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Adverse Impact of Intraoperative Conversion on the Postoperative Course Following Laparoscopic Pancreaticoduodenectomy

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Purpose: The aim of the current study was to evaluate the adverse clinical impact of intraoperative conversion during laparoscopic pancreaticoduodenectomy (LPD).

Materials and Methods: The medical records of patients who underwent pancreaticoduodenectomy (PD) were retrospectively reviewed. Perioperative clinical variables were compared between patients who underwent converted PD (cPD) and initially planned open PD (OPD) to investigate the clinical impact and predictive factors of intraoperative conversion during LPD.

Results: A total of 171 patients were included. Among them, 31 patients (19.3%) were found to have intraoperative conversion during LPD. Failure of progression due to severe adhesion (12 patients, 7%) and major vessel invasion (7 patients, 4%) were the two most frequent reasons for conversion. On multivariate analysis, age $[Exp(\beta)=1.044, p=0.044]$ and pancreatic texture $[Expa(\beta)=2.431, p=0.039)$ were found to be independent factors for predicting intraoperative conversion during LPD. In comparative analysis with the OPD group, the cPD group had a longer operation time (516.8 min vs. 449.9 min, p=0.001), higher rate of postoperative hemorrhage (12.1% vs. 0.85%, p=0.008), higher reoperation rate (9.1% vs. 0%, p=0.01), and higher cost (21886.4 USD vs. 17168.9 USD, p=0.018).

Conclusion: Intraoperative conversion during LPD can have an adverse clinical impact on the postoperative course following LPD. Appropriate patients selection and improvement of surgical techniques will be crucial for unnecessary intraoperative conversion and safe LPD.

Key Words: Laparoscopic, pancreaticoduodenectomy, conversion, complication, morbidity

INTRODUCTION

Laparoscopic pancreaticoduodenectomy (LPD) is a complicated and technically demanding surgical procedure. Since Gagner and Pomp¹ reported the first experience of LPD in 1994, LPD has been regarded as a technically feasible and safe surgery by hepatobiliary and pancreas experts. Recently, more encouraging perioperative outcomes of LPD have been reported,

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compared with open PD (OPD) in treating periampullary tumors.²⁻⁶ Recently, the PADULAP randomized control trial demonstrated that LPD was associated with a significantly lower duration of hospital stay and fewer Clavien-Dindo grade \geq 3 complications, while the resection margin and lymph node harvest were comparable.⁷ The meta-analysis by Chen, et al.⁸ also showed that LPD had lower transfusion rates, shorter hospital stay, and less blood loss. However, in general, the technical feasibility and safety of LPD still remain controversial.^{1,9}

The inflammatory response secondary to obstructive cholangitis and pancreatitis can cause dense adhesion and unexpected local invasion of the tumor into major vessels, which do not favor safe and effective laparoscopic dissection. In addition, laparoscopic management of the soft remnant pancreas with small pancreatic duct is difficult, and these conditions are clinically relevant to the development of a postoperative pancreatic fistula (POPF).^{10,11} Indeed, POPF can be a critical complication after pancreatectomy, and it was reported to occur in 3.8%–50% of cases in previous meta-analyses.^{2,3,12-14} Therefore, performing safe LPD to minimize postoperative morbidity is a major concern in reconstruction during LPD. Certain intraoperative circumstances leading to difficult laparoscopic dissection and reconstructions are considered main reasons for intraoperative conversion during LPD.

Intraoperative conversion to OPD (converted PD, cPD) is a practical issue for both pancreatic surgeons and patients. PD is a very complicated surgical procedure, and timely intraoperative conversion is essential to ensure the safety of LPD. However, several previous reports lacked specific data on intraoperative conversion during LPD.^{2,3,7,15} According to literature, it is estimated that the overall conversion rate during LPD is 3.1%–24.1% in experienced surgeons.¹⁶⁻²¹ However, few studies have investigated the potential impact of intraoperative conversion during LPD on the perioperative clinical course.

In this study, the perioperative clinical impact of intraoperative conversion during LPD was evaluated, and the potential predictive factors for intraoperative conversion were also investigated. This study is expected to assist in selecting appropriate patients to avoid unnecessary intraoperative conversion and achieve the goal of safe LPD.

