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Minimally invasive versus open radical antegrade modular pancreatosplenectomy for pancreatic ductal adenocarcinoma: an entropy balancing analysis

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Abstract

Background: The safety and efficacy of minimally invasive radical antegrade modular pancreatosplenectomy (MI-RAMPS) remain to be established in pancreatic cancer (PDAC)

Methods: Eighty-five open (O)-RAMPS were compared to 93 MI-RAMPS. The entropy balance matching approach was used to compare the two cohorts, eliminating the selection bias. Three models were created. Model 1 made O-RAMPS equal to the MI-RAMPS cohort (i.e., compared the two procedures for resectable PDAC); model 2 made MI-RAMPS equal to O-RAMPS (i.e., compared the two procedures for borderline-resectable PDAC); model 3, compared robotic and laparoscopic RAMPS.

Results: O-RAMPS and MI-RAMPS showed "non-small" differences for BMI, comorbidity, back pain, tumor size, vascular resection, anterior or posterior RAMPS, multi-visceral resection, stump management, grading, and neoadjuvant therapy. Before reweighting, O-RAMPS had fewer clinically relevant postoperative pancreatic fistulae (CR-POPF) (20.0% vs. 40.9%; p = 0.003), while MI-RAMPS had a higher mean of lymph nodes (25.7 vs. 31.7; p = 0.011). In model 1, MI-RAMPS and O-RAMPS achieved similar results. In model 2, O-RAMPS was associated with lower comprehensive complication index scores (MD = 11.2; p = 0.038), and CR-POPF rates (OR = 0.2; p = 0.001). In model 3, robotic-RAMPS had a higher probability of negative resection margins.

Conclusion: In patients with anatomically resectable PDAC, MI-RAMPS is feasible and as safe as O-RAMPS.

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Introduction

Minimally invasive distal pancreatectomy is now considered the standard of care in patients with left-sided pancreatic tumors requiring pancreatic resection.[1] However, in pancreatic ductal adenocarcinoma (PDAC), clearance of retroperitoneal lymph-neural tissue needs to be more radical than other tumor types and should be achieved en-bloc with the tumor. Radical antegrade modular pancreatosplenectomy (RAMPS) was developed in the open setting (O-RAMPS) to address these oncological issues[1–4] and is now performed in most patients with left-sided

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PDAC. From a technical point of view, RAMPS applies to left-sided pancreatic tumors the same oncological principles adopted for radical resection of tumors of the head of the pancreas. In O-RAMPS, access to the superior mesenteric artery (SMA) and celiac trunk (CT) is obtained by early division of the neck of the pancreas, the splenic vein, and the splenic artery. Retroperitoneal dissection then proceeds along the right side of the SMA and CT until the aorta, and hence medial-to-lateral until the specimen is fully mobilized en-bloc with the spleen. Based on the depth of the posterior plane of dissection, RAMPS can be anterior (i.e., including the anterior renal fascia), or it can be posterior (i.e., removing en-bloc and also the left adrenal gland).[5–7] In minimally invasive RAMPS (MI-RAMPS), retroperitoneal dissection occurs in a cranial direction with an early approach to the posterior plane that does not necessarily requires early division of the above-mentioned structures. Overall, RAMPS offers the advantage of vessel-oriented dissection, permitting radical clearance of the extrapancreatic nerve plexus, and improves visualization of the posterior plane, potentially reducing the margin positivity rate at this level. The final dissection is supposed to be identical in O-RAMPS and MI-RAMPS, but this occurs from a different anatomical approach that raises an important question about the safety and feasibility of MI-RAMPS.[15]

Only a few studies have specifically focused on MI-RAMPS for PDAC,[8–12] and no prospective and randomized trial has compared MI-RAMPS to O-RAMPS for PDAC. In this context of low evidence, two metanalyses[13,14] suggested that MI-RAMPS and O-RAMPS are associated with similar short and long-term results. The generalizability of these results remains to be established since both metanalyses were not restricted to studies assessing RAMPS in PDAC. On practical grounds, there is no current good evidence supporting that MI-RAMPS is equivalent to O-RAMPS in patients with PDAC.

