



A Prognostic Impact of Splenectomy in Laparoscopic Distal Pancreatectomy on Benign/Borderline Pancreatic Tumors: A Change of the Era

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Purpose: In the past, spleen preservation during distal pancreatectomy (DP) was preferred; however, more recent studies reported comparable results between splenectomy and spleen preserving. We retrospectively reviewed patients in a single center who underwent laparoscopic DP with/without splenectomy, and evaluated the chronologic changes of surgical outcomes of the two procedures.

Materials and Methods: Patients who underwent laparoscopic DP with or without splenectomy due to benign/borderline tumor from 2005 to 2019 were included in this study. We divided this period into Era 1 (2005–2012) and Era 2 (2013–2019), and compared the chronological evolution of surgical outcomes of laparoscopic distal pancreatectomy (LDPS) to those of laparoscopic spleen-preserving distal pancreatectomy (LSpDP), including the long-term postoperative immunologic profiles.

Results: A total of 198 cases were included (LSpDP: 80 cases; LDPS: 118 cases). As the period changed from Era 1 to Era 2, the ratio of LSpDP decreased and the surgical outcomes of LDPS improved. In Era 1, LSpDP group showed superior results compared to LDPS group in terms of hospital days and postoperative pancreatic fistula ratio; however, in Era 2, the surgical outcomes showed no statistical differences. No significant differences were observed in all of the immunologic markers.

Conclusion: We carefully conclude that during laparoscopic DP, combined splenectomy can be equivalent to spleen preserving in surgical and immunological outcomes, and inevitable splenectomy can be safely conducted.

Key Words: Laparoscopic, distal pancreatectomy, spleen preserving, chronologic change, surgical outcomes

INTRODUCTION

Minimally-invasive spleen-preserving distal pancreatectomy (DP) is indicated for benign or borderline malignant lesions

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confined to the pancreatic body and tail. Resection of the pancreatic body at any point left of the portal vein is termed DP, and is traditionally combined with splenectomy (distal pancreatectomy, DPS).¹ The effect of spleen preservation during laparoscopic DP remained controversial for past a few decades.² Two surgical techniques are available to preserve the spleen. First, Warshaw described a technique in which splenic vessels are ligated with the preservation of the short gastric and left gastroepiploic vessels. Second, the operation can also be performed by sparing the splenic vessels, which assures increased blood supply to the spleen.³

Until the early 2000s, many papers have been published demonstrating the superior results of laparoscopic spleen-preserving DP compared to DPS.

Shoup, et al.⁴ reported that in the comparison of splenecto-

my (n=79) and splenic preservation groups (n=46), the splenectomy group showed higher incidence of infectious and more severe complications (Clavien-Dindo classification Grade III or IV) and longer hospital stay. They insisted that splenic preservation should be considered in benign and low-grade malignant disease.⁴ However, this conclusion was driven from old data, compiled from the 1980s to early 2000, and should be reevaluated, as recent surgical techniques of laparoscope and postoperative management have improved and surgical complication has decreased.

Recent studies reported more comparable results between splenectomy and spleen preserving groups. Milito, et al.⁵ reported the impact of spleen-preserving laparoscopic DP on postoperative infectious complications via systematic review and meta-analysis. In their study, 632 patients in 10 observational studies were included. In the splenectomy group (n=296), there was more significant risk of postoperative surgical site infection [odds ratio (OR)=2.30, $p=0.024$], overall complications (OR=1.51, $p=0.048$), and open conversion rate (OR=3.15, $p=0.005$). However, in hospital stay, pancreatic fistula, postoperative bleeding, and reoperation rate showed no statistical differences between the two groups. They concluded that these results should be interpreted with caution, and further studies should be performed.⁵

These contradictory results according to chronologic changes have led to the need for re-evaluation of how splenectomy affects surgical outcomes. In this respect, we retrospectively reviewed patients in a single center who underwent laparoscopic DP with/without splenectomy, and evaluated the chronologic changes of surgical outcomes of the two procedures.

