Disentangling seemingly contradictory results of the first two randomised controlled trials comparing open and robotic pancreatoduodenectomy

Ugo Boggi, Niccolò Napoli, and Emanuele F. Kauffmann*

Division of General and Transplant Surgery, University of Pisa, Pisa, Italy

The Lancet Regional Health - Europe 2024;40: 100900

Published Online xxx https://doi.org/10.1016/j.lanepe.2024.100900

Minimally invasive pancreatoduodenectomy has recently surged in popularity, particularly with the introduction of robotic assistance offering a promising avenue for broader adoption.[1] Several retrospective studies have demonstrated that robotic pancreatoduodenectomy (RPD) may be comparable to open PD (OPD), although the criteria for patient selection remain contentious.[2,3] Furthermore, while approximately 40 RPD cases are needed to overcome the initial learning curve, the full potential of RPD may not be realized until 250 procedures.[4] The importance of achieving proficiency in minimally invasive pancreatoduodenectomy before implementing randomised controlled trials (RCTs) was highlighted by the LEOPARD-2 trial, which was closed due to safety concerns.[5]

In recent weeks, results from two RCTs comparing RPD with OPD have been published, one from Heidelberg (EUROPA trial) and the other from China.[6,7] Notably, a US-based RCT (trial registry: NCT04171440) could not be completed due to difficulties in recruiting patients for OPD and was "converted" into an observational study on perioperative outcomes of RPD. While patients' choices cannot dictate scientific evidence, it is noteworthy that the EUROPA trial saw 12% of patients declining participation, while 21% did so in the Chinese trial. Additionally, in the Chinese trial, 5% of patients initially assigned to OPD underwent RPD due to withdrawal of consent.

Table 1 compares key variations between the EUROPA and Chinese trials. The EUROPA trial was a single-centre, investigator-initiated, exploratory (IDEAL stage 2b), open-label RCT without a power calculation, focusing on the comprehensive complication index. Conversely, the Chinese trial was a multicentre superiority phase-3 RCT aiming to demonstrate a reduction in hospital stay with RPD. Both trials were open-label, with participating surgeons having completed a learning curve of at least 40 RPD cases. However, neither trial stratified cases based on anticipated difficulty or pancreas-specific risk factors. On the contrary, both RCTs included patients requiring vascular resections who, quite obviously, are not ideal candidates for RPD. The high rate of (elective) conversion in the Europa trial (23%) possibly reflects a suboptimal process of patient selection and asks the difficult question if potential advantages of RPD were blurred by cases that were likely to be too difficult to be approached robotically. Despite that, no patient died after RPD in the EUROPA trial.

The most notable disparities between the two RCTs (EUROPA vs. Chinese trial) were observed in operative time (431 vs. 245 min), blood loss (742 vs. 75 mL), conversion rate (23 vs. 3.7%), major intraoperative adverse events (0 vs. 17%), vascular reconstruction (17.2 vs. 4%), hard pancreatic texture (13.8 vs. 47%), postoperative pancreatic fistula grade B/C (37.9 vs. 14%), biliary leak grade B/C (17.2 vs. 4%), delayed gastric emptying grade B/C (34.4 vs. 11%), length of hospital stay (17 vs. 11 days), reoperation (13.8 vs. 3%), readmission (17.2 vs. 7%), and malignant histology (55% vs. 72%). Conversely, few outcomes exhibited similarity between the two RCTs (e.g., postpancreatectomy haemorrhage grade B/C: 13.8 vs. 9%; mortality: 0 vs. 1%). Some of these differences can be explained by the different patient populations (i.e., Western vs. Eastern), but others could be related to variations in patient selection and/or operative approach.

Notwithstanding the aforementioned differences, overall, the two RCTs demonstrated that RPD is a safe approach to pancreatoduodenectomy. Despite the high complexity of many procedures in the EUROPA trial, there were no emergency conversions or serious intraoperative complications. Additionally, RPD did not increase the rate of reintervention and hospital readmission, and no patient died. The rate of grade B/C postoperative pancreatic fistula was similar in the two study arms, despite RPD having fewer pancreases of hard consistency. The high rate of grade B/C delayed gastric emptying could be related to variability in the techniques used for digestive reconstruction rather than the operative approach. Therefore, what may appear as a negative trial actually demonstrates that RPD can be safely applied even to "difficult" pancreatoduodenectomy. On the other hand, the Chinese trial, presumably in the context of "easier" pancreatoduodenectomy, showed that RPD, in selected patients, can improve surgical outcomes.

RCT results are pivotal in shaping surgical practice. The first two RCTs comparing RPD to OPD differ in design and come to different, and sometimes seemingly

DOI of original article: https://doi.org/10.1016/j.lanepe.2024.100864
*Corresponding author.
E-mail address: u.boggi@med.unipi.it (U. Boggi).

