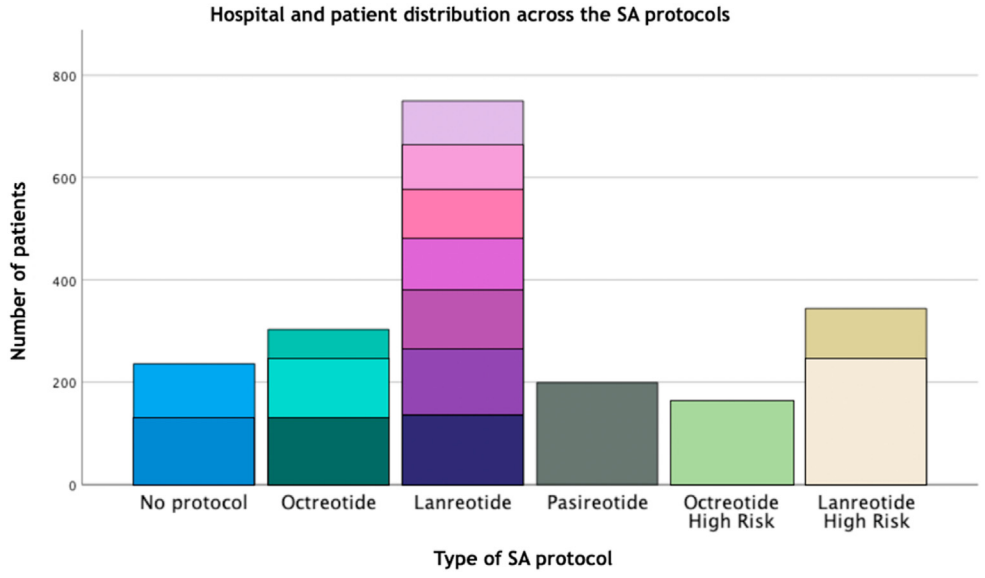

Fig. 1. Hospital and patient distribution amongst the different SA protocol groups. Each color represents a different hospital.

Table 2
Patient and treatment-related characteristics

No. (%)	None	Octreotide	Lanreotide	Pasireotide	Octreotide-HR	Lanreotide-HR	*p-value*
	($n = 236$)	($n = 303$)	($n = 750$)	($n = 199$)	($n = 160$)	($n = 344$)	
Patient characteristics							
Age (year)	66 ± 11	67 ± 10	66 ± 11	65 ± 12	67 ± 9	65 ± 11	*0.178*
Male sex	137 (58.1)	153 (50.5)	441 (58.8)	129 (64.8)	78 (48.8)	178 (51.7)	***0.002***
ASA-score *I-II*	164 (71.9)	227 (75.4)	586 (79.5)	143 (71.9)	134 (83.8)	259 (77.5)	***0.019***
III-IV	64 (28.1)	74 (24.6)	151 (20.50)	56 (28.1)	26 (16.3)	75 (22.5)	
BMI	24.99 ± 4.08	25.08 ± 4.29	25.45 ± 4.22	24.7 ± 4.05	25.51 ± 4.47	24.93 ± 5.12	*0.185*
BMI > 25	112 (48.7)	126 (43.6)	355 (48.6)	87 (44.6)	73 (48.0)	112 (41.1)	*0.249*
Pancreatic duct size < 3 mm	35 (24.5)	24 (14.5)	95 (24.4)	28 (23.7)	48 (30.8)	46 (28.2)	***0.018***
Operative characteristics							
Soft gland	107 (57.5)	175 (63.6)	453 (64.5)	101 (54.3)	83 (53.2)	162 (55.5)	***0.007***
Whipple	75 (31.8)	61 (20.1)	306 (40.8)	170 (85.4)	73 (45.6)	87 (25.3)	***<0.0001***
PPPD	161 (68.2)	242 (79.9)	444 (59.2)	29 (14.6)	87 (54.4)	257 (74.7)	***<0.0001***
Intraoperative drain	221 (95.7)	288 (97.3)	728 (97.7)	196 (98.5)	143 (96.6)	335 (99.1)	*0.128*
Pathology							
Adenocarcinoma	173 (79.7)	235 (79.9)	550 (75.7)	139 (73.2)	113 (79.6)	270 (80.8)	*0.181*
Neuroendocrine tumor	7 (3.0)	10 (3.3)	54 (7.2)	12 (6.0)	4 (2.5)	12 (3.5)	***0.007***
ua-FRS							*0.072*
Low	2 (1.9)	2 (1.3)	1 (0.3)	0 (0.0)	2 (1.4)	1 (0.8)	*0.428*
Intermediate	54 (50.5)	76 (48.7)	138 (37.4)	44 (39.6)	58 (40.3)	62 (47.7)	***0.046***
High	51 (47.7)	78 (50.0)	230 (62.3)	67 (60.4)	84 (58.3)	67 (51.5)	***0.020***