In this study, we aim to provide some novel and more objective information about the safety and efficacy of MI-RAMPS for PDAC by using an entropy balance analysis. Entropy balance analysis is a sophisticated statistical method that aims to reverse treatment groups.[16] This is achieved by creating a virtual cohort of patients having the same characteristics as the actual comparator group. In our study, for example, a virtual O-RAMPS cohort can be created in which the patients have the same characteristics as those who have actually undergone MI-RAMPS. This type of comparison creates a model that shows what would have happened if O-RAMPS patients (suitable for a minimally invasive approach) had received an MI-RAMPS. The opposite can be investigated by reversing the comparison (i.e., by creating a virtual MI-RAMPS cohort of patients who would have been good O-RAMPS candidates based on actual selection criteria). Therefore, this statistical analysis avoids interference from all confounders related to arbitrary treatment allocation in retrospective studies. Compared to classical propensity matching, entropy balancing did not eliminate “the uncommon cases,” avoiding the reduction of sample size and the loss of information contained in excluded cases.

Materials and methods

This retrospective study involved O-RAMPS and MI-RAMPS performed at six high-volume centers between January 2011 and December 2021. Participating centers were: Division of Pancreatic Surgery, IRCCS “Azienda Ospedaliero-Universitaria” of Bologna (Italy), Division of General and Transplant Surgery, University of Pisa (Italy), Section of Pancreatic Surgery, Humanitas Clinical and Research Center-IRCCS, Milan (Italy), Digestive Surgery Unit, Fondazione Policlinico Universitario "A. Gemelli" IRCCS di Roma (Italy), Department of Digestive Surgery and Transplantation, Saint-Eloi Hospital, Montpellier University Hospital, Montpellier (France), and Department of Surgery, Centre Hospitalier de Luxembourg, Luxembourg.

Demographics, clinical, radiological, pathological, and survival data were extracted from prospectively maintained databases. Patients were included in this study if (i) tumor type was PDAC; (ii) the procedure was a RAMPS (either anterior or posterior); (iii) there was a clear description of the surgical approach (i.e., open, laparoscopic, or robotic); (iv) the tumor was resectable or borderline resectable according to NCCN classification.[17] All procedures were performed by skilled pancreatic surgeons, experts in minimally invasive pancreatic resection. Both groups included resectable and borderline resectable PDAC.

At each center, patients were selected for either O-RAMPS or MI-RAMPS based on the preference of the senior surgeon, considering local expertise and patient-specific factors. The same surgical team performed all RAMPS at each center, irrespective of the surgical approach. All centers used the same pre-formed clinical research form for the data collection.

Patients undergoing either laparoscopic or robotic RAMPS were included in the MI-RAMPS group. Anterior and posterior RAMPS were defined as reported by Strasberg *et al.*[5–7] Extended resections were defined as en-bloc resection of a neighboring organ such as the stomach or colon.[18] Postoperative course was classified prospectively at discharge, according to the Clavien-Dindo Classification (CDC).[19] Complications graded >IIIa, were considered severe. The Comprehensive Complication Index (CCI®)[20] was calculated for each patient using an online calculator (www.assessurgery.com/about_cci-calculator/). Clinically relevant postoperative pancreatic fistula (CR-POPF), post-pancreatectomy hemorrhage (PPH), and delayed gastric emptying (DGE) were defined according to the 2016 update ISGPF and ISGPS definitions.[21–23] We also examined the length of postoperative stay (LOS) and intensive care unit (ICU) stay, margin status, number of examined lymph nodes, and overall survival (OS). In accordance with the Royal College of Pathologists, resection margins were defined microscopically positive (R_1) when cancer cells were found $\leq$1 mm from any resection margin.[24]

Study design

The analysis was carried out in four steps. The analysis started with a crude comparison between the two groups. In the second step, the O-RAMPS cohort was transformed into a virtual cohort with the MI-RAMPS group's characteristics. Thus, the two cohorts were compared (model 1). In the third step, the MI-RAMPS original cohort was remodeled to obtain a virtual group similar to the O-RAMPS group. The two cohorts were compared (model 2). Finally, in the fourth step, a sub-group analysis was made considering only patients who underwent MI-RAMPS. This comparison was made before and after the correction of selection bias. In this model, L-RAMPS patients were reweighted to be similar to the R-RAMPS cohort.

Statistical analysis

Data were reported in percentages or mean and standard deviation (SD). Differences between the two groups were measured using standardized differences (d-value). A d-value $\leq$0.2 indicates a percentage of the non-overlap population $\leq$15% (small difference); a d-value >0.2 and $\leq$0.5 (medium difference) means that the percentage of the non-overlapped population was >15% but $\leq$33%; a d value >0.5 to 0.8 (large difference) indicates a percentage of non-overlap population >33%.[25] All endpoints were reported for the unmatched and matched populations. Hainmueller's "entropy balance" was applied.[16] This is a relatively novel approach that permits eliminating all confounding bias simulating a "quasi" randomized control trial.[16] The entropy balancing was used to mitigate the selection bias due to retrospective design. In contrast to other preprocessing methods, such as propensity score matching, entropy balancing involves a reweighting scheme that directly incorporates covariate balance into the weight function that is applied to the sample units. Entropy balancing not eliminates the uncommon cases, but it reweights the characteristics of patients (covariates) of one group to be similar to the comparative one. This recalibration of the unit weights effectively adjusts for systematic and random inequalities in representation.

