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ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Michele Ammendola, MD, Research Associate, Surgical Oncologist, Science of Health Department, Digestive Surgery Unit, University of "Magna Graecia" Medical School, Catanzaro 88100, Italy. michele.ammendola@unicz.it

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EDITORIAL

Exploring the landscape of minimally invasive pancreatic surgery: Progress, challenges, and future directions

Greta Donisi, Alessandro Zerbi

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Greta Donisi, Alessandro Zerbi, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele 20090, Milan, Italy

Greta Donisi, Alessandro Zerbi, Department of Pancreatic Surgery, IRCCS Humanitas Research Hospital, Rozzano 20089, Milan, Italy

Corresponding author: Greta Donisi, MD, Academic Fellow, Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, Pieve Emanuele 20090, Milan, Italy. greta.donisi@humanitas.it

Abstract

Minimally invasive surgery (MI) has become the standard of care for many surgical procedures aimed at reducing the burden on patients. However, its adoption in pancreatic surgery (PS) has been limited by the pancreas's unique location and the complexity of the dissection and reconstruction phases. These factors continue to contribute to PS having one of the highest morbidity and mortality rates in general surgery. Despite a rough start, MIPS has gained widespread acceptance in clinical practice recently. Robust evidence supports MI distal pancreatectomy safety, even in oncological cases, indicating its potential superiority over open surgery. However, definitive evidence of MI pancreaticoduodenectomy (MIPD) feasibility and safety, particularly for malignant lesions, is still lacking. Nonetheless, reports from high-volume centers are emerging, suggesting outcomes comparable to those of the open approach. The robotic PS increasing adoption, facilitated by the wider availability of robotic platforms, may further facilitate the transition to MIPD by overcoming the technical constraints associated with laparoscopy and accelerating the learning curve. Although the MIPS implementation process cannot be stopped in this evolving world, ensuring patient safety through strict outcome monitoring is critical. Investing in younger surgeons with structured and recognized training programs can promote safe expansion.

Key Words: Minimally invasive surgery; Minimally invasive pancreatic surgery; Pancreatic surgery; Robotic; Laparoscopic; Pancreaticoduodenectomy; Distal pancreatectomy

Core Tip: Implementation of minimally invasive pancreatic surgery (MIPS) is a process that cannot be stopped. Minimally invasive (MI) distal pancreatectomy is now well-supported by evidence showing its safety and potential superiority over open surgery. Although the feasibility and definitive evidence for MI pancreaticoduodenectomy (MIPD) remain under investigation, high-volume centers have reported promising outcomes. The rise of robotic pancreatic surgery is poised to overcome technical limitations and enhance the transition to MIPD. Ensuring patient safety through rigorous monitoring and structured training of surgeons is crucial for the continued safe implementation of MIPS.

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INTRODUCTION

Minimally invasive surgery (MIS) has become the standard of care for many surgical procedures with the aim of reducing the surgical burden on patients. Diagnostic laparoscopy dates back to the beginning of the 20th century, with the first reports of its application to abdominal surgery in the 1980s[1,2]. The success of the laparoscopic approach can be attributed to its numerous advantages, including reduced pain, shorter hospital stays, faster postoperative recovery, and improved visualization of anatomical secluded areas that would otherwise require larger incisions for proper exposure [3]. However, these advantages come with certain trade-offs, such as diminished dexterity, reduced tactile feedback, and inherent limitations owing to the constrained movement of laparoscopic instruments. These limitations may result in longer operative times for complex procedures than for open surgery[4]. In recent years, robotic surgical platforms have emerged as alternatives to laparoscopy. Robotic surgery has potential advantages, including tremor filtration, enhanced dexterity, greater freedom of movement facilitated by the Endo Wrist system, and superior visualization of the operative field through three-dimensional (3D) imaging. Nonetheless, these benefits need to be carefully balanced against drawbacks, such as the lack of tactile feedback and the substantial costs associated with the initial investment in acquiring the robotic platform and the expenses incurred per operation.

THE CHALLENGE OF MI PANCREATIC SURGERY

The intrinsic complexity of pancreatic surgery (PS) is related to a challenging resection phase owing to the deep location of the pancreas and its close relation to major vascular structures. This difficult reconstruction phase, bearing the risk of postoperative pancreatic fistula and its dreadful-related complications, has hampered the widespread implementation of MIPS.