MATERIALS AND METHODS

Study design

The medical records of patients who underwent LPD by single surgeon from September 2012 to July 2018 were retrospectively reviewed. Both benign and malignant lesions were included. The selection criteria for LPD included patients in good general condition who were able to endure long operation time for pneumoperitoneum, with no history of upper gastrointestinal surgery with resectable periampullar tumors and without distant metastasis nor overt major vessel involvement on preoperative radiological images. Initial OPD was indicated when patients who refused to have LPD, and they had tumor conditions expected to undergo intraoperative conversion, such as high risk of tumor invasion around the major vascular structures, and severe intraabdominal adhesion. Intraoperative conversion was defined as resection that had to be completed by laparotomy due to technical difficulties or failure to progress during LPD. The primary end point of this study was to evaluate the perioperative adverse impacts of unplanned intraoperative conversion during LPD (cPD) by comparative analysis with initial OPD. The costs associated with unplanned conversion were also compared.

Data collection

The patients' demographic parameters, including age, American Society of Anesthesiologists (ASA) physical status, body mass index (BMI), and neoadjuvant therapy, were evaluated. The reoperation rate, readmission rate, postoperative hemorrhage rate, occurrence of delay gastric emptying and POPF (defined by the International Study Group on Pancreatic Fistula, ISGPF),²² 30-day mortality, and morbidities were assessed. Furthermore, the transfusion rate, short-term surgical outcome (including transfusion rate), number of retrieved lymph nodes, and R-status of the resection specimen were also evaluated. In addition, we examined the reasons for unplanned conversion, such as major vascular invasion, failure to progress due to adhesion, easy bleeding tendency, and anatomical anomalies. The Institutional Review Board of Severance Hospital approved this study protocol (IRB No. 4-2018-0863).

Surgical procedure

During LPD, the resection and reconstruction of pancreaticojejunostomy and hepaticojejunostomy were performed intracorporeally. The surgical specimen was retrieved through a minilaparotomy wound by extending the umbilical port site where the duodenojejunostomy was performed.^{5,23-25}

Statistical analysis

Continuous variables were described as the mean±standard deviation, and categorical variables were described as the frequency (%). Categorical variables were analyzed using the chi-squared test, and the Student's t-test was used for continuous variables. To identify the predictive factors for conversion, multivariate analyses were performed for different variables using a logistic regression model. *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

General characteristics of the patients

From September 2012 to July 2018, a total of 171 LPDs were per-

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formed; 93 patients were male and 78 patients were female, with an age range of 61.1±12.0 years. Among them, 155 patients (91%) underwent laparoscopic pylorus-preserving pancreaticoduodenectomy (Lap-PPPD), 15 patients (9%) underwent laparoscopic total pancreatectomies (Lap-TP), and 1 patient (0.6%) underwent conventional pancreaticoduodenectomy (Lap-PD). Only 4 patients (2%) received neoadjuvant therapy before surgery.

Over 70% of the surgeries were performed for malignant diseases. Among these, common bile duct cancer was the most common (40 patients, 23%), followed by the ampulla of Vater cancer (35 patients, 20%). In benign and low-grade malignant tumors of the pancreas, intraductal papillary mucinous neoplasms were the most common (26 patients, 15%) (Table 1).

Incidence and reasons for intraoperative conversion during LPD

Among the 171 attempted LPDs, 31 patients had to convert to an open approach during LPD (cPD) and the overall conversion rate was 19.3%. Moreover, the intraoperative conversion rate during LPD was found to be steady over time (range, 13.3%–

Table 1. Diagnosis in 171	Laparoscopic Pancreaticoduodenectomy
Cases	

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CBD cancer	40 (23)
AoV cancer	35 (20)
PDAC	29 (17)
IPMN	26 (15)
Metastatic cancer	15 (9)
NET	14 (8)
AoV adenoma	10 (6)
SPN	6 (4)
GIST	5 (3)
Duodenal cancer	4 (0.6)
SCN	2 (1)
Pancreatitis	1 (0.5)
Ganglioma	1 (0.5)
Hamartoma	1 (0.5)

Data are presented as n (%).

CBD, common bile duct; AoV, ampulla of vater; PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; SPN, solid pseudopapillary neoplasm; GIST, gastrointestinal stromal tumor; SCN, serous cystic neoplasm. 42.8%, chi-square, Fisher's exact test, linear-to-linear association, p=0.013) (Fig. 1).