In other words, Entropy balancing thereby exactly adjusts inequalities in representation with respect to the first, second, and possibly higher moments of the covariate distributions. These balance improvements can reduce model dependence for the subsequent estimation of treatment effects. The method assures that balance improves on all covariate moments included in the reweighting. For models 1 and 2, all available covariates were used for reweighting: sex, age, BMI, comorbidity, back pain, weight loss, new onset or worsening diabetes, tumor size, type of RAMPS, need for vascular or extended, pancreatic stump closure, grading or need for neoadjuvant therapy. In model 3, all covariates were balanced except the technique used for pancreatic stump closure because the laparoscopic approach almost always required this technique. The reweighting for models 1 and 2 was performed on O-RAMPS patients to generate a virtual group similar to the MI-RAMPS group and vice-versa. Subsequently, classical statistical analyses were carried out, introducing obtained weights and applying bootstrap resamples to minimize the possibility of a type I error due to the spurious increase in the sample of O-RAMPS patients. For model 3, the L-RAMPS cohort was reweighted to be similar to the R-RAMPS cohort. For all models, the balancing was performed by adjusting the first, second, and third moments of the covariate distributions (covariate means, variances, and skewness).

It should be noted that, in the table, the frequency and percentage of discrete variables did not change after reweighting in virtual groups, but it is the weight of each class within the same variable that changes. In other words, this method did not change the distribution of covariates, transforming the group to the original in virtual. Indeed, entropy balancing re-calibrates the effect of covariates to obtain a comparison that is not biased between the two groups. Indeed, in model 1, the weight of covariates in virtual O-RAMPS is recalibrated to be similar to MI-RAMPS, while in model 2, the weight of covariates in virtual MI-RAMPS is recalibrated to be similar to O-RAMPS. Finally, in model 3, the weight of covariates in virtual MI-RAMPS is recalibrated to be similar to O-RAMPS. The statistical analyses were computed using STATA software (StataCorp. 2011. College Station, TX: StataCorp LP). Entropy balance was performed with the "ebalance" module.

Results

One hundred seventy-eight patients (85 O-RAMPS and 93 MI-RAMPS) met the inclusion criteria and were analyzed in this study (Table 1). No missing data were observed in the included cohort. Twenty-five out of 93 MI-RAMPS (26.9%) were performed under robotic assistance. The overall conversion rate was 12.9% (12/93 MI-RAMPS). All conversions occurred in the laparoscopic sub-group. The following "non-small" differences were recorded in O-RAMPS versus MI-RAMPS: BMI (24.4 vs. 25.3 kg/m^2; d = 0.213), the prevalence of associated diseases (45.9% vs. 63.4%; d = 0.395), presence of back pain (18.8% vs. 31.2%; d = 0.369), tumor size (34 vs. 29.9 mm; d = 0.310), need for vascular resection (20% vs. 12.9%; d = 0.289), posterior RAMPS (4.7% vs. 8.6%; d = 0.357), need for extended resection (16.5% vs. 16.1%), management of pancreatic stump (d = 0.262), tumor grading (d = 0.215), and delivery of neoadjuvant therapy (28.2% vs. 8.6%; d = 0.787). After reweighting, an optimal balance (d < 0.200) was obtained for all the variables in both models. OS was 36 months (30–48, 95 CI).

O-RAMPS versus MI-RAMPS without reweighting

Postoperative results of unweighted groups are reported in Table 2. Postoperative mortality at 90 days was 0.6%. Incidence of severe complications, PPH, and DGE, as well as the length of ICU stay and LOS were similar in the two groups. CCI scores were slightly higher in MI-RAMPS (17.4 vs. 13.6; p = 0.095), but