Moreover, similar to any technical revolution, MIS requires dedicated learning time, with the length of the learning curve proportional to the complexity of the procedure to be performed. The relative rarity of pancreatic diseases and the complexity of most cases make the process of achieving proficiency a long and difficult path accompanied by a surge in morbidity and mortality[5].

Despite initial doubts and challenges, two pioneering surgeons reported the first MI pancreatic surgical procedure in the early ’90s. In 1992, Gagner performed the first laparoscopic pancreaticoduodenectomy (LPD), and although the 10-h operation was deemed feasible, no advantage over open surgery was noted[6]. In 1996, Cuschieri reported the first five laparoscopic distal pancreatectomies (LDP), concluding that the laparoscopic approach appears favorable and may also expedite postoperative recovery and shorten the length of stay[7].

Pancreatic surgeons have validated these initial findings in recent years. This first exploratory phase, facing several detractors, lasted a few years until recent technological advances improving laparoscopic instruments, along with the implementation of robotic platforms, increased the number of reports on MIPS worldwide.

MI DISTAL PANCREATECTOMY

Evidence in MI distal pancreatectomy

Compared with other pancreatic resections, notably PD, distal pancreatectomy (DP) appears to be a relatively easier procedure owing to its less complex resection phase, which is related to the more favorable anatomy of the left pancreas and the absence of a reconstruction phase. Therefore, it is not surprising that the first widespread attempts at MIPS focused on MIDP. Starting in 2004, several reports became available in the literature supporting the feasibility and safety of this procedure. By 2012, the first published meta-analysis, which included approximately 2000 patients, concluded that the laparoscopic technique had advantages over the open technique regarding blood loss and length of hospital stay[8,9]. Despite the excitement surrounding MIDP, real-world implementation of the technique progressed slowly initially, with MIDP used in only 30% of cases in the United States between 2010 and 2011[10] and a similar proportion reported by

European surgeons in a 2014 survey[11]. Nevertheless, reports on MIDP experience increased exponentially in later years, with approximately 30 reviews and meta-analyses comparing MIDP with open surgery[12]. Despite the growing body of evidence and individual perceptions among pancreatic surgeons worldwide, high-level evidence demonstrating incontrovertibly superiority of MIDP was still lacking. In recent years, efforts have been made to complete three multicenter randomized clinical trials (RCTs) (Table 1). The LEOPARD[13] and LAPOP[14] trials, published in 2019 and 2020, respectively, compared LDP and open DP (ODP) regardless of indication. They concluded that despite a comparable complication rate, LDP was associated with a reduced time to functional recovery and a shorter length of stay. In 2019, the Miami International evidence-based guidelines strongly recommended that MIDP for benign and low-grade malignant tumors should be considered superior to ODP for its advantages, including a shorter hospital stay, reduced blood loss, and equivalent complication rates[13-15]. Conversely, the authors did not draw definitive conclusions regarding the superiority of MIDP in pancreatic cancer. Despite data from systematic reviews and meta-analyses suggesting comparable oncological outcomes regarding resection margin, 30-day mortality, disease-free survival, and overall survival between MIDP and ODP, some authors raised concerns about the appropriateness of MIDP in an oncological setting due to a decreased number of harvested lymph nodes relative to ODP[16–22]. To address these concerns, the DIPLOMA[23] trial focused on MIDP for pancreatic cancer and concluded that MIDP was non-inferior to ODP in patients with resectable pancreatic cancer. In 2023, the Brescia internationally validated European guidelines on MIPS[24], reflecting current evidence, concluded that MIDP should be considered superior to the open approach in cases of benign and premalignant left pancreatic lesions and should be considered as an alternative approach in the management of resectable pancreatic ductal adenocarcinoma (PDAC) in the pancreatic body and tail when performed by experienced surgeons in high-volume centers. Conversely, to date, reports recommending the use of the MI approach for pancreatic cancer requiring vascular resection are lacking[15]. A snapshot of the current use and the process of implementation of MIDP over the years can be extrapolated from the Dutch experience, which reports how the proportion of MIDP moved from 42% in 2014 to 66% in 2021, with a decrease in blood loss and conversion rates and an increased proportion of oncological resections[25,26].

