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Perioperative Outcomes and Surgical Indications of Minimally Invasive Pancreatectomy for Solid Pseudopapillary Tumor in Pediatric Patients

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: We evaluated perioperative and long-term outcomes of minimally invasive surgery (MIS) and established indications of MIS in solid pseudopapillary tumor (SPT) in pediatric patients.
Methods: From October 1992 to April 2018, 66 patients (age, <18 years) diagnosed with SPT underwent either open pancreatectomy (OP) or MIS. Variables including postoperative complications and recurrence rates were retrospectively analyzed.
Results: Thirty-five patients underwent open surgery and 31 underwent laparoscopic/robotic surgery. Mean tumor size in MIS was significantly smaller than that in OP (4.3±1.8 cm vs. 7.6±3.5 cm, p=0.005). There were 4 cases of open conversion from laparoscopic surgery because of vessel encasements (n=2), bleeding (n=1), and pancreatic ductal injury (n=1). Solitary pseudopapillary carcinoma was diagnosed in 6 patients. Recurrence was observed in 3 and 1 patients who underwent OP and MIS, respectively (p=0.634). Tumor size, mass size/abdominal diameter (MS/AD) ratio, and degree of the portal or superior mesenteric vein involvement were the most important indications for MIS.
Conclusion: MIS is being widely used in pediatric surgeries with increased expertise and safety, especially in pancreatic diseases. Careful patient selection for MIS in regards with parameters such as MS/AD ratio and vessel abutment might be a feasible choice.

Keywords: Solid pseudopapillary tumor; Minimally invasive surgery; Laparoscopic surgery; Robotic surgical procedures

INTRODUCTION

Since the first description of solid pseudopapillary tumor (SPT) by Frantz in 1959, SPT is considered a low-grade malignant neoplasm that predominantly affects adolescent girls and young women [1,2]. Although SPT is rare, its incidence has been steadily increasing for the last two decades [3-5]. SPT accounts for approximately 1%–3% of all primary exocrine pancreatic tumors [6-8] and classically presents as a solitary, large, well-demarcated lesion which can be purely cystic, solid, or mixed in ultrasonography or computed tomography (CT) [9]. These neoplasms rarely metastasize, with an incidence of 9%–15%. Common sites include the liver, peritoneum, greater omentum, and regional lymph nodes [3,10].

The mainstay treatment of SPT in pediatric patients is surgical resection with excellent prognosis [3,6,11]. Surgical plans will vary according to the tumor location. Pancreaticoduodenectomy (PD) or pylorus-preserving pancreatoduodenectomy (PPPD) is performed for pancreatic head tumors and distal pancreatectomy (DP) for pancreatic body or tail tumors. Furthermore, enucleation may be a treatment option for biopsy-proven SPT without main pancreatic duct involvement [12,13].

Open pancreatectomy (OP) is still primarily considered in large tumors since huge SPT can abut nearby structures obscuring dissection. However, with increasing expertise and feasibility in the era of minimally invasive surgery (MIS), laparoscopic pancreatectomy (LP) is widely and increasingly performed in pediatric patients [14-17]. However, pediatric patients with large tumor size should be carefully selected for MIS because of the high chance of open conversion due to bleeding, vessel invasion and comparatively small abdominal cavity. Currently, evidence and guidelines that support the feasibility and safety of MIS in pediatric patients are limited.

In this study, we aim to evaluate the perioperative and long-term outcomes of MIS and to establish indications of MIS in SPT in pediatric patients.

METHODS

From October 1992 to April 2018, 66 patients (age, <18 years) diagnosed with SPT underwent either OP or MIS. We retrospectively reviewed patient's clinical characteristics, surgical and pathologic data, and surgical outcome from medical records. This study reviewed by Institutional Review Board of Asan Medical Center (approval number: 2018-1317). SPT had been diagnosed pathologically on the basis of gross and microscopic appearances of each tumor. In addition, all specimens had been assessed through immunohistochemical staining, including staining with antibodies against beta-catenin, E-cadherin, and synaptophysin, to confirm the diagnosis. Data variables included patient demographics such as age and sex, as well as their clinical presentation, tumor size, tumor grade, metastasis, tumor markers, surgery type, complications, hospital stay, time to oral feeding, duration of follow-up, and status at the end of follow-up.