Failure of dissection due to severe adhesion was the most common reason for conversion during LPD (12 patients, 38.7%), followed by suspicion of major vessel [superior mesenteric vein (SMV)/portal vein (PV)] invasion (7 patients, 22.5%) (Table 2). The main reasons for adhesion were severe inflammation due to cholangitis, pancreatitis, post neoadjuvant therapy, desmoplastic changes surrounding pancreatic head, and direct tumor invasion to major vasculatures. In addition, combined segmental resection of the colon was necessary in two conversion cases due to incidental ischemic change of colon following excision or shaving of colonic mesentery for tumor invasion.

Predictive factors for intraoperative conversion during LPD

In univariate analysis, age (p=0.013), sex (p=0.019), ASA physical status (p=0.039), total bilirubin (p=0.06), size of the pancreatic duct (p=0.047), and pancreatic texture (p=0.015) were associated with conversion during LPD. Diagnosis, neoadjuvant therapy, BMI, and the size of bile duct were not found to be related to conversion (p>0.05) (Table 3). On multivariate analysis, age {Exp(β)=1.044 [95% confidence interval (CI): 1.001–5.660], p=0.044} and pancreatic texture [hard pancreas; Exp(β)=2.431 (95% CI: 1.044–5.660), p=0.039] were found to be independent

Table 2. Reasons for Conversion during Lap-PD

Reasons for conversion	Frequency (%)
Failure to progress due to severe adhesion	12 (39)
Suspicious SMV/PV invasion	7 (23)
Hepatic artery invasion	3 (9.6)
Combined colon segmental resection	2 (6.4)
Internal obesity	2 (6.4)
Consecutive positive bile duct resection margin	2 (6.4)
Sustained high pCO ₂	2 (6.4)
Vascular anomaly (RHA penetrating pancreatic head)	1 (<3.2)
Suspicious IVC invasion	1 (<3.2)
Easy bleeding tendency	1 (<3.2)
Small bowel internal rotation	1 (<3.2)

Lap-PD, laparoscopic pancreaticoduodenectomy; SMV, superior mesenteric vein; PV, portal vein; RHA, right hepatic artery; IVC, Inferior vena cava.

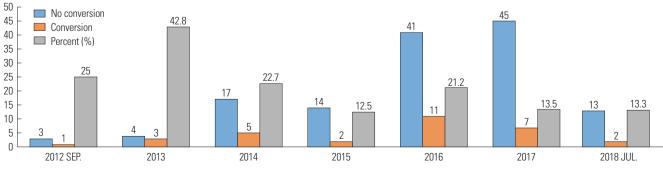


Fig. 1. Incidence of converting pancreaticoduodenectomy in chronological order.

	Successful LPD (n=138)	Converting PD (n=33)	<i>p</i> value
Age (yr)	59.9±12.1	65.7±10.9	0.013
Sex (male/female)	69/69	24/9	0.019
Diagnosis 1 (benign & low-grade/malignant)	50/88	9/24	0.609
Diagnosis 2 (PC/non-PC)	21/117	8/25	0.215
ASA (1/2)	13/77	0/17	0.039
ASA (3/4)	48/0	15/1	
Neo-Tx (no/yes)	135/3	32/1	0.579
Total bilirubin	1.0±0.9	1.41.1	0.076
BMI	23.5±2.9	23.0±2.5	0.431
BD-size	1.2±1.0	1.3±0.5	0.403
PD-size	3.6±2.2	4.8±3.1	0.047
Pancreatic texture (soft/hard)	96/30	16/14	0.015

PD, pancreaticoduodenectomy; LPD, laparoscopic pancreaticoduodenectomy; PC, pancreatic cancer; ASA, American Society of Anesthesiologists; Neo-Tx, neoadjuvant treatment; BMI, body mass index; BD-size, bile duct size; PD-size, pancreatic duct size.

 Table 4. Preoperatively Detectable Clinical Factors Associated with Hard Remnant Pancreas*

	Soft pancreas (n=112)	Hard pancreas (n=44)	<i>p</i> value
Age (yr)	59.8±12.1	64.1±11.1	0.041
Sex (male/female)	60/52	27/17	0.474
Diagnosis 1 (benign & low-grade/malignant)	7/34/71	0/7/37	0.024
Diagnosis 2 (PC/non-PC)	11/101	17/44	< 0.001
ASA (1/2/3/4)	12/67/33/0	1/20/22/1	0.013
Neo-Tx (no/yes)	110/2	42/2	0.578
Total bilirubin	1.0±0.8	1.3±1.1	0.060
BMI	23.5±3.1	23.5±2.6	0.965
BD-size	1.1±0.4	1.4±1.1	0.042
PD-size	3.1±2.0	5.5±2.5	< 0.001

PC, pancreatic cancer; ASA, American Society of Anesthesiologists; Neo-Tx, neoadjuvant treatment; BMI, body mass index; BD-size, bile duct size; PD-size, pancreatic duct size.