Laparoscopic vs robotic DP

Once the role of the MI approach in DP is consolidated, it is necessary to clarify the roles of the different MI platforms used. Currently, the laparoscopic technique is the most widely adopted technique in the context of DP; however, reports on robotic DP (RDP) have increased in recent years. According to Korrel *et al*[26], the proportion of DP performed using a robotic approach increased from 5.5% in 2014 to 29.7% in 2021. A report from Italian group of MI pancreatic surgery, the Italian registry of MIPS, showed that 30% of MIDP in Italy were performed robotically, with the proportion increasing to 55% in cases of spleen-preserving DP[27]. RCTs answering the question of superiority are still lacking, with the Miami guidelines[15] concluding that both represent viable options with preferences based on the surgeons' experience and local resources. Several systematic reviews and meta-analyses reported similar results for the two approaches; however, RDP appeared to be associated with a lower conversion rate, higher spleen preservation rate, and higher lymph node yield than LDP in patients with PDAC[28–32]. The main concern was the high cost of robotic platforms. Cost analysis in surgery remains challenging due to the complex calculations related to the participation of direct and indirect costs, differences in healthcare systems worldwide, and inter-hospital variability. Moreover, in the case of a robotic platform, it is challenging to include the acquisition and maintenance costs of the robot, which are amortized at the hospital level, owing to the multidisciplinary use of the device. Partelli *et al*[33] showed that MIDP was a more cost-effective approach compared with open surgery due to the decreased expenses related to a shorter hospital stay and faster return to work, with LDP protecting against high costs. Conversely, Spanish and French reports showed that the total cost of robotic and laparoscopic procedures was comparable[34,35]. An RCT is needed to evaluate whether the robotic approach for DP confers a real clinical advantage over laparoscopy, whether the situation changes in the case of spleen preservation, and whether the alleged advantages provided by the robotic approach may overcome the impact of increased cost. To address this unanswered question, the DIPLOMA 3 trial, starting soon, will compare LDP and RDP in benign and low-grade malignant tumors with the aim of demonstrating the non-inferiority of the laparoscopic approach.

Long-term results and quality of life

After years of MIDP implementation, the first reports on long-term outcomes and quality of life (QoL) evaluation of the MI approach are now available. Following up on patients enrolled in the LEOPARD clinical trial, Korrel *et al*[36] reported no differences in quality-adjusted life years, as measured using the EQ-5D, QLQ-C30, and PAN26 questionnaires, and QoL between the MI and open surgery groups, despite MIDP scoring higher in cosmetic satisfaction. Johansen *et al*[37] reported significant differences in favor of MIDP for emotional functioning, pain, insomnia, pancreatic pain, future worries, and indigestion, despite higher satisfaction with healthcare for ODP in patients enrolled in the LAPOP trial.

MINIMALLY-INVASIVE PD

Evidence in MIPD

Although the fundamental role of MIDP is now incontrovertible, the same cannot be said for MIPD. PD remains the most complex pancreatic operation, with a challenging demolition phase due to the anatomy of the pancreatic head and also a complex reconstructive phase associated with a high risk of dreadful complications and mortality, approximately 40% and 5%, respectively, even in high-volume centers[38]. After the first exploratory reports on LPD in the late 20th century proved its feasibility, Gagner[39] concluded that it appeared not to provide any advantage over the open approach,

Table 1 Minimally invasive *vs* open distal pancreatectomy published randomized clinical trials