Table 1 Characteristics of 178 patients included in the study

Parameters	Before weighting			Model 1[a,c]		Model 2[b,c]	
	O-RAMPS (N = 85)	MI-RAMPS (N = 93)	|d-value|[d]	Virtual O-RAMPS	|d-value|[d]	Virtual MI-RAMPS	|d-value|[d]
Sex							
Female	47 (55.3)	47 (50.5)	0.105	47 (55.3)	0	47 (50.5)	0
Male	38 (44.7)	46 (49.5)		38 (44.7)		46 (49.5)	
Age, years	67.6 ± 11.4	68.6 ± 8.8	0.102	67.6 ± 11.4	0	68.4 ± 8.8	0
BMI (kg/m^2)	24.4 ± 4.4	25.3 ± 4.4	0.213	24.4 ± 4.4	0	25.3 ± 4.4	0
Comorbidity							
No	46 (54.1)	34 (36.6)	0.395	46 (54.1)	0	34 (36.6)	0
One or more	39 (45.9)	59 (63.4)		39 (45.9)		59 (63.4)	
Back pain							
No	69 (81.2)	64 (68.8)	0.369	69 (81.2)	0	64 (68.8)	0
Yes	16 (18.8)	29 (31.2)		16 (18.8)		29 (31.2)	
Weight loss							
No	75 (88.2)	82 (88.2)	0.003	75 (88.2)	0	82 (88.2)	
Yes	10 (11.8)	11 (11.8)		10 (11.8)		11 (11.8)	
New onset or worsening diabetes							
No	78 (91.8)	83 (89.3)	0.162	78 (91.8)		83 (89.3)	
Yes	7 (8.3)	10 (10.8)		7 (8.3)		10 (10.8)	
Size of tumor (mm)	34 ± 15.6	29.9 ± 10.9	0.310		0		0
Vascular resection							
No	68 (80)	81 (87.1)	0.289	68 (80)	0	67 (83.8)	0
PMV ± CA	17 (20)	12 (12.9)		12 (14.1)		10 (10.8)	
RAMPS							
Anterior	81 (95.3)	85 (91.4)	0.357	81 (95.3)	0	85 (91.4)	0
Posterior	4 (4.7)	8 (8.6)		4 (4.7)		8 (8.6)	
Extended resection							
No	71 (83.5)	78 (83.9)	0.268	71 (83.5)	0	78 (83.9)	0
Yes	14 (16.5)	25 (16.1)		14 (16.5)		25 (16.1)	
Pancreatic stump closure							
Hand-sewn	44 (51.7)	28 (30.1)	0.262	44 (51.7)	0	28 (30.1)	0
Stapler	31 (36.5)	59 (63.4)		31 (36.5)		59 (63.4)	
Others	10 (11.8)	6 (6.5)		10 (11.8)		6 (6.5)	
Grading							
G1	14 (16.5)	12 (12.9)	0.215	14 (16.5)	0	12 (12.9)	0
G2	48 (56.5)	46 (49.5)		48 (56.5)		46 (49.5)	
G3	23 (27.1)	35 (37.6)		23 (27.1)		35 (37.6)	
Neoadjuvant therapy							
No	61 (71.8)	85 (91.4)	0.787	61 (71.8)	0	85 (91.4)	0
Yes	24 (28.2)	8 (8.6)		24 (28.2)		8 (8.6)	

RAMPS, radical antegrade modular distal pancreatectomy procedure; MI, minimally invasive; O, open; MI, minimally invasive.
[a] In model 1, a virtual cohort of patients was generated; in this cohort, the patients have identical characteristics to the MI-RAMPS one, but they were resected with an open approach.
[b] In model 2, a virtual cohort of patients was generated; in this cohort, the patients have identical characteristics to the O-RAMPS one, but they were resected with a minimally invasive approach.
[c] It should be noted that, according to the entropy balancing, the frequency and percentage of discrete variables did not change after reweighting in virtual groups; however, it is the weight of each class within the same variable that changes: in model 1, the weight of covariates in virtual O-RAMPS is recalibrated to be similar to MI-RAMPS while in model 2, the weight of covariates in virtual MI-RAMPS is recalibrated to be similar to O-RAMPS.
[d] Effect size categories: 0 to 0.2 small (percentage of non-overlap population < 15%); >0.2 to 0.5 medium (percentage of non-overlap population < 33%); >0.50 to 0.80 large (percentage of non-overlap population < 50%); over 0.8 very large (percentage of non-overlap population > 50%).