To evaluate the difficulty of MIS in each patient, we investigated tumor size and mass size/abdominal diameter (MS/AD) ratio. The degree of vascular abutment in the portal vein (PV), superior mesenteric vein (SMV), and splenic vein (SV) was also calculated. These parameters were measured using the preexisting abdominal CT. Since the size of the abdominal cavity in children varied by age and physical condition, the tumor size alone does not directly reflect the degree of operative difficulty. We measured the width of the abdominal cavity (abdominal diameter [AD]) at the level of the largest point of each tumor and calculated relative figures for the standardization of tumor sizes by the size of the abdominal cavity. We also calibrated the degree of compression in each vessel around each tumor (**Fig. 1**).

SPSS software version 23.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Significance level was set at a p-value of less than 0.05.

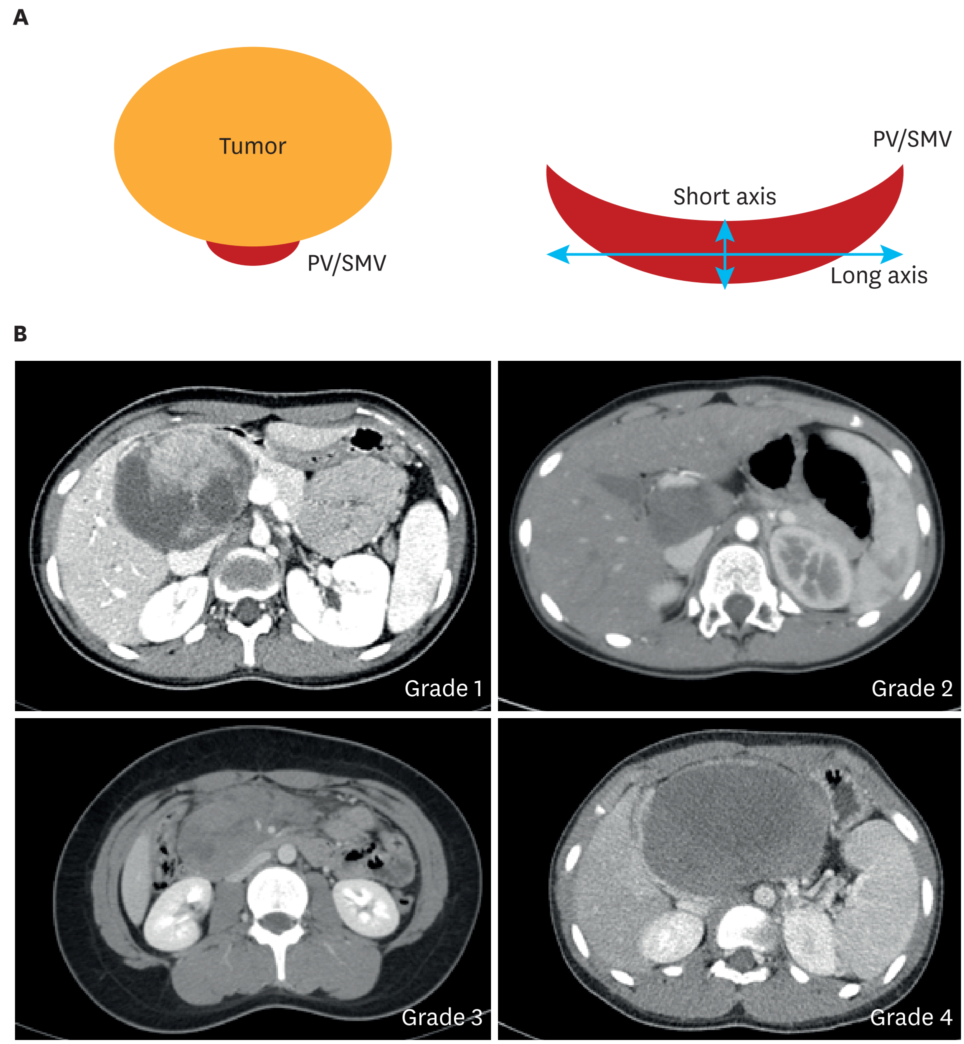

Fig. 1. Degree of PV or SMV compression. (A) PV compression model and (B) Grades 1–4 in computed tomography imaging.
Grade 1, PV or SMV abutment; Grade 2, long-axis < short-axis ×2; Grade 3, long-axis > short-axis ×2; Grade 4, complete collapse; PV, portal vein; SMV, superior mesenteric vein.