	de Rooij T 2019 (LEOPARD), Lps *vs* Open[11]			Björnsson 2020 (LAPOP), Lps *vs* Open[14]			Korrel 2023 (DIPLOMA), Lps/Robotic *vs* Open[23]		
Enrollment period	2015-2017			2015-2019			2018-2021		
	MI	O	*P* value	MI	O	*P* value	MI	O	*P* value
n	51	57		29	29		114	110	
OT (minute)	217	179	0.005	120	120	NS	240	209	0.01
EBL (mL)	150	400	0.001	50	100	0.018	200	200	0.06
CR-POPF (%)	39	23	0.07	31	37	NS	21	17	NS
DGE (%)	6	19	0.04	3	17	NS	2	3	NS
PPH (%)	4	4	NS	3	0	NS	2	3	NS
SSI (%)	4	5	NS				5	5	NS
Reintervention (%)	2	5	NS				17	17	NS
Severe morbidity (Clavien-Dindo ≥ 3) (%)	25	38	NS	14	27	NS	19	20	NS
LOS (days)	6	8	0.004	6	8	0.008	7	7	NS
Readmission (%)	29	25	NS	4	6	NS	22	21	NS
90-day mortality (%)	0	2	NS	0	1	NS	1	2	NS
R0 (%)							83	76	0.039
N harvested Lymph nodes (*n*)							22	23	NS

OT: Operative time; EBL: Estimated blood loss; CR-POPF: Clinically relevant-post-operative pancreatic fistula; DGE: Delayed gastric emptying; PPH: Post-pancreatectomy hemorrhage; SSI: Surgical site infection; LOS: Length of stay.

hindering the widespread implementation of MIPD for over a decade. Since the late 2000s, reports on monocentric, small cohorts of patients who underwent MIPD have been published worldwide, showing conflicting data on the safety of the procedure. Adam *et al*[40], in a United States nationwide analysis including 7061 patients, with 52% of patients operated in low-volume centers, showed that in the real world, MIPD was performed in only 14% of cases, and the MI approach was associated with a higher mortality rate (5.1% *vs* 3.1%) without any reported advantage. Dokmak *et al*[41] and Chopinet *et al*[42] provided somewhat similar results, reporting a higher rate of severe morbidity, grade C postoperative pancreatic fistula, post-pancreatectomy hemorrhage, and reoperation in cases of LPD. Conversely, promising reports from high-volume centers showed morbidity, mortality, number of retrieved lymph nodes, and R0 margins in cases of malignancy were comparable to those in open procedures with reduced intraoperative blood loss, wound infection rate, and length of hospital stay at the price of a significantly longer operative time[43–49]. Nevertheless, the Pan-European 2014 survey reported that MIPD was performed by only 21% of surgeons, with only 4% performing more than 10 procedures[11]. RCTs were initiated to provide a definitive answer regarding the safety of MIPD and determine whether it can provide clinically significant advantages (Table 2). The first two available RCTs, the PLOT[50] and PADULAP[51] trials provided reassuring results on the safety of LPD with comparable perioperative outcomes, confirming a reduced length of stay in the case of LPD despite a longer operative time. Moreover, Poves *et al*[51] found a significant reduction in major morbidity and re-intervention rates when a laparoscopic approach was used. However, the third published trial, LEOPARD 2[52], a multicenter study including four centers performing ≥ 20 PDs annually and with a previous experience of 20 LPDs before trial participation, was prematurely terminated for safety concerns due to an unexpected mortality rate of 10% in the LPD group compared to 2% in the open group. The authors' explanation for this worrisome outcome was the relatively scarce center experience in complex laparoscopic procedures and LPD before the start of the trial. This raises serious questions about the actual length of the learning curve and patient safety during this relatively long phase.

To address these concerns, the Miami international guidelines[15] concluded that insufficient data were available to recommend MIPD over OPD and that this procedure should be limited to surgeons in high-volume centers to minimize risk. Cases should be collected from national and international registries to monitor outcomes and ensure patient safety. The most recent and largest trial by Wang *et al*[53], which included 656 patients randomly assigned to LPD or OPD, concluded that in highly experienced surgeons, LPD was associated with a shorter length of stay and similar short-term morbidity and mortality rates compared to OPD. Nonetheless, the clinical benefit of LPD compared with that of OPD is marginal despite extensive procedural expertise. Despite the comforting safety results reported by expert centers, the general perception of MIPD remains that it is a niche procedure with little measurable advantage. A 2023 international survey reported that 70% of participants considered OPD to be superior to MIPD. Nevertheless, the proportion of PD

Table 2 Minimally invasive *vs* open pancreaticoduodenectomy published randomized clinical trials