MATERIALS AND METHODS

Patient selection

We retrospectively reviewed patients who underwent laparoscopic DP with/without splenectomy due to benign or borderline malignant tumor from 2005 to 2019 in Severance Hospital, Seoul, Korea. We divided this period into Era 1 (2005–2012) and Era 2 (2013–2019), and compared the chronological evolution of surgical outcomes of laparoscopic distal pancreatectomy (LDPS) to those of laparoscopic spleen-preserving distal pancreatectomy (LSpDP). Surgical outcomes consisted of the overall complication, postoperative pancreatic fistula (POPF), operation time, length of hospital stay (LOH), estimated blood loss (EBL), and transfusion. We also compared the long-term postoperative immunologic profiles of patients using immunologic markers. Lambda-chain, Kappa-chain, IgA, IgM, and IgG were used as immunologic markers. This study was approved by the Institutional Review Board of Yonsei University College of Medicine (4-2020-0983).

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences, version 23 (SPSS, IBM Corp., Armonk, NY, USA). Values are expressed as means and standard deviations or medians and ranges, as appropriate. Categorical variables were compared using the chi-square test and reported as number and percentage (%). Chi-square linear-by-linear association was used to analyze the frequency of LSpDP and LDPS by year. Continuous variables were compared using the independent t-test or the Mann-Whitney test, as appropriate. The p -value for statistical significance was set at 0.05.

RESULTS

Chronological change of laparoscopic DP

A total of 198 cases were included in this study, consisting of 80 cases in LSpDP group and 118 cases in LDPS group. In Era 1, 40 cases were in LSpDP group and 43 cases in LDPS group.

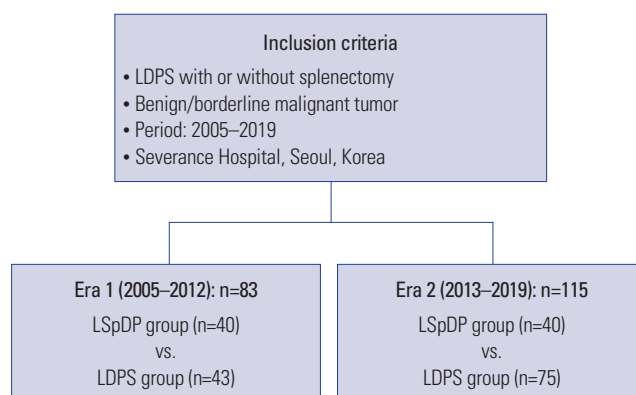


Fig. 1. Patient selection. A total of 198 cases were included in this study, consisting of 80 cases in LSpDP group and 118 cases in LDPS group. In Era 1, 40 cases were in LSpDP group and 43 cases in LDPS group. In Era 2, 40 cases were in LSpDP group and 75 cases in LDPS group. LSpDP, laparoscopic spleen-preserving distal pancreatectomy; LDPS, laparoscopic distal pancreatectomy.

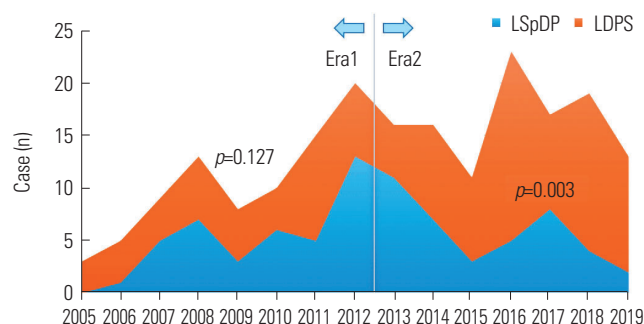


Fig. 2. Number of cases according to the year. Except for 2005 and 2006, in Era 1, LSpDP showed a similar or higher frequency compared to LDPS; but as the period got closer to Era 2, the ratio of LSpDP began to decrease (Era 1: $p=0.127$, Era 2: $p=0.003$). LSpDP, laparoscopic spleen-preserving distal pancreatectomy; LDPS, laparoscopic distal pancreatectomy.

In Era 2, 40 cases were in LSpDP group and 75 cases in LDPS group (Fig. 1). We analyzed the frequency of LSpDP and LDPS by year. Except for 2005 and 2006, in Era 1, LSpDP showed a similar or higher frequency compared to LDPS; but as the period got closer to Era 2, the ratio of LSpDP began to decrease (Era 1: $p=0.127$; Era 2: $p=0.003$) (Fig. 2).