*Laparoscopic TP were excluded.

factors for predicting conversion during LPD.

When correlating preoperatively detectable parameters for predicting the pancreatic texture, age (p=0.041), diagnosis (p=0.024 and <0.001), ASA physical status (p=0.013), bile duct size, and pancreatic duct size (p<0.001) were significantly associated with hard remnant pancreas (Table 4). Subsequent multivariate analysis showed that pancreatic texture was independently associated with pancreatic duct size [Exp(β)=1.473 (95% CI: 1.234–1.758), p<0.001] and diagnosis of pancreatic cancer [Exp(β)=3.852 (95% CI: 1.440–10.305), p=0.007].

Table 5. Demographics between Converting PD and Initial Open PD

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	Converting PD (n=33)	Initial open PD (n=117)	<i>p</i> value
Age (yr)	65.7±10.9	64.1±9.9	0.392
Sex (male/female)	24/9	71/46	0.227
Diagnosis 1 (benign & low-grade/malignant)	9/24	9/108	0.017
Diagnosis 2 (PC/non-PC)	8/25	52/65	0.044
ASA (1/2/3/4)	0/17/15/1	7/53/51/6	0.882
Neo-Tx (no/yes)	32/1	94/23	0.028
Total bilirubin	1.4±1.1	1.3±1.2	0.631
BMI	23.0±2.5	23.3±3.1	0.744
Operating time	516.8±96.6	449.9±102.9	0.001
EBL	645.5±559.4	562.1±439.2	0.368
Transfusion (no/yes)	30/3	102/15	0.764
Tumor size	3.4±2.1	2.9±1.6	0.224
No. of retrieved LNs	12.4±7.5	13.9±8.9	0.380
No. of metastatic LNs	1.9±2.8	1.6±2.9	0.522
R-status	0/33	4/111	0.575

PC, pancreatic cancer; ASA, American Society of Anesthesiologists; Neo-Tx, neoadjuvant treatment; BMI, body mass index; PD, pancreaticoduodenectomy; EBL, estimated blood loss; LN, lymph nodes.

Table 6. Adverse Impact of Converting PD on Postoperative Course

	Converting PD (n=33)	Initial open PD (n= 117)	<i>p</i> value
POPF (no/yes)	28/5	98/19	0.463
POBF (no/yes)	32/1	113/4	1.000
DGE (no/yes)	26/7	99/18	0.598
PPH (no/yes)	29/4	116/1	0.008
LOH	21.7±7.5	17.9±8.6	0.140
Reoperation (no/yes)	30/3	117/0	0.010
Readmission (no/yes)	29/4	108/9	0.484
30-day mortality (no/yes)	33/0	117/0	NA
90-day mortality (no/yes)	33/0	117/0	NA
Cost (USD)	21886.4±10594.4	17168.9±4973.1	0.018

PD, pancreaticoduodenectomy; POPF, postoperative pancreatic fistula; POBF, postoperative bile fistula; DGE, delayed gastric emptying; PPH, postpancreatectomy hemorrhage; LOH, length of hospital stay.

Clinical adverse impact of intraoperative conversion during LPD

When cPD and initial OPD were compared, age, sex, estimated blood loss, transfusion rate, number of retrieved lymph nodes, and R-status showed no significant difference between the two groups (p>0.05) (Table 5). Malignant disease (p=0.017), pancreatic cancer (p=0.044), and neoadjuvant treatment (p=0.024) were more frequent in initial OPD than in cPD. However, the cPD group had a significantly longer operating time (516.8±96.6 min vs. 449.9±102.9 min, p=0.001). In addition, the incidence of post-pancreatectomy hemorrhage (PPH) (p=0.008) and reoperation (p=0.010) were shown to be significantly higher in the cPD group (Table 6). Regarding PPH, one patient required transfusion of

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three units of packed red blood cells during the postoperative period. The other two patients were associated with POPF, which required interventional angiography and embolization. Another patient required reoperation for bleeding from the liver bed due to detachment of the gallbladder. It was also observed that emergent diverting loop ileostomy was required in a case of combined colon resection during cPD, and secondary wound closure was necessary in one patient. Finally, the medical cost was reported to be much higher in the conversion group than in the initial OPD group {24591443±11903768.2 (\mathbb{W}) [21886.4± 10594.4 (\mathbb{S})] vs. 19290897.2±5587761.9 (\mathbb{W}) [17168.9±4973.1 (\mathbb{S})]; *p*=0.018} (Table 6).