	Palanivelu 2017 (PLOT), Lps *vs* Open[50]			Poves 2018 (PADULAP), Lps *vs* Open[51]			Van Hilst 2019 (LEOPARD 2), Lps *vs* Open[52]			Wang 2021, Lps *vs* Open[53]			Klotz 2024 (EUROPA), Robotic *vs* Open[62]			Liu 2024, Robotic *vs* Open[63]		
Enrollment period	2013-2015			2013-2017			2016-2017			2018-2019			2020-2022			2022		
	MI	O	p	MI	O	p	MI	O	p	MI	O	p	MI	O	p	MI	O	p
n	32	32		34	32		50	59		297	297		29	33		81	80	
OT (minute)	359	320	0.041	486	365	0.001	410	274	0.001	325	300	0.001	431	367	0.021	245	298	0.001
EBL (mL)	250	401	0.001				300	450	NS	200	300	0.001	742	814	NS	75	150	0.001
CR-POPF (%)	6	12	NS	13	28	NS	28	24	NS	10	11	NS	38	21	NS	14	13	NS
Bile leakage (%)	9	6	NS	3	10	NS	12	10	NS	13	14	NS	17	9	NS	16	23	NS
Gastro/duodenojejunal fistula (%)				0	0	NS	4	0	NS									
Chyle leak (%)							4	14	0.09				7	3	NS			
DGE (%)	16	22	NS	9	24	NS	34	20	NS	30	32	NS	34	6	0.005	25	33	NS
PPH (%)	9	12	NS	9	21	NS	10	14	NS	13	11	NS	14	3	NS	14	19	NS
SSI (%)	12	25	0.015				4	14	0.09				10	10	NS	10	11	NS
Reintervention (%)	3	3	NS	3	17	0.06	12	6	NS	3	4	NS	14	15	NS	3	4	NS
Severe morbidity (Clavien-Dindo ≥ 3) (%)	9	12	NS	16	38	0.048	50	39	NS	29	23	NS				22	24	NS
LOS, days	7	13	0.001	13.5	17	0.024	11	10	NS	15	16	0.02	17	13	NS	11	13.5	0.029
Readmission (%)	6	9	NS	22	14	NS	16	20	NS	3	2	NS	17	16	NS	7	6	NS
90-day mortality (%)	3	3	NS	0	2	NS	10	2	NS	2	2	NS	0	9		1	1	NS
R0 (%)	97	94	NS	60	52	NS	82	76	NS	98	97	NS	80	100	NS	96	96	NS
N harvested Lymph nodes (*n*)	18	17	NS	15	21	NS	11	11	NS	12	13	NS	29	26	NS	13	13	NS

OT: Operative time; EBL: Estimated blood loss; CR-POPF: Clinically relevant-post-operative pancreatic fistula; DGE: Delayed gastric emptying; PPH: Post-pancreatectomy hemorrhage; SSI: Surgical site infection; LOS: Length of stay.

performed MI increased from 29% to 45.7% in 5 years, with an associated relative increase in robotic procedures over laparoscopic procedures[54].

Role of robotic PD

The development and widespread diffusion of robotic approaches have modified the role of MIPD. Certainly, the robotic approach provides some advantages in pancreatic procedures involving complex anastomoses and a more difficult demolition phase owing to its benefits, such as better dexterity, higher degrees of freedom, and better operative field visualization with 3D imaging. A recent meta-analysis observed a lower conversion rate and, in some reports, a lower estimated blood loss and a higher number of harvested lymph nodes in the case of RPD relative to LPD; however, most studies failed to demonstrate the strict superiority of one approach over the other, showing similar postoperative outcomes[55–60]. Despite the lack of high-level evidence proving the superiority of RPD over LPD, we are currently observing a net shift toward robotic approaches. The Italian experience shows that, excluding hybrid procedures, more than 60% of MIPD in Italy are performed robotically, with a decrease in the major complication rate and a trend toward postoperative mortality reduction[27]. In the Netherlands, the Dutch LEOPARD 2 experience put a brake on the diffusion of LPD in the nation and promoted the development of training programs for RPD, with the outcomes of the LAELAPS-3 program demonstrating that the implementation of RPD is feasible and safe in expert centers after appropriate training [61].