Table 2 Postoperative results in unbalanced groups

Postoperative and long term results	O-RAMPS (N = 85)	MI-RAMPS (N = 93)	P
CCI	13.6 (13.2)	17.4 (17.2)	0.095[a]
CDC ≥IIIa			
No	72 (84.7)	74 (79.6)	0.373[b]
Yes	13 (15.3)	19 (20.4)	
CR-POPF			**0.003**[b]
No	68 (80)	55 (59.1)	
Yes	17 (20)	38 (40.9)	
PPH			0.282[b]
No	83 (97.7)	87 (93.5)	
Yes	2 (2.3)	6 (6.5)	
DGE			0.245[b]
No	78 (91.8)	80 (86)	
Yes	7 (8.2)	13 (14)	
ICU stay	0.8 (1.9)	0.8 (1.3)	0.921[a]
LOS (days)	11.9 (6.4)	13 (0.7)	0.283[a]
Lymph-nodes harvested (mean, days)	25.7 ± 14.7	31.6 ± 15.7	**0.011**[a]
R1 (all margins)			0.816[b]
No	49 (57.7)	52 (55.9)	
Yes	36 (42.3)	41 (44.1)	
R1 (posterior margin)			0.871[b]
No	60 (70.6)	64 (68.8)	
Yes	25 (29.4)	29 (31.2)	
R1 (anterior margin)			1.000[b]
No	65 (76.5)	72 (77.4)	
Yes	20 (23.5)	21 (22.6)	
R1 (remnant)			1.000[b]
No	82 (96.5)	89 (95.7)	
Yes	3 (3.5)	4 (4.3)	
Survival	38 ± 2.6	36 ± 2.4	0.427[b]

RAMPS, radical antegrade modular distal pancreatectomy procedure; O, open; MI, minimally invasive; CCI, comprehensive complication index[16]; CDC, Clavien-Dindo Classification[15]; POPF, postoperative pancreatic fistula according to 2016 update International Study Group of Pancreatic Fistula (ISGPF) definition[17]; PPH, post-pancreatectomy hemorrhage[18]; DGE, delayed gastric emptying[19]; ICU, intensive care unit; LOS, length of postoperative stay.
[a] Student T test.
[b] Fisher's exact test.

the difference was not significant. CR-POPF occurred more frequently after MI-RAMPS (40.9% vs. 20%; p = 0.003). The mean number of examined lymph nodes was higher in MI-RAMPS (31.6 vs. 25.7; p = 0.011). R1 rate and OS were similar between the two groups.

Model 1: MI-RAMPS versus virtual O-RAMPS

Postoperative results after reweighting in model 1 are summarized in Table 3. After balancing, the two approaches had similar CCI, severe complications, CR-POPF, PPH, DGE, length of ICU stay, and LOS. In addition, oncologic results were comparable with similar R_1 rates and OS.

Model 2: virtual MI-RAMPS versus O-RAMPS

In model 2, after entropy balancing, the two approaches had similar severe complications, PPH, DGE, length of ICU stay, LOS, R_1 rate, and OS. CCI score (MD −11.2; p = 0.038) and CR-POPF (OR 0.2; p = 0.001) were lower in O-RAMPS than in MI-RAMPS.

Model 3: L-RAMPS versus R-RAMPS

The baseline characteristics of the 93 MI-RAMPS are reported in Table 4. There were 68 laparoscopic RAMPS (73.1%) and 25 robotic RAMPS (26.9%) The "non-small" differences between the two groups were: sex (d = 0.321), age (69.3 vs. 66.7 years; d = 0.285), BMI (25.8 vs. 24.0 kg/m^2; d = 0.416), back pain

Table 3 Postoperative and long term results of 178 RAMPS after re-weighting

Postoperative results	Model 1		Model 2	
	MI-RAMPS vs. virtual Open RAMPS OR/MD/HR (95 CI)[a]	P	Virtual MI-RAMPS vs. Open RAMPS OR/MD/HR (95 CI)[a]	P
CCI	3.7 (–3.4 to 10.9)	0.300	–11.2 (–21.8 to –0.6)	0.038
CDC ≥IIIa	1.2 (0.3–4.4)	0.874	0.5 (0.2–1.5)	0.225
CR-POPF	1.1 (0.4–3.2)	0.883	0.2 (0.1–0.5)	0.001
PPH (No vs. Yes)	1.4 (0.2–9.8)	0.728	1.1 (0.2–5.9)	0.955
ICU stay (days)	0.1 (–0.5 to 0.5)	0.934	0.1 (–0.6 to 0.7)	0.874
LOS (days)	1.5 (–1.1 to 4.2)	0.259	–2.9 (–6.3 to 0.4)	0.085
Lymph-nodes harvested (number)	2.7 (–3.5 to 9.0)	0.380	–6.3 (–12.2 to 0.3)	0.079
R1 (all margins)	0.9 (0.4–2.6)	0.957	1.2 (0.5–2.8)	0.688
R1 (posterior margin)	1.0 (0.3–2.9)	0.974	1.2 (0.5–3.2)	0.697
R1 (pancreatic margin)	0.4 (0.1–3.6)	0.410	1.2 (0.2–7.3)	0.905
Survival	1.3 (0.7–2.4)	0.427	0.8 (0.4–1.4)	0.427