± = Mean ± SD; HR = high-risk; ASA = American Association of Anesthesiologists; BMI = body mass index; PPPD = pylorus preserving pancreatoduodenectomy; ua-FRS = updated alternative fistula risk score.

Table 3
Postoperative outcomes

Outcome − no. (%)	None ($n = 236$)	Octreotide ($n = 303$)	Lanreotide ($n = 750$)	Pasireotide ($n = 199$)	Octreotide-HR ($n = 160$)	Lanreotide-HR ($n = 344$)	*p-value*
POPF ***No/Grade A***	206 (87.3)^{L}	249 (82.2)$^{L,\ O-HR}$	675 (90.0)$^{O,P,\ L-HR}$	161 (80.9)$^{L,\ O-HR}$	145 (90.6)^{O,P}	292 (84.9)^{L}	***0.001***
Clinically relevant POPF	30 (12.7)	54 (17.8)$^{L,\ O-HR}$	75 (10.0)$^{O,P,\ L-HR}$	35 (19.1)$^{L,\ O-HR}$	15 (9.4)^{O,P}	52 (15.1)^{L}	***0.001***
Grade B	23 (9.7)	42 (13.8)$^{L,\ O-HR}$	52 (6.9)$^{O,P,\ L-HR}$	23 (13.1)^{L}	11 (6.9)^{O}	42 (12.2)^{L}	***0.002***
Grade C	7 (3.0)	12 (4.0)	23 (3.1)	12 (6.0)	4 (2.5)	10 (2.9)	*0.358*
Bleeding ***No***	173 (73.3)$^{P,\ O-HR}$	200 (66.0)$^{P,\ O-HR}$	537 (71.6)$^{P,\ O-HR}$	114 (57.3)^{all}	134 (83.8)^{all}	237 (68.9)$_{P,\ O-HR}$	***0.000***
Grade A	46 (19.5)$^{P,\ O-HR}$	78 (25.7)$^{O-HR}$	117 (23.6)$^{P,\ O-HR}$	62 (31.2)$^{N,L,\ O-HR,\ L-HR}$	19 (11.9)^{all}	78 (22.7)$^{P,\ O-HR}$	***0.001***
Grade B	8 (3.4)	13 (4.3)	19 (2.5)	7 (3.5)	3 (1.9)	16 (4.7)	*0.379*
Grade C	9 (3.8)	12 (4.0)	17 (2.3)^{P}	16 (8.0)$^{L,\ O-HR,\ L-HR}$	4 (2.5)^{P}	13 (3.8)^{P}	***0.007***
Pneumonia	7 (11.5)	13 (14.3)	15 (8.9)	8 (11.0)	4 (13.3)	7 (6.6)	*0.555*
Wound infection	11 (8.3)^{P}	10 (4.5)^{P}	28 (6.7)^{P}	30 (23.4)^{all}	3 (2.9)^{P}	18 (8.3)^{P}	***0.000***
Re-intervention	63 (27.4)^{P}	93 (30.7)$^{P,\ O-HR}$	187 (26.4)^{P}	79 (39.9)^{all}	32 (20.1)$^{O,P,\ L-HR}$	101 (29.4)$^{P,\ O-HR}$	***0.001***
Endoscopic	12 (5.3)	21 (7.0)$^{L,\ O-HR}$	26 (3.7)$^{O,P,\ L-HR}$	19 (9.6)$^{L,\ O-HR}$	2 (1.3)$^{O,P,\ L-HR}$	23 (6.7)$^{L,\ O-HR}$	***0.000***
Radiologic	44 (19.3)^{O,L}	64 (21.2)^{L,P}	80 (11.3)$^{N,O,P,\ L-HR}$	58 (29.3)^{all}	25 (15.7)^{P}	69 (20.2)^{L}	***0.003***
Reoperation	17 (7.5)^{P}	26 (8.6)^{P}	64 (9.1)^{P}	29 (14.6)^{all}	8 (5.0)^{P}	24 (7.0)^{P}	***0.033***
Length of stay (days)	12 (8–21)	12 (9–18)	13 (9–18)	11 (8–20)	11 (8–16)	11 (8–20)	*0.237*
Readmission	32 (15.8)	50 (17.9)	125 (17.7)	33 (18.1)	36 (26.5)	56 (16.8)	*0.174*
In-hospital mortality	10 (4.5)	12 (4.0)	27 (3.6)	12 (6.2)	6 (4.2)	9 (2.6)	*0.471*