RESULTS

Sixty-six patients underwent pancreatectomy for SPT. Surgical procedures in these patients are described in **Table 1** and **Fig. 2**. Thirty-five patients underwent open surgery, whereas 31 patients underwent MIS; whom 2 underwent robotic DP and 29 underwent LP. Patient demographics, as summarized in **Table 2**, showed no difference in proportion in sex, age, weight, and most of the preoperative laboratory findings. Amylase levels were significantly higher in the open surgery group (p=0.040). Lipase levels showed no statistical significance but tended to be higher in the open surgery group (p=0.059).

Duration of operation in MIS was significantly shorter in the OP group (p=0.005) (**Table 3**). Furthermore, tumor size in the MIS group was significantly smaller than the OP group (p<0.001), and hospital stay was longer in the OP group than in the MIS group (p=0.001). Time to initial oral intake and time to full feeding was significantly shorter in the MIS group (p=0.027 and

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Table 1. Operative procedure for solid pseudopapillary tumor in pediatric patients

Operative procedures	Method	Location		
		Head and neck	Body and tail	Total
Enucleation (n=15, 22.7%)	Open	5	3	8
	MIS	4	3	7
DP (n=8, 12.1%)	Open		6	6
	MIS		2	2
SSDP (n=22, 33.3%)	Open		3	3
	MIS		19	19
Central pancreatectomy (n=4, 18.2%)	Open		3	3
	MIS		1	1
PD/PPPD (n=16, 24.2%)	Open	14		14
	MIS	2		2
Total pancreatectomy (n=1, 1.5%)	Open	1		1
	MIS	0		0
Total		26 (39.4)	40 (60.6)	66 (100.0)

Values are presented as number or number (%).
DP, distal pancreatectomy, MIS, minimally invasive surgery; SSDP, spleen sparing distal pancreatectomy; PD, pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy.

Table 2. Patient characteristics

Characteristics	Surgical method			p-value
	Open (n=35)	MIS (n=31)	Total (n=66)	
Sex (male:female)	7:28	3:28	10:56	0.250
Age (yr)	15.5±7.2	13.3±3.4	14.5±5.8	0.126
Weight (kg)	48.2±14.5	49.1±13.5	48.7±13.8	0.815
Preoperative laboratory findings				
WBC (cells/uL)	7,076±2,745	7,006±1,704	7,040±2,257	0.905
Hemoglobin (g/dL)	12.5±1.4	12.7±1.5	12.6±1.4	0.731
PLT ($\times 10^3$/uL)	265±81	271±59	268±68	0.741
AST (IU/L)	23.3±19.5	19.5±4.8	21.4±11.7	0.216
ALT (IU/L)	19.6±29.3	11.9±6.1	15.7±21.1	0.158
Total bilirubin (mg/dL)	0.6±0.3	0.6±0.4	0.6±0.3	0.408
Amylase (U/L)	130.1±133.6	68.8±25.7.2	101.4±102.8	0.040
Lipase (U/L)	142.2±284.7	29.3±15.6	89.3±213.6	0.059
CA 19-9 (U/mL)	15.5±13.7	8.8±6.6	12.9±11.7	0.186

Values are presented as the mean±standard deviations.
MIS, minimally invasive surgery; WBC, white blood cell; PLT, platelet; AST, aspartate transaminase; ALT, alanine transaminase; CA 19-9, carbohydrate antigen 19-9.