RAMPS, radical antegrade modular distal pancreatectomy procedure; MI, minimally invasive; CCI, comprehensive complication index[12]; CDC, Clavien-Dindo Classification[11]; ICU, intensive care unit; LOS, length of postoperative stay; CR-POPF, postoperative pancreatic fistula according to 2016 update International Study Group of Pancreatic Fistula (ISGPF) definition[13]; PPH, post-pancreatectomy hemorrhage[14]; DGE, delayed gastric emptying[15].

[a] The re-weighted results are reported as odds ratio (OR), mean difference (MD), and HR (hazard ratio).

(26.5% vs. 44.0%; d = 0.430), weight loss (8.8% vs. 11.8%; d = 0.523), new-onset or worsening of diabetes (13.2% vs. 4%; d = 0.716), tumor size (28.7 vs. 33.1 mm; d = 0.407), need for vascular resection (10.3% vs. 20.0%; d = 0.429), need for extend resection (11.8% vs. 8.0%; d = 0.236), posterior RAMPS (10.3% vs. 4%; d = 0.599), pancreatic stump management (d = 1.556), and delivery of neoadjuvant therapy (10.3% vs. 4%; d = 0.559). After reweighting, an optimal balance ($d < 0.200$) was obtained except for pancreatic stump management. It is worth noting that in 77.9% of L-RAMPS, the pancreatic neck was divided using an endoscopic stapler, while in 76.0% of R-RAMPS, it was divided using a harmonic scalpel or a monopolar cautery and was closed by sutures. Even before entropy balance analysis, postoperative and long-term results were similar (Table 5). The only significant difference was a larger number of examined lymph nodes in R-RAMPS (MD 7.6; p = 0.037). Comparing virtual L-RAMPS to R-RAMPS, the risk of R_1 resection (all margins) was higher in L-RAMPS for the posterior margin (OR = 0.3; p = 0.047) as well as for all margins (OR 0.2; p = 0.009).

Discussion

In the absence of a prospective and randomized trial, this study provides new insights into the clinical and oncologic value of MI-RAMPS for PDAC. In the present analysis, both groups (MI-RAMPS and O-RAMPS) included resectable and borderline resectable PDAC. However, the crude data show that surgeons prefer an open approach in case of larger tumors and associated vein involvement. This imbalance is typical of retrospective design and requires statistical adjustments such as entropy balancing. Avoiding adding complexity to an already complex procedure probably reflects the safe practice and shows some relative contraindications to MI-RAMPS. However, it also shows that major selection bias exists when comparing unmatched O-RAMPS to MI-RAMPS. In this study, imbalances between O-RAMPS and MI-RAMPS were eliminated using a novel statistical method: the "entropy balancing approach." This approach is similar to propensity score matching but shows some major advantages, making the final analysis much closer to the statistical value of a prospective and randomized trial. The more relevant advantage is that "uncommon" patients, namely those who have characteristics less frequently observed in one of the two groups (e.g., need for vascular resection or larger tumor size in MI-RAMPS), are not excluded, such as in propensity score matching analysis, avoiding the loss of some relevant information. Indeed "uncommon patients" remained in the group analysis and contributed to the average effect of the treatments.[16] In this study, entropy balancing permitted to obtain of two virtual cohorts: a virtual O-RAMPS cohort that was similar to the actual MI-RAMPS cohort and a virtual MI-RAMPS cohort that was similar to the actual O-RAMPS cohort. Thus, three interesting models were generated.

