Mini-Review

Current status and future perspectives of minimally invasive and open radical antegrade modular pancreatosplenectomy for pancreatic ductal adenocarcinoma: a review

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Abstract: Radical antegrade modular pancreatosplenectomy (RAMPS) is a commonly used standardized technique to obtain sufficient tangential retroperitoneal resection margins for left-sided pancreatic ductal adenocarcinoma (PDAC) during open surgery. Despite recent developments in minimally invasive (MI) surgery, evidence of MI RAMPS over open RAMPS for PDAC is still lacking. Although the recent Miami International Evidence-based Guidelines on MI Pancreas Resection have stated that MI distal pancreatectomy for PDAC appears to be a safe, feasible, and oncologically efficient, there has been no statement regarding the adoption of RAMPS for PDAC. Herein, we review the current evidence of RAMPS for left-sided PDAC, focusing on the comparison between MI and open RAMPS. Indications and patient selection should be carefully determined, especially when performing MI RAMPS. Although data on MI RAMPS over open RASMPS are limited, the safety and feasibility of MI RAMPS have been reported from retrospective series. Considering favorable outcomes following MI RAMPS compared with open RAMPS, the use of MI RAMPS should be expanded in well-selected patients with PDAC. However, further high-level evidence is needed to confirm the efficacy of MI and open RAMPS for PDAC. The results of current ongoing randomized controlled trials investigating the efficiency of MI RAMPS may determine the future direction of RAMPS for PDAC.

Keywords: Distal pancreatectomy; laparoscopic; robotic; pancreatic ductal adenocarcinoma (PDAC); radical antegrade modular pancreatosplenectomy (RAMPS)

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Introduction

The incidence and mortality of pancreatic ductal adenocarcinoma (PDAC) are increasing annually worldwide (1). The Global Cancer Statistics 2020 has reported almost as many mortality (466,000) as new cases (496,000) for PDAC in 2020, with almost as many related deaths as incidence (2). Although PDAC is usually diagnosed at an advanced stage due to the complex anatomical location of the pancreas, complete surgical resection remains the mainstream treatment for PDAC (1). In fact, Bengtsson *et al.* found that 5-year survival rate in surgically resected patients increased from 1.5% in 1975 to 17.4% in 2011 for all stages of pancreatic cancer (3). Among several factors predicting

oncological outcomes, R0 resection may be important for improving survival after resection for PDAC (4). Radical antegrade modular pancreatosplenectomy (RAMPS) was developed by Strasberg *et al.* to obtain sufficient tangential retroperitoneal resection margins for left-sided PDAC (5). Although the role of RAMPS is still under debate (6), further discussion is required in the era of minimally invasive (MI) surgery. Herein, we aimed to review the current status of RAMPS for left-sided PDAC, focusing on the comparison between MI and open RAMPS. Moreover, the future perspectives of MI and open RAMPS are discussed.

RAMPS

The RAMPS technique is commonly used to achieve a negative dissection margin for left-sided PDAC during open surgery. In general, the retroperitoneal dissection line can be divided into three levels during distal pancreatectomy (DP) (7). Standard DP facilitates retroperitoneal dissection in front of the anterior surface of Gerota's fascia (level 1). In contrast, the retroperitoneal dissection line of RAMPS is posterior to the anterior surface of Gerota's fascia and above (level 2, anterior RAMPS) or behind (level 3, posterior RAMPS) the adrenal gland. The original RAMPS involves retroperitoneal dissection from the medial to lateral side (5). With respect to MI RAMPS, the adoption of medial to lateral dissection, as described in the original RAMPS, has often been reported to be challenging, particularly for laparoscopic surgery due to the superiority of caudal approach to medial approach in laparoscopic surgery (8). However, robotic surgery can overcome this issue, including technical difficulties, in laparoscopic RAMPS. Recently, the efficacy of robotic RAMPS using the supracolic anterior superior mesenteric artery approach was reported, showing a medial approach similar to the original RAMPS for PDAC (7).

Indication of MI RAMPS

The recent Miami International Evidence-based Guidelines on MI Pancreas Resection have stated that MIDP for PDAC appears to be a safe, feasible, and oncologically efficient in experienced hands with the GRADE recommendation of 2B (benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks, and burdens) (9). However, there has been no statement regarding the adoption of RAMPS for PDAC.

Patient selection should be carefully determined when performing MI RAMPS for PDAC patients. The Yonsei criteria are commonly used for patient selection in MI RAMPS (10). The Yonsei criteria for patient selection include the following conditions: (I) tumor confined to the pancreas; (II) intact fascial layer between the distal pancreas and left adrenal gland and kidney; and (III) tumor located at least 1–2 cm away from the celiac axis. In contrast, an indication for MI RAMPS for tumors involving major vessels, such as the celiac axis, mesenteric artery, or portal vein, should be carefully considered. Although the feasibility of MI RAMPS with vascular resection has been reported (11,12), there is no evidence regarding the use of vascular resection in MIDP according to the Miami guidelines (9).