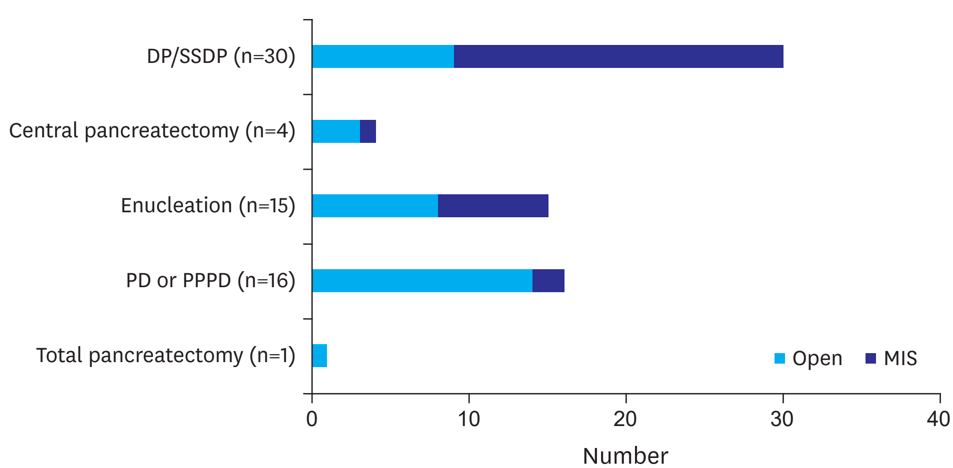

Fig. 2. Operative procedure for SPT.
SPT, solid pseudopapillary tumor; DP, distal pancreatectomy; SSDP, spleen-sparing distal pancreatectomy; PD, pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy; MIS, minimally invasive surgery.

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Table 3. Perioperative findings

Variables	Surgical method			p-value
	Open (n=35)	MIS (n=31)	Total (n=66)	
Operation time (min)	386±201	259±145	327±187	0.005
No. of transfusion	5	1	6	0.111
Open conversion		4		
No. of location				
Head	20	6	26	
Body and tail	15	25	40	
Tumor size (cm)	7.6±3.5	4.3±1.8	6.1±3.3	<0.001
Distance to margin (cm)	1.1±1.2	1.3±1.6	1.2±1.5	0.150
No. of margin involvement	1	4	5	
Resection margin	0	1	1	0.325
Radial margin	1	3	4	0.270
No. of malignancy invasion	4	2	6	0.662
Capsule	2	0	2	0.431
Peripancreatic soft tissue	2	0	2	0.431
Perineural tissue	0	1	1	0.325
Lymphovascular tissue	0	1	1	0.325
LN involvement	1	0	1	0.352
No. of postoperative complications				
Fluid collection	4	6	10	0.378
Postoperative pancreatic fistula	17	25	42	0.006
ISGPF grade A	11	21	32	0.003
ISGPF grade B	6	4	10	0.638
ISGPF grade C	0	0	0	-
Bleeding or hematoma	1	0	1	0.351
Portal vein thrombus	0	1	1	0.325
Chylous ascites	3	1	4	0.371
Splenic infarct	1	3	4	0.270
Time to oral intake (day)	10.2±8.0	6.3±5.9	7.8±7.1	0.027
Time to full feeding (day)	13.0±8.1	8.9±6.8	10.5±7.5	0.010
Hospital stay (day)	18.2±8.2	13.9±8.3	15.6±8.5	0.001
No. of recurrence	2	1	3	0.634
Local recurrence	0	1	1	
LN involvement	1	0	1	
Distant metastasis	1	0	1	

Values are presented as mean with standard deviations not otherwise specified.
MIS, minimally invasive surgery; LN, lymph node; ISGPF, International Study Group for Pancreatic Fistula.

0.010, respectively). Although postoperative pancreatic fistula showed statistical value (p=0.006), most patients experienced International Study Group for Pancreatic Fistula (ISGPF) grade A, which had no effect on patient clinical course. All of our patients with ISGPF grade A had elevated Jackson-Pratt drain amylase levels but all received routine postoperative management. Moreover, ISGPF grade B showed no statistical value (p<0.638). Other postoperative complications including postoperative fluid collection, splenic infarct, hematoma, PV thrombus, and chylous drainage showed no difference. For solid pseudopapillary carcinoma (SPC), there were 6 cases of whom four had open surgery and 2 had laparoscopic surgery (p=0.662). Invasion in the capsule, soft tissue, perineural tissue, and lymphovascular tissue showed no statistical difference (**Table 3**).

The median tumor size and MS/AD ratio in patients undergoing enucleation was larger in the OP group (7.8±2.8 cm vs. 4.1±1.6 cm, p=0.007 and 0.40±0.12 cm vs. 0.20±0.08 cm, p=0.002, respectively; **Table 4**). Furthermore, the median tumor size and MS/AD ratio was significantly greater in the OP than in the MIS DP/spleen sparing distal pancreatectomy (SSDP) group (8.8±4.0 cm vs. 4.4±2.0 cm, p=0.002 and 0.33±0.16 cm vs. 0.20±0.08 cm, p=0.440, respectively).