The first model compared actual MI-RAMPS and virtual O-RAMPS. These patients have an anatomically resectable PDAC, permitting upfront resection based on current NCCN guidelines.[21] These tumors are relatively small and do not require additional resections of either vascular segments or adjacent organs. Therefore, this model aimed to simulate a Randomized Clinical Trial (RCT) in which patients with anatomically resectable PDAC were randomly allocated to O-RAPMS or MI-RAMPS. In this setting, the two surgical approaches showed similar outcomes. These results align with previous studies showing that

Table 4 Characteristics of 93 patients who underwent MI-RAMPS included in the study

Parameters	Before weighting			Model 3[a]	
	L-RAMPS (N = 68)	R-RAMPS (N = 25)	|d-value|[d]	Virtual L-RAMPS	|d-value|[b,d]
Sex					
Female	37 (54.4)	10 (40)	0.321	47 (55.3)	0
Male	31 (45.6)	15 (60)		38 (44.7)	
Age, years	69.3 ± 8.6	66.7 ± 9.4	0.285	66.7 ± 11.9	0
BMI (kg/m^2)	25.8 ± 4.8	24 ± 2.5	0.416	24 ± 4.5	0
Comorbidity					
No	25 (36.8)	9 (36)	0.018	46 (54.1)	0
One or more	43 (63.2)	16 (64)		39 (45.9)	
Back pain					
No	50 (73.5)	14 (56)	0.430	69 (81.2)	0
Yes	18 (26.5)	11 (44)		16 (18.8)	
Weight loss					
No	62 (91.2)	82 (88.2)	0.523	75 (88.2)	0
Yes	6 (8.8)	11 (11.8)		10 (11.8)	
New onset or worsening diabetes					
No	59 (86.8)	24 (96)	0.716	78 (91.8)	0
Yes	9 (13.2)	1 (4)		7 (8.3)	
Size of tumor (mm)	28.7 ± 10.4	33.1 ± 11.5	0.407	33.1 ± 8.1	0
Vascular resection					
No	61 (89.7)	20 (80)	0.429	68 (80)	0
PMV ± CA	7 (10.3)	5 (20)		12 (14.1)	
RAMPS					
Anterior	61 (89.7)	24 (96)	0.559	24 (96)	0
Posterior	7 (10.3)	1 (4)		1 (4)	
Extended resection					
No	60 (88.2)	23 (92)	0.236	71 (83.5)	0
Yes	8 (11.8)	2 (8)		14 (16.5)	
Pancreatic stump closure[c]					
Hand-sewn	9 (13.2)	19 (76)	1.556	19 (76)	1.556
Stapler	53 (78)	6 (24)		6 (24)	
Others	6 (8.8)	0 (0)		0 (0)	
Grading					
G1	11 (16.2)	1 (4.0)	0.149	14 (16.5)	0
G2	31 (45.6)	15 (60)		48 (56.5)	
G3	26 (38.2)	9 (36)		23 (27.1)	
Neoadjuvant therapy					
No	61 (89.7)	24 (96)	0.559	61 (71.8)	0
Yes	7 (10.3)	1 (4)		24 (28.2)	

RAMPS, radical antegrade modular distal pancreatectomy procedure; L, laparoscopic; R, robotic.
[a] In model 3, a virtual cohort of patients was generated; in this cohort, the patients have identical characteristics to the R-RAMPS one, but they were resected with a laparoscopic approach.
[b] It should be noted that, according to the entropy balancing, the frequency and percentage of discrete variables did not change after reweighting in virtual groups; however, it is the weight of each class within the same variable that changes.
[c] The prevalence in using the stapler is a prerogative of the laparoscopic approach and for this reason, we decide not to perform the balancing for this factor.
[d] Effect size categories: 0 to 0.2 small (percentage of non-overlap population < 15%); >0.2 to 0.5 medium (percentage of non-overlap population < 33%); >0.50 to 0.80 large (percentage of non-overlap population < 50%); over 0.8 very large (percentage of non-overlap population > 50%).

Table 5 Postoperative results of MI-RAMPS before and after re-weighting

Postoperative results	Before re-weighting		After re-weighting	
	L-RAMPS vs. R-RAMPS OR/MD/HR (95 CI)	P	Virtual L-RAMPS vs. R-RAMPS OR/MD/HR (95 CI)	P
CCI	6.9 (−1.1 to 14.7)	0.089	4.2 (−7.4 to 15.8)	0.476
CDC ≥IIIa	1.3 (0.4−4.0)	0.605	0.8 (0.2−3.6)	0.809
CR-POPF	1.5 (0.6−3.8)	0.397	1.5 (0.4−5.7)	0.524
PPH (No vs. Yes)	0.5 (0.1−4.7)	0.566	0.2 (0.1−2.1)	0.167
ICU stay (days)	−0.2 (−0.7 to 0.4)	0.605	−0.4 (1.2−0.4)	0.297
LOS (days)	1.2 (−2.1 to 4.5)	0.488	−0.1 (−4.3 to 4.3)	0.996
Conversion to open surgery	NC		NC	
Lymph-nodes harvested (number)	7.6 (0.5−14.8)	0.037	5.9 (−2.4 to 14.3)	0.163
R1 (all margins)	0.5 (0.2−1.3)	0.158	0.2 (0.1−0.6)	0.009
R1 (posterior margin)	0.6 (0.2 1.8)	0.367	0.3 (0.1−0.9)	0.047
R1 (pancreatic margin)	NC		NC	
Survival^	1.9 (0.9−4.2)	0.104	1.9 (0.9−4.2)	0.104