DISCUSSION

Since the first LPD was performed in 2008 in our center, the annual number of LPD has steadily increased. However, the overall conversion rate was estimated to be 19.3% in this study, which is similar to that in other studies. To the best of our knowledge, no previous study has directly compared perioperative outcomes between cPD and initial OPD to investigate the potential clinical impact of cPD. Therefore, this study is thought to be the first to investigate the potential adverse impact of conversion during LPD. In this study, the conversion group had a longer operating time, higher occurrence of postoperative hemorrhage, higher reoperation rate, and consequently higher medical costs. For the patients' safety during LPD, unnecessary intraoperative conversion during LPD should be avoided. This can be ensured by careful preoperative patient selection. Therefore, prediction of the potential risk of intraoperative conversion before surgery is important.

To ensure safety of the patients, surgeons should consider the potential adverse impacts of intraoperative conversion during LPD. The average conversion rate in LPD is reported to be around 20%–25%. Palanivelu, et al.²⁰ performed the first RCT comparing LPD with OPD for periampullary cancer, and showed a shorter hospital stay and relatively low conversion rate of only 3.1%. The PADULAP randomized controlled trial showed that although LPD was associated with a shorter length of hospital stay, the conversion rate was 23.5% (8/34).⁷ However, with accumulating experience, conversion rate can be stabilized, which is supported by the present data. In this study, it appears that the intraoperative conversion was reduced as more experiences were accumulated (range, 13.3%–42.8%, chi-square, Fisher's exact test, linear-to-linear association, p=0.013).

The consequences of unplanned conversion in other laparoscopic surgeries have been evaluated in many previous studies, such as the impact of conversion during laparoscopic hepatectomy. The study by Silva, et al.²⁶ showed higher transfusion rates, longer hospital stay, and higher morbidity in unplanned conversion group. Furthermore, Belizon, et al.²⁷ showed that the overall conversion rate in laparoscopic colorectal resection was 19.6%, and the morbidity was significantly higher, especially in terms of wound infection and longer hospital stay. In contrast, the study by Casillas, et al.²⁸ showed no significant differences in operative time, length of stay, costs, or unexpected remissions.

Despite these previous studies, the impact of intraoperative conversion during LPD has not been fully investigated. Recently, Torphy, et al.¹⁶ evaluated the clinical impact of conversion to the open approach in their subgroup analysis of minimally invasive PD. They found that 84 robotic pancreaticoduodenectomies (RPD, 15.3%) and 823 LPD (25.7%) were converted to OPD. The LPD patients requiring conversion had no significant differences in terms of 90-day mortality compared to those who completed LPD [odds ratio (OR), 1.48; 95% CI, 0.97-2.24]. For RPD, while the conversion group showed a 4-fold increase in 90-day mortality, no significant difference observed in the conversion rate over time (p=0.605). Furthermore, the lower the volume of minimally invasive PD centers, the higher the conversion rate; therefore, the conversion group likely had longer operative times and more blood loss. A recent multicenter study²⁹ found that elective conversion (e.g., vascular involvement) in minimally invasive distal pancreatectomy for pancreatic ductal adenocarcinoma was associated with comparable short-term oncological outcomes to OPD, while emergency conversions (e.g., bleeding) were associated with worse outcomes over both short and long terms. This finding suggests that careful patient selection and timely conversion are required to safely conduct minimally invasive pancreatectomy.

The current study shows that both age and pancreatic texture were independent factors that could predict conversion during LPD. Practically, pancreatic texture (hard pancreas) can be predicted by pancreatic duct size $[Exp(\beta)=1.473 (95\% \text{ CI: } 1.234-1.758), p<0.001]$ and diagnosis of pancreatic cancer $[Exp(\beta)=3.852 (95\% \text{ CI: } 1.440-10.305), p=0.007]$ in preoperative clinical setting. Moreover, recent literatures have also successfully demonstrated the safety of short-term and long-term oncologic outcomes of LPD for pancreatic cancers.³⁰ However, it is believed that both the accumulation of laparoscopic experience and well-organized selection criteria should be based on excellent clinical results. Therefore, although LPD for pancreatic cancer is considered to be feasible, it should be the last indication only when matured experience and technical skills are fully obtained.