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Table 4. Mass size and MS/AD ratio in each type of surgery

Variables	Surgical method			p-value
	Open (n=35)	MIS (n=31)	Total (n=66)	
Enucleation				
Mass size (cm)	7.8±2.8	4.1±1.6	6.1±2.9	0.007
MS/AD ratio	0.40±0.12	0.20±0.08	0.30±0.14	0.002
Operation time (min)	276±165	246±128	262±145	0.794
DP/SSDP				
Mass size (cm)	8.8±4.0	4.4±2.0	6.1±3.6	0.002
MS/AD ratio	0.33±0.16	0.20±0.08	0.24±0.13	0.044
Operation time (min)	393±227	244±137	301±188	0.047
PD/PPPD				
Mass size (cm)	7.5±3.0	4.2±0.2	7.1±3.0	0.150
MS/AD ratio	0.32±0.14	0.21±0.02	0.30±0.14	0.231
Operation time (min)	516±170	505±134	515±162	0.933

Values are presented as mean with standard deviations.
MS/AD, mass size/abdominal diameter; MIS, minimally invasive surgery; DP, distal pancreatectomy; SSDP, spleen-sparing distal pancreatectomy; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy.

After removing 11 cases from the early 1990s when open surgery was considered the standard treatment, tumor size and MS/AD ratio between 19 OP and 31 MIS cases were compared (**Table 5**). The OP group showed higher MS/AD ratio (0.36±0.10 vs. 0.20±0.08, p<0.001) and larger mass size (7.2±2.9 vs. 4.3±1.8, p<0.001). The total average of the MS/AD ratio was 0.3. Of 19 open surgery cases, 13 cases had MS/AD ratio higher than 0.3 and only 3 cases of 31 in the MIS group had higher MS/AD ratio of 0.3 (p<0.001).

A total of 28 patients had either PV or SMV abutment (**Table 6**). The number of PV or SMV abutment in the OP group was larger compared with the MIS group (p<0.001). Although the number of grades 1 and 2 PV and SMV compression between the two groups did not show statistical difference, grades 3 and 4 showed statistical difference (p<0.001). There were total of 34 SV compressions, none of which showed any difference.

Of 66 patients, 4 patients experienced recurrence (**Table 7**). Of the 4 patients with recurrence, 2 were pathologically confirmed as SPC and other 2 were confirmed as SPT. Recurrence

Table 5. Tumor size and MS/AD ratio of 50 cases after MIS

Variables	Open surgery (n=19)	MIS (n=31)	Total (n=50)	p-value
MS/AD	0.36±0.14	0.20±0.08	0.30±0.14	<0.001
No. of MS/AD over 0.3	13	3	16	<0.001
Mass size (cm)	7.5±2.9	4.3±1.8	6.1±2.9	<0.001
Operation time (min)	276±165	246±128	262±1 45	0.794

Values are presented as mean with standard deviations not otherwise specified.
MIS, minimally invasive surgery; MS/AD, mass size/abdominal diameter.

Table 6. Vascular abutment and compression (n=62)

Variables	Compression	Open surgery	MIS	p-value
PV and SMV (n=28)	PV	24 (38.7)	4 (6.5)	<0.001
	Grade 1	6 (9.7)	3 (4.8)	0.375
	Grade 2	4 (6.5)	1 (1.6)	0.214
	Grades 3, 4	14 (22.6)	1 (1.6)	<0.001
SV (n=34)	SV	14 (22.6)	20 (32)	0.441
	Grade 1	3 (4.8)	6 (9.7)	0.489
	Grade 2	5 (8.1)	10 (16.1)	0.647
	Grades 3, 4	6 (9.7)	4 (6.5)	0.489

Values are presented as number (%).
MIS, minimally invasive surgery; PV, portal vein; SMV, superior mesenteric vein; SV, splenic vein.

Table 7. Characteristics of recurred SPC/SPT cases

Characteristics	Site of recurred mass	Size of recurred mass (cm)	Sex/age	First operation	Initial size (cm)	Disease-free survival (m)	Initial pathology	Survival
P1	Liver	4, 3, 1	F/17	DP	13	82	SPC	Yes
P2	Resection margin	2.5	F/12	Lap-enucleation	3.5	25	SPT	Yes
P3	Aortocaval node	2.5	F/19	PPPD	8.3	47	SPT	Yes
P4	Liver	2.5	F/16	PPPD	13.5	39	SPC	Yes

SPC, solid pseudopapillary carcinoma; SPT, solid pseudopapillary tumor; DP, distal pancreatectomy; PPPD, pylorus-preserving pancreatoduodenectomy.

sites included liver, aortocaval node, and resection margin from the previous operation. These recurred patients received liver segmentectomy, aortocaval node dissection and mass excision according to the recurred site. Until this day, these patients are followed in our outpatient clinic.