RAMPS, radical antegrade modular distal pancreatectomy procedure; MI, minimally invasive; CCI, comprehensive complication index[12]; CDC, Clavien-Dindo Classification[11]; ICU, Intensive Care Unit; LOS, Length of postoperative stay; CR-POPF, postoperative pancreatic fistula according to 2016 update International Study Group of Pancreatic Fistula (ISGPF) definition[13]; PPH, post-pancreatectomy hemorrhage[14]; DGE, delayed gastric emptying[15]; NC, data not computable for absence of events in arm R-RAMPS.

laparoscopic distal pancreatectomy is feasible and safe in patients with small pancreatic tumors.[26] In addition, the R_0 rate and the number of retrieved lymph nodes were also similar between the two groups, showing that MI-RAMPS is not expected to provide inferior local tumor clearance. Therefore, in these patients, MI-RAMPS appears to be non-inferior to O-RAMPS.

The second model compared virtual MI-RAMPS to actual O-RAMPS. This comparison aimed to explore the limitations of MI-RAMPS by simulating what could have happened if patients undergoing O-RAMPS would instead undergo MI-RAMPS. This model simulated an RCT in which borderline resectable tumors, possibly requiring additional resections, are operated by either MI-RAMPS or O-RAMPS. Indeed, this model assumes that approximately one-third of the patients received neoadjuvant oncologic treatments. Interestingly, MI-RAMPS was associated with higher CCI scores and increased frequency of CR-POPF. These results are in keeping with outcomes reported for MI pancreatoduodenectomy with vascular resection[25] and echo recommendations from Miami guidelines.[1] Indeed, even if few reports have shown the feasibility of minimally invasive pancreatic resections with associated vascular procedures,[27−29] the generalizability of these achievements remains to be established. These resections should probably be reserved for high-volume centers with advanced laparoscopic skills and sound experience in minimally invasive pancreatic resections.[30,31] Neoadjuvant chemotherapy or chemo-radiotherapy is currently recommended in borderline resectable pancreatic cancer,[32] and implementation of this oncologic strategy[33−35] on a large scale is expected to increase the number of these patients referred for surgery. Therefore, prospective studies on RAMPS with vascular resection and reconstruction are urgently needed.

The third and final model was a subgroup analysis comparing L-RAMPS and R-RAMPS. Some "non-small" differences observed before matching reveal that robotic assistance is associated with tumors of a larger size requiring vascular resections. In other words, tumors treated by robotic RAMPS are similar to those of patients undergoing O-RAMPS. Moreover, additional non-causal differences were noted between L-RAMPS and R-RAMPS, such as BMI, symptoms, use of a stapler for pancreatic transection, and rate of neoadjuvant oncologic treatments. Of course, all causal and non-causal differences raised the issue of imbalance between the two groups. Entropy balancing eliminated these differences and allowed us to verify what could have happened if patients undergoing L-RAMPS had undergone R-RAMPS. After reweighting, R-RAMPS was associated with a higher probability of R_0 resection.

This study has some limitations. First, the design is retrospective. However, data were retrieved from prospectively maintained databases at high-volume centers. In addition, entropy balance is expected to have minimized the selection bias inherently associated with all retrospective studies. Second, despite entropy balance being the closest possible approximation to an RCT, randomization is the ideal solution to compare MI-RAMPS to O-RAMPS. Therefore, results from the DIPLOMA trial are very much needed.[36] Third, although we are reporting on 178 RAMPS for PDAC, study groups are relatively small and could be underpowered to detect some smaller differences between the two groups. However, this is the largest study reporting on MI-RAMPS versus O-RAMPS for PDAC.

In conclusion, this study shows that in patients with anatomically resectable PDAC located in the body-tail of the pancreas, MI-RAMPS is feasible and as safe as O-RAMPS. Further data on MI-RAMPS in the setting of borderline resectable PDAC are urgently needed. Within the minimally invasive group, robotic assistance improved the ability to resect borderline resectable tumors and was associated with higher rates of negative margin resections.

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Conflict of interest

None declared.

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