	Chinese trial	EUROPA trial		
Study design	• Multicentre • Superiority • Phase-3 RCT	• Single-centre • Investigator-initiated • Exploratory • Open-label RCT		
Inclusion criteria	• Patients suitable both RPD and OPD • Age 18–75 years • ECOG PS 0–1 • ASA ≤3 • Resectable tumor	• Adult patients suitable for elective PD (both RPD and OPD) for any indication		
Exclusion criteria	• Borderline resectable • Neoadjuvant therapy • Distant metastases • Major comorbidity • Synchronous malignant tumour of other organs • Pregnancy • Refused to participate in the trial	• Borderline resectable or unresectable tumor (NCCN definition) • Distant metastases • ASA score >3 • Participation in another trial that could interfere with the intervention and outcome of this trial • Language difficulties or lack of compliance		
	RPD	**OPD**	**RPD**	**OPD**
Patients	81	80	29	33
Duration of surgery, min	245 (220–330)	298 (245–385)	431 ± 103	367 ± 106
Conversion, number (%)	3 (3.7)	NA	6 (20.6)	NA
Emergency conversion, number (%)	2 (2.4)	NA	0	NA
Major intraoperative complications, number (%)	14 (17)	19 (24)	0	1 (3.0)
Blood loss, mL	75 (50–145)	150 (100–290)	742 ± 512	814 ± 685
Blood transfusion, number (%)	2 (3)	7 (9)	3 (10.3)	2 (6.1)
Pylorus preservation, number (%)	NA	NA	5 (17.7)	18 (54.5)
Arterial resection, number (%)	NA	NA	0	2 (6.1)
Venous resection, number (%)	3 (4)	4 (5)	5 (17.2)	3 (9.1)
Multivisceral resection, number (%)	NA	NA	4 (13.8)	6 (18.2)
Pancreas texture, number (%)				
Soft	43 (53)	46 (58)	13 (44.8)	12 (36.4)
Medium			12 (41.4)	8 (24.2)
Hard	38 (47)	34 (43)	4 (13.8)	13 (39.4)
Size of pancreatic duct, number (%)				
≤3 mm	30 (37)	33 (41)	11 (37.9)	14 (42.4)
>3 mm	51 (63)	47 (59)	18 (62.1)	19 (57.6)
Length of ICU stay, days	NA	NA	0 (0–0)	0 (0–4)
ICU admission, number (%)	4 (5)	10 (13)	NA	NA
Length of hospital stay, days	11.0 (9.0–19.5)	13.5 (11.5–18.0)	17 ± 15	13 ± 8
Time to functional recovery, days	NA	NA	17 ± 15	13 ± 8
Postoperative pancreatic fistula grade B/C, number (%)	11 (14)	10 (13)	11 (37.9)	7 (21.2)
Biliary leak grade B/C, number (%)	3 (4)	5 (6)	5 (17.2)	3 (9.1)
Post-pancreatectomy haemorrhage grade B/C, number (%)	7 (9)	9 (11)	4 (13.8)	1 (3.0)
Delayed gastric emptying grade B/C, number (%)	9 (11)	11 (14)	10 (34.4)	2 (6.0)
Chyle leak, number (%)	NA	NA	2 (6.9)	1 (3.0)
Reoperation, number (%)	2 (3)	3 (4)	4 (13.8)	5 (15.2)
Readmission, number (%)	6 (7)	5 (6)	5 (17.2)	5 (16.1)
Comprehensive complication index	NA	NA	34.01 ± 23.48	36.45 ± 27.65
Severe postoperative complications, number (%)	18 (22)	19 (24)	NA	NA
Mortality, number (%)	1 (1)	1 (1)	0	3 (9.1%)
Benign histology, number (%)	23 (28)	18 (23)	13 (45.0)	15 (45.5)
Malignant histology, number (%)	58 (72)	62 (78)	16 (55.0)	18 (54.5)
Examined lymph nodes, number (%)	13 (12–16)	13 (11–15)	29 ± 14	26 ± 9
R1, number (%)	3 (4)	3 (4)	3 (18.8)	0

ICU: Intensive Care Unit.

Table 1: **The first two randomized trials comparing open and robotic pancreatoduodenectomy**

opposite, conclusions. Achieving unbiased assessment in RCTs requires defining key outcome metrics and addressing confounding factors such as surgical proficiency, technique, as well as anticipated difficulty level. Resolving these issues is imperative for obtaining reliable data and guiding the future of pancreatic surgery, including investment in robotic training for the newer generations of pancreatic surgeons.

Contributors

Ugo Boggi, Niccolò Napoli and Emanuele Kauffmann equally contributed to this comment.

Declaration of interests

The authors have no interests to disclose.

References

1 Boggi U, Donisi G, Napoli N, et al. Correction to: prospective minimally invasive pancreatic resections from the IGOMIPS registry: a snapshot of daily practice in Italy on 1191 between 2019 and 2022. *Updates Surg*. 2024;76(1):327–328. https://doi.org/10.1007/s13304-023-01709-y.

2 Napoli N, Kauffmann EF, Vistoli F, Amorese G, Boggi U. State of the art of robotic pancreatoduodenectomy. *Updates Surg*. 2021;73(3):873–880. https://doi.org/10.1007/s13304-021-01058-8.

3 Napoli N, Cacace C, Kauffmann EF, et al. The PD-ROBOSCORE: a difficulty score for robotic pancreatoduodenectomy. *Surgery*. 2023;173(6):1438–1446. https://doi.org/10.1016/j.surg.2023.02.020.

4 Zhang T, Zhao ZM, Gao YX, Lau WY, Liu R. The learning curve for a surgeon in robot-assisted laparoscopic pancreaticoduodenectomy: a retrospective study in a high-volume pancreatic center. *Surg Endosc*. 2019;33(9):2927–2933. https://doi.org/10.1007/s00464-018-6595-0.

5 van Hilst J, De Rooij T, Bosscha K, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. *Lancet Gastroenterol Hepatol*. 2019;4(3):199–207. https://doi.org/10.1016/S2468-1253(19)30004-4.

6 Klotz R, Mihaljevic AL, Kulu Y, et al. Robotic versus open partial pancreatoduodenectomy (EUROPA): a randomised controlled stage 2b trial. *Lancet Reg Health Eur*. 2024;39:100864. https://doi.org/10.1016/j.lanepe.2024.100864.

7 Liu Q, Li M, Gao Y, et al. Effect of robotic versus open pancreaticoduodenectomy on postoperative length of hospital stay and complications for pancreatic head or periampullary tumours: a multicentre, open-label randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2024. https://doi.org/10.1016/S2468-1253(24)00005-0.