Especially in pancreatic cancer, resectability is determined by the degree of the vascular invasion adjacent to the pancreas [PV/SMV, superior mesenteric artery (SMA)], and successful laparoscopic resection depends on the dissection of the pancreas from the major vessels. Resectability can be evaluated preoperatively by various imaging modalities, such as CT scan or endoscopic ultrasonography (EUS). However, there are many cases where image findings do not correlate with intraoperative findings. In our study, there were seven cases of open conversion due to SMV/PV invasion. However, in preoperative CT scan, SMV invasion of less than 180 degrees was suspected in only three cases. In the other four cases, the tumor did not invade or abutted SMV/PV in preoperative CT scan. At present, it is considered impossible to fully predict the possibility of laparoscopic resection through preoperative image studies. However, the common point of open conversion cases is that all of the patients have undergone biopsy of the tumor via EUS or endoscopic retrograde cholangiopancreatography, which can result in tissue injury and inflammation. The adhesion due to inflammation can mimic tumor invasion to the major vessels. It is recommended to avoid unnecessary biopsy for lesions requiring surgical excision regardless of the biopsy results.

Torphy, et al.¹⁶ mainly reported factors associated with a higher risk of conversion in a minimally invasive group; these included the male sex, tumor size >34 mm, and a low PD volume center. In this study, the patients' BMI was around 23 kg/m², which was not associated with conversion during LPD (23.0±2.5 vs. 23.3 \pm 3.1, p=0.744). However, Cesaretti, et al.³¹ recommended that patients with a BMI >40 m/kg² and locally advanced lesions should be reconsidered for LPD. Although the present study failed to reveal the impact of BMI on intraoperative conversion, according to our experiences, in patients with high BMI, it was difficult to ensure an operative field, especially when dissecting uncinate processes due to the bulky omentum and colon hiding in this area, which make the surgery very difficult. In particular, this area, known as the retroperitoneal margin (SMA lateral margin), is oncologically very important in patients with pancreatic cancer. Therefore, BMI should also be considered as one of the preoperative selection criteria for LPD. In the near future, in order to precisely predict the potential risk of conversion during LPD, correlation between preoperative visceral fat measurement and conversion risk should be further investigated.

Our study had several limitations. First, this was a retrospective study with a limited number of patients. In addition, selection bias should be considered when interpreting the study results. However, the present study demonstrated that intraoperative conversion during LPD can have negative impacts on the postoperative clinical course. Therefore, preoperative patients selection and technical proficiency are required to perform safe LPD. Considering the patients' general condition, tumor biology, anatomic relationship with the major vascular structures, and the surgeons' technique, the surgical approach can be individualized to improve safety. A large populationbased multicenter collaborative study needs to be performed in the near future to validate the current observations.

Another limitation of our study was that it only involved a single surgeon's experience on minimal invasive pancreatecticoduodenectomy in our institute; therefore, the study size was not large enough. Since minimally invasive pancreatecticoduodenectomy requires higher level of laparoscopic technical skills and a long learning curve, our institute only had one surgeon who was experienced enough to perform the procedure. However, the results of our study did show some significance on the morbidities of unexpected conversion to open surgery. With the advancement in the laparoscopic techniques worldwide, a growing number of pancreatic surgeons are performing laparoscopic or even RPD. A multicenter collaborative study would be worthwhile to justify the safety of unplanned conversion to open surgery for minimally invasive LPD performed by different surgeons, and to prevent its adverse effects.

AUTHOR CONTRIBUTIONS

Conceptualization: Chang Moo Kang. Data curation: Law Cho Kwan Connie and Seung Soo Hong. Formal analysis: Law Cho Kwan Connie and Seung Soo Hong. Investigation: Incheon Kang and Seung Yoon Rho. Methodology: Incheon Kang and Seung Yoon Rho. Project administration: Ho Kyoung Hwang and Woo Jung Lee. Resources: Ho Kyoung Hwang and Woo Jung Lee. Software: Ho Kyoung Hwang and Woo Jung Lee. Supervision: Chang Moo Kang. Validation: Chang Moo Kang. Visualization: Law Cho Kwan Connie and Seung Soo Hong. Writing—original draft: Law Cho Kwan Connie and Seung Soo Hong. Writing—review & editing: Law Cho Kwan Connie, Seung Soo Hong, and Chang Moo Kang. Approval of final manuscript: all authors.

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