DISCUSSION

SPT causes abdominal discomfort and pain often after abdominal trauma or can be found incidentally upon physical examination. In adults, SPT is usually detected incidentally during health screening [3,16]. The majority of SPT is located in the pancreatic body or tail (59.3%) with some involving the pancreatic head or uncinate process (36%). The mean tumor size in adult patients was 9.8 cm before 2000 and has decreased to 8.1 cm in 2000–2012 ($p<0.05$) [3]. The mean tumor size is known to be significantly larger in children [18]. Despite its size, the prognosis of SPT is favorable with a survival rate of 95% even with metastasis in both adult and pediatric patients [10,19]. Comparative analysis revealed that malignant SPT, also known as SPC, tends to be larger in size and have more solid components [20]. Although SPT shows excellent survival outcomes, recurrence has been observed without pathologic or clinical risk factors. Four patients in this study experienced recurrence. One patient had incomplete resection margin, and three had tumors exceeding 8 cm. These patients are visiting the outpatient clinic for routine check-ups.

LP has become one of the mainstay treatments in pancreatic disease with increased safety. Laparoscopic distal pancreatectomy (LDP) in pancreatic body or tail cancer in adult patients has been shown to be feasible. Kim et al. [15] showed that LDP had superior clinical outcomes over open distal pancreatectomy (ODP). In this study, nasogastric tubes were removed significantly earlier in laparoscopic surgery compared with its open counterpart (0.6±0.7 days vs. 1.7±1.0 days, $p<0.001$). Furthermore, patients were started on diets earlier in LDP (2.8±1.3 days vs. 4.5±1.6 days, $p<0.001$). Moreover, patients were discharged significantly earlier in laparoscopic surgery (median [range] of hospital stays: 10 [5–36] days vs. 16 [8–65] days, $p<0.001$). There was no statistical difference in postoperative complications. Similar results were observed in a systematic review published recently [17]. In this study, LDP showed significantly faster oral intake, shorter hospital stays, and lower postoperative complication rate. Stewart et al. [4] and Kang et al. [16] also reported similar results. In these studies, the authors state several key factors of utilizing MIS for pancreatic diseases. First, laparoscopic surgery provides excellent cosmetic outcomes in young women. Second, LDP can be performed because most SPT occurs frequently in the tail. Third, SPT smaller than 5 cm can be considered benign, disregarding malignant potentials.

Laparoscopic pylorus-preserving pancreatoduodenectomy (L-PPPD), first introduced by Gagner and Pomp [21] in 1994, is also becoming more prevalent. Zureikat et al. [22] showed that OPD and LPD had no statistical difference in postoperative outcomes. Although the number of total patients was small, R0 resection was achieved in all LPD patients. Tumor size was smaller in the LPD group (2.2 [0.8–4.7] cm vs. 3.6 [3–5] cm, p=0.02), but the mean number of retrieved lymph node showed no difference. Kim et al. [23] stated that, even though they have not directly compared L-PPPD from open PPPD, L-PPPD is technically safe and feasible with acceptable levels of morbidity in benign and malignant periampullary cancer. Recently, published literature comparing the long-term results of LPD and OPD in pancreatic cancer showed positive results towards the LPD group [24]. LPD was associated with significantly longer operative time (median: 375 minutes vs. 518 minutes, p<0.001), but decreased blood loss (median: 600 mL vs. 250 mL, p<0.001) and decreased use of packed red blood cell transfusions (46.6% vs. 25.9%, p=0.005).

Although there is increasing evidence proving superiority of MIS over OP, there is still a lack of evidence regarding MIS in pediatric patients. According to our previous study [6], LDP was superior than open DP in terms of shorter time to oral intake, time to full feeding, and hospitalization. There was no difference in perioperative morbidity. Similar results were observed in this study. However, in case of PPPD, open PPPD was mainly performed in pediatric patients for three reasons. First, L-PPPD is not widely accepted among surgeons; second, pancreatic main ducts are too small for laparoscopic anastomosis; and third, laparoscopy is not accessible for huge masses. Nonetheless, MIS is becoming more popular and being acknowledged by many surgeons. In our center, we are opening the possibility of MIS for all eligible SPT cases, and we have already performed two cases of L-PPPD. Thus, we would like to set some guidelines as to when MIS is feasible based on our experience.