In our opinion, the cancer which is confined to the pancreas and is no more than 4 cm across (T1–T2) would be a good indication for MI RAMPS. MI approach for the tumor confined to the pancreas with bigger than 4 cm (T3) could be applicable. However, the cancer growing outside the pancreas and into nearby major vessels (T4) should be treated with open approach.

Comparison of MI *vs.* open RAMPS

Following a literature search of PubMed Central, seven studies investigating outcomes between MI and open RAMPS were identified (*Table 1*). The first retrospective study [Lee *et al.* (10)] was conducted to compare the outcomes of patients undergoing MI (n=12) and open (n=78) RAMPS for treating left-sided PDAC. After the propensity score matching analysis, hospital stays in the MI group were shorter than those in the open group (12.7 *vs.* 22.1 days, P=0.05). However, other patient characteristics and postoperative outcomes were comparable between the groups. Moreover, the safety and feasibility of laparoscopic RAMPS compared with the open approach for selected patients with PDAC have been reported, showing comparable postoperative and oncological outcomes in retrospective studies from Asian countries (13-17). In a study by Rosso *et al.* (11), laparoscopic RAMPS was performed with (n=4) or without (n=13) vascular resection and open RAMPS (n=6). The authors concluded that laparoscopic RAMPS with vascular resection in selected patients is safe and feasible and could lead to results comparable to open RAMPS in terms of postoperative and oncological outcomes. Regarding neo- and adjuvant therapy, neoadjuvant therapy was not performed in most of

Table 1 Summary of literatures reporting outcomes between minimally invasive and open radical antegrade modular pancreatosplenectomy for pancreatic cancer

Author	N	Neoadjuvant therapy (%)	Operative time (min)	Blood loss (mL)	Complication (%)	Mortality (%)	N of LND	LNM (%)	R0 resection (%)	Adjuvant therapy (%)	Long-term outcome
Lee *et al.* (10)	12 MIS	2 (16.6) CRT	324.3 (154.2)	445.8 (346.1)	3 (25.0)	0 (0)	10.5 (7.1)	3 (25.0)	12 (100.0)	7 (58.3)	5-year OS: 55.6%
	78 Open	17 (21.8) CRT	270.1 (140.4)	669.5 (776.1)	29 (37.2)	2 (2.6)	13.8 (11.1)	37 (47.4)	67 (85.9)	55 (70.5)	5-year OS: 30.0%
Zhang *et al.* (13)	22 MIS	0 (0)	188 (39.0)	210 (130.0)	NA	0 (0)	11.2 (4.6)	8 (36.0)	20 (91.0)	22 (100.0)	OS: 29.6 (3.7) months
	76 Open	0 (0)	160 (35.0)	240 (120.0)		0 (0)	14.4 (5.5)	31 (41.0)	66 (87.0)	76 (100.0)	OS: 27.6 (2.1) months
Zhang *et al.* (14)	25 MIS	0 (0)	212.2 (66.3)	402 (258.8)	4 (16.0)	0 (0)	15.8 (6.7)	NA	23 (92.0)	23 (92.0)	OS: 24.5 months
	23 Open	0 (0)	203.1 (39.7)	506.5 (418.4)	3 (13.0)	0 (0)	18.2 (8.0)		21 (91.0)	19 (82.6)	OS: 28.7 months
Rosso *et al.* (11)	17 MIS	4 (23.5) CT	395–412	NA	9 (52.9)	0 (0)	30–35	15 (88.0)	17 (100.0)	NA	NA
	6 Open	6 (100.0) CT	450		3 (50.0)	0 (0)	37	6 (100.0)	6 (100.0)		
Kawabata *et al.* (15)	30 MIS	0 (0)	389 [280–576]	18 [0–180]	4 (13.3)	0 (0)	18 [5–51]	NA	29 (96.7)	20 (66.7)	2-year OS: 90.9%
	33 Open	0 (0)	382 [256–674]	215 [30–1,030]	6 (18.2)	0 (0)	25 [7–80]		30 (90.9)	28 (84.8)	2-year OS: 78.9%
Huang *et al.* (16)	20 MIS	0 (0)	273.8 (90.3)	252.5 (198.3)	5 (25.0)	0 (0)	9.6 (6.4)	6 (30.0)	20 (100.0)	14 (70.0)	2-year OS: 50.2%
	31 Open	0 (0)	264.3 (77.1)	472.6 (428.0)	13 (41.9)	0 (0)	12.8 (5.8)	12 (39.0)	30 (97.0)	25 (80.6)	2-year OS: 38.3%
Hirashita *et al.* (17)	19 MIS	0 (0)	397 (78.0)	299 (237.0)	NA	0 (0)	14 (17.0)	5 (26.0)	17 (89.0)	13 (68.4)	NA
	31 Open	0 (0)	319 (80.0)	576 (78.0)		0 (0)	19 (18.0)	16 (52.0)	27 (97.0)	21 (67.7)	

Values are shown as mean (standard deviation) or median [range]. N, number; LND, lymph node dissection; LNM, lymph node metastasis; MIS, minimally invasive surgery; OS, overall survival; CRT, chemoradiotherapy; CT, chemotherapy; NA, not available.

included studies. In contrast, adjuvant chemotherapy was usually performed.