± = Mean ± SD; HR = high-risk; POPF = postoperative panreactic fistula.
Statistical differences between protocols are in superscript: N = none, O = octreotide, L = lanreotide, P = pasireotide, O-HR = octreotide HR, L-HR = lanreotide-HR.

Table 4
Multivariable analysis of POPF grade B or C

Factor	OR (95% CI)	*p*-value
No SA protocol	–	*0.000*
Octreotide	1.267 (0.578–2.780)	*0.555*
Lanreotide	**0.387 (0.180–0.834)**	***0.015***
Pasireotide	1.742 (0.770–3.940)	*0.182*
Octreotide-HR	0.666 (0.280–1.581)	*0.356*
Lanreotide-HR	0.877 (0.369–2.082)	*0.766*
Male sex	1.208 (0.738–1.865)	*0.392*
BMI	**2.811 (1.793–4.406)**	***0.001***
Aspect pancreas (soft tissue)	**6.801 (3.586–12.898)**	***0.000***
Pancreatic duct size <3 mm	**1.709 (1.090–2.678)**	***0.019***
Neuroendocrine tumor	1.023 (0.395–2.649)	*0.963*
ASA III/IV	1.146 (0.704–1.867)	*0.583*
Hospital volume	1.044 (0.514–2.123)	*0.904*

HR = high-risk; BMI = body mass index; ASA = American Association of Anesthesiologists.

Table 5
Sub-analysis according to ua-FRS

ua-FRS	POPF no. (%)	None (*n = 107*)	Octreotide (*n* = 156)	Lanreotide (*n = 369*)	Pasireotide (*n = 111*)	Octreotide-HR (*n* = 144)	Lanreotide-HR (*n = 130*)	*p-value*
Low-intermediate (0–19.9%)	No/Grade A	55 (98.2)	74 (94.9)	137 (98.6)	41 (93.2)	60 (100)	62 (98.4)	*0.141*
	POPF (Grade B or C)	1 (1.8)	4 (5.1)	2 (1.4)	3 (6.8)	0 (0)	1 (1.6)	
High (>20%)	No/Grade A	40 (78.4)	57 (73.1)	205 (89.1)	49 (73.1)	70 (83.3)	54 (80.6)	***0.006***
	POPF (Grade B or C)	11 (21.6)^{L}	21 (26.9)^{L}	25 (10.9)^{N,O,P}	18 (26.9)^{L}	14 (16.7)	13 (19.4)	

ua-FRS = updated Alternative Fistula Risk Score; POPF = postoperative pancreatic fistula; HR = high-risk.
Statistical differences between protocols are shown in the superscript: N = none, O = octreotide, L = lanreotide, P = pasireotide.

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