The recently published Europa trial[62] and the Chinese trial by Liu *et al*[63] compared RPD and OPD and supported the safety of RPD, excluding increases in intraoperative adverse events, postoperative complications, and mortality. Liu *et al*[63] also reported a decrease in operative time, estimated blood loss, and postoperative length of stay. Conversely, the Europa trial showed an increase in clinically relevant postoperative pancreatic fistula (CR-POPF) and delayed gastric emptying rates, in addition to increased operative time and higher cost. A possible explanation for these controversial results may be the lack of patient selection for MIPD, both regarding patients' performance status and the intrinsic complexity of the surgery, which required vascular reconstruction in 17% of cases and open conversion in 23% of cases.

The preliminary results of the DIPLOMA 2 trial[64], the most recent pan-European multicenter RCT, were presented at the International Hepato-Pancreato-Biliary Association meeting in Cape Town in May 2024. A trial comparing MIPD and OPD confirmed a predilection for the robotic approach, as approximately 90% of MI procedures were performed robotically. Moreover, short-term outcomes appeared favorable for MIPD, with a comparable Charlson Comorbidity Index and mortality rate among groups and a significantly decreased CR-POPF rate, surgical site infection rate, shorter length of stay, and time to functional recovery in patients with MIPD. Although the trial was not designed to evaluate the robotic approach exclusively, the percentage of cases who preferred RPD and the favorable outcomes confirmed that the surgical world was leaning toward the robotic approach.

Should MIPD be limited to a few centers?

The correlation of outcomes and center volume in PS is a well-recognized paradigm and has gained even greater relevance in the context of MIPD, where it has been shown that the learning curve of RPD ranges from 20 to 40 procedures, but proficiency is reached only after over 200 operations[65–69]. Accordingly, the Miami and Brescia guidelines have recognized that the minimum cutoff to maintain safe implementation is at least 20 MIPD performed yearly. The aforementioned DIPLOMA 2 trial, which included 288 patients from 14 centers across six countries and provided a reliable picture of the current European situation, utilized stricter criteria for center inclusion, defined as a center experience of at least 30 MIPD/year and a surgeon experience of at least 60 MIPD and 60 OPD, reflecting the outcomes of a few excellent referral centers. Considering the robust evidence of the volume-related outcomes in PS and the added complexity in the case of the MI approach, we should, on the one hand, rely on data from these centers to draw definitive conclusions on the feasibility and safety of MIPD. On the other hand, the generalizability of these findings should remain limited to high-volume centers to guarantee adequate outcomes for MIPD. In addition, it should be noted that patient selection for MI plays a crucial role in ensuring optimal intraoperative and postoperative outcomes[70].

CONCLUSION

After years of experimentation and learning, with all recent technological advances, MIPS needs to be considered. We have already reached a phase in which an MI approach is considered the gold standard for DP. Despite the growing body of evidence supporting the feasibility and safety of MIPD, because of the limitations of the available literature, such as pooling together LPD and RPD, the lack of patient selection, and the non-completion of the learning curve of some of the operating surgeons, no veritable evidence promoting MIPD superiority over open surgery or the superiority of robotic *vs* laparoscopic approaches is available. Nevertheless, the implementation of MIPD is flourishing worldwide, and this process cannot be stopped. With younger generations of surgeons being exposed to laparoscopic and robotic platforms from the early stages of their careers and receiving training encompassing simulation components, biotissue practice, video library reviews, and on-the-field practice, it is reasonable to expect that these acquired skills will also be applied to the field of PS. Nevertheless, in this evolving world, it is crucial to carefully assess and guide the process of MIPS diffusion, keeping in mind that the patient's safety is critical and cannot be "sacrificed" to progress development. Scientific societies, national and international registries, and field experts must develop strategies to expand MIPS safely. Investing in the training of younger surgeons through structured and recognized programs designed to minimize the learning curve and ensure safe implementation may lead to a paradigm shift in which we will not select patients who may undergo MIPS; conversely, we will carefully select patients who may benefit from an open approach.

FOOTNOTES

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Country of origin: Italy

ORCID number: Greta Donisi 0000-0002-5873-6577; Alessandro Zerbi 0000-0002-9176-0448.

Corresponding Author's Membership in Professional Societies: European Pancreatic Club, 1798; Associazione Italiana Studio Pancreas.

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