Among many parameters, the most important factors are tumor size, MS/AD ratio, and the degree of abutment or compression on PV or SMV. In this study, tumor size, MS/AD ratio, and operative time were analyzed according to the surgery and approach, whether open or laparoscopic/robotic. The tumor size and MS/AD ratio was significantly different between open and minimally invasive enucleation and DP/SSDP. From these results, patients with larger tumor size or higher MS/AD ratio should undergo open surgery rather than MIS. In our experience, tumors with compression grade 3 or higher do not offer appropriate surgical field for the surgeon, making ligation of the perforation vessel extremely difficult. Since clipping was not applicable in most cases, open suture ligation was necessary. In this study, there were 4 cases of open conversion due to vessel encasement (n=2), bleeding (n=1), and pancreatic duct injury during enucleation (n=1).

There is a tendency in recent literature siding with MIS. Even in our center, we can notice that the MS/AD ratio in the MIS group is increasing (**Fig. 3**). With increasing evidence proving superiority of MIS over OP, surgeons are performing MIS despite bigger masses and harder cases. To reduce the risk of MIS, surgeons must carefully select patients feasible for MIS. We carefully suggest MS/AD ratio smaller than 0.3 and PV/SMV compression of grade 2 or lower, to be considered a feasible candidate for MIS. As mentioned before, SV compression is not an absolute indication. Since, SPT cases are rare, it is very difficult for a single pediatric surgeon to complete a learning curve. However, with the advancement in laparoscopic technique in other diseases, we believe that the range of surgical indications will expand.

Although this study has suggested some indications for MIS in pediatric patients, it has several limitations. This study was retrospective in nature, and the sample size in open vs. laparoscopic/robotic enucleation, DP/SSDP, and PD/PPPD was small. Furthermore, most of our patients received open PPPD compared to its laparoscopic counterpart (14 open PPPD vs. 2 L-PPPD).

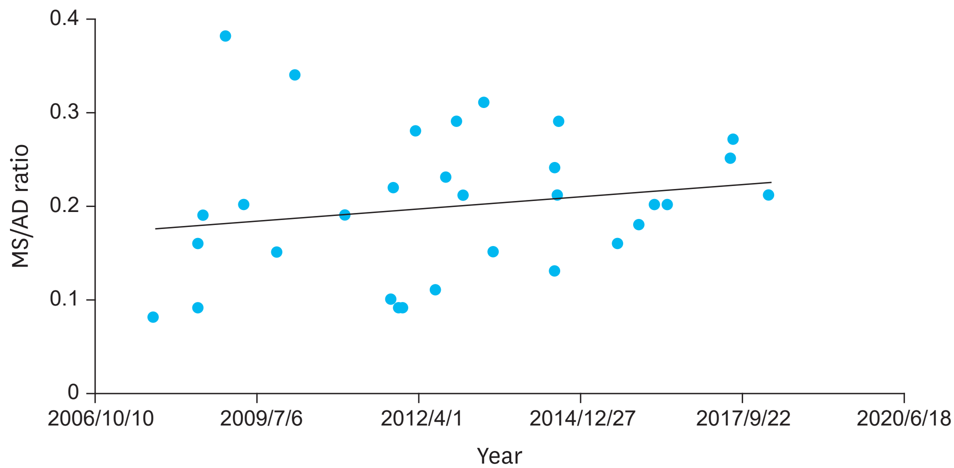

Fig. 3. MS/AD ratio of MIS along time.
MS/AD, mass size/abdominal diameter; MIS, minimally invasive surgery.

Since patients with pancreatic head or uncinate process received open PPPD when there was high degree of either PV or SMV compression, selection bias naturally occurred. However, this study is the first to suggest indications for MIS in pediatric patients. Further validation is needed.

In conclusion, MIS is widely utilized in pediatric patients including pancreatectomy. Careful selection of MIS is required in pediatric patients using parameters such as MS/AD ratio and vessel abutment. MS/AD ratio lower than 0.3 and vessel compression of grade 2 or below are considerable candidates for MIS.

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