Based on limited data from retrospective series, we performed meta-analyses to investigate the surgical and oncological outcomes of MI and open RAMPS for treating left-sided PDAC (18). The results of the meta-analyses comparing MI (n=145) with open RAMPS (n=278) demonstrated significantly longer operative time [mean difference (MD) =30.0, 95% confidence interval (CI) =7.58–52.4, P=0.009] and less estimated blood loss (MD =−163, 95% CI = −293 to −33.4, P=0.01) in the MI approach than in the open approach. Regarding pathological outcomes, the results revealed no significant difference in R0 resection rates [odds ratio (OR) =1.78, 95% CI =0.76–4.15, P=0.18], but significantly smaller numbers of dissected lymph nodes (MD =−3.14, 95% CI =−4.75 to −1.53, P<0.001) and lymph node metastases (OR =0.55, 95% CI =0.31–0.97, P=0.04). The findings might have been affected by the selection bias.

With respect to the long-term outcomes, data on the long-term outcomes comparing MI and open RAMPS for PDAC are lacking (*Table 1*). Therefore, meta-analyses for long-term outcomes were not performed. Only a study by Lee *et al.* (10) reported 5-year overall survival, showing 55.6% in the MI RAMPS group and 30.0% in the open group (P=0.02). However, no significant difference was observed in the median overall survival between the MI and open groups that met the Yonsei criteria (60.0 *vs.* 60.7 months, P=0.62). Other studies with short-term follow-up suggested comparable long-term outcomes between the groups (13-16).

Learning curve of RAMPS

The evaluation of the learning process is important for guiding surgical training and expanding the application of the procedure. However, data on the learning curve of MI and open RAMPS are limited. Recently, Li *et al.* (19) investigated the learning curve of robotic RAMPS, assessing the learning curve of 100 robotic posterior RAMPS. Cumulative sum analysis revealed that the inflection points of the learning curve were 25 and 65 cases. The results found that the operation time was relatively long in the initial learning phase (case 1–25), reached a plateau phase (case 26–65) (270.0 *vs.* 220.0 min, P<0.01), and decreased significantly in the maturation phase (cases 66–100) (P<0.01). In addition, estimated blood loss decreased in the maturation phase compared with the initial learning phase (150.0 *vs.* 245.0 mL, P<0.01). However, there were no significant differences in the conversion rate, complications, or mortality among the three phases. The authors demonstrated the safety and feasibility of robotic RAMPS even during the initial learning phase. Considering the limited data regarding the learning curve of MI or open RAMPS, further studies should be conducted to evaluate the learning curve of this complex procedure.

Future perspectives

Despite recent increasing evidence on MIDP, the evidence of MI RAMPS over open RAMPS remains controversial. Considering favorable outcomes following MI RAMPS compared with open RAMPS, the use of MI RAMPS should be expanded in well-selected patients with left-sided PDAC. To date, two randomized controlled trials (RCTs) comparing MI and open DP have been published, demonstrating that MIDP may be regarded as the preferred option for DP (20,21). However, no RCT has been published comparing the outcomes of MI and open RAMPS for PDAC. To our knowledge, there are ongoing RCTs in this field. The open distal pancreatectomy for pancreatic ductal adenocarcinoma (DIPLOMA) trial, organized by the European Consortium on MI Pancreatic Surgery, was designed to investigate the non-inferiority of MIDP *vs.* open DP in terms of the microscopic radical resection rate of PDAC in an international setting (22). Another RCT was performed to evaluate the surgical and oncological outcomes of robotic RAMPS over robotic standard DP for PDAC (23). Moreover, there are actively recruiting RCTs comparing laparoscopic and open DP for PDAC (NCT03792932 and NCT03957135). The results of these ongoing RCTs should help determine the most beneficial approach for individual patients with PDAC.

In the era of multidisciplinary treatment for PDAC, neoadjuvant therapy has been standard treatment for borderline resectable and locally advanced PDAC, even for resectable PDAC (24). We suggested that the increased chance of effective neoadjuvant therapy might contribute to expanding an indication of MI-RAMPS, despite lacking the evidence on this issue.

Conclusions

RAMPS is a commonly used standardized technique for left-sided PDAC in open surgery. The safety and feasibility of the MI RAMPS have also been reported. However, evidence of MI RAMPS over open RAMPS for PDAC is

still lacking. The results of current ongoing RCTs may determine the future direction of RAMPS for PDAC.

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