Chronological change in perioperative outcomes of LDPS

To evaluate the chronologic changes of LDPS, we compared the clinical characteristics and surgical outcomes of LDPS during Era 1 and Era 2 (Table 1). We found that the surgical outcomes of LDPS improved according to the chronological change. There were no statistical differences in age, sex, body mass index (BMI), diagnosis, and tumor size between the two periods. However, the LOH decreased from 12.0 to 9.1 days ($p=0.044$), EBL decreased from 259.8 to 144.5 mL ($p=0.011$), and

Table 1. Clinical Characteristics and Surgical Outcomes of LDPS according to Era

	Era 1: 2005–2012 (n=43)	Era 2: 2013–2019 (n=75)	p value
Clinical characteristics			
Age (yr)	50.07±14.61	53.11±15.65	0.301
Sex, male	15 (34.9)	27 (36.0)	0.903
BMI (kg/m ²)	22.84±3.08	24.07±3.61	0.061
Diagnosis			0.244
IPMN	9	14	
NET	4	18	
SPN	10	11	
MCN	7	6	
SCN	5	5	
Metastatic cancer	2	4	
Chronic pancreatitis	4	5	
Other benign	2	10	
Other cancer	0	2	
Tumor size (cm)	3.75±1.80	3.69±2.26	0.899
Surgical outcomes			
Operation time (min)	218.4±108.6	216.2±88.7	0.908
Hospital stay (days)	12.0±8.8	9.1±3.8	0.044*
Estimated blood loss (mL)	259.8±261.1	144.5±161.7	0.011*
Transfusion	4 (9.3)	0 (0.0)	0.016*
Complication	18 (41.9)	30 (40.0)	0.843
G1+G2	11 (25.6)	27 (36.0)	0.027*
G3+G4	7 (16.3)	3 (4.0)	
POPF	19 (50.0)	28 (37.3)	0.197
CR-POPF	6 (14.0)	2 (2.7)	0.050*

LDPS, laparoscopic distal pancreatectomy; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; SPN, solitary pseudopapillary neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; POPF, postoperative pancreatic fistula; BMI, body mass index; CR-POPF, clinically relevant POPF.

*Statistically significant.

Data are presented as mean±standard deviation, n (%), or number only.

transfusion rate decreased from 9.3% to 0.0% ($p=0.016$).

In terms of postoperative complications, the overall complication rate did not show difference between the two periods ($p=0.843$); however, the ratio of clinically relevant (CR) complications (Clavien-Dindo classification grade III or IV) decreased from 16.3% to 4.0% ($p=0.027$). Also, in POPF, the total ratio did not differ between the two groups ($p=0.197$), but CR-POPF decreased significantly ($p=0.050$) from 14.0% to 2.7%.

Chronological change in perioperative outcomes between LDPS and LSpDP

In Era 1, there was no difference in clinical characteristics between the two groups. However, it was noted that LSpDP group showed superior results compared to LDPS group in terms of LOH (8.8 days vs. 12.0 days, $p=0.043$) and POPF ratio (22.5% vs. 44.2%, $p=0.037$) (Table 2).

In Era 2, clinical characteristics between the two groups did

Table 2. Clinical Characteristics and Surgical Outcomes of Two Groups in Era 1

	LSpDP (n=40)	LDPS (n=43)	p value
Clinical characteristics			
Age (yr)	55.08±13.97	50.07±14.61	0.115
Sex, male	13 (32.5)	15 (34.9)	0.818
BMI (kg/m ²)	23.26±3.40	22.84±3.08	0.550
Diagnosis			0.762
IPMN	12	9	
NET	6	4	
SPN	9	10	
MCN	4	7	
SCN	6	5	
Metastatic cancer	1	2	
Chronic pancreatitis	1	4	
Other benign	1	2	
Other cancer	0	0	
Tumor size (cm)	3.01±2.25	3.75±1.80	0.146
Surgical outcomes			
Operation time (min)	224.3±83.9	218.4±108.6	0.784
Hospital stay (days)	8.8±4.6	12.0±8.8	0.043*
Estimated blood loss (mL)	239.8±382.8	259.8±261.1	0.780
Transfusion	4 (10.0)	4 (9.3)	>0.999
Complication	12 (30.0)	18 (41.9)	0.261
G1+G2	9 (22.5)	11 (25.6)	0.694
G3+G4	3 (7.5)	7 (16.3)	
POPF	9 (22.5)	19 (44.2)	0.037*
CR-POPF	3 (7.5)	6 (14.0)	0.485

LSpDP, laparoscopic spleen-preserving distal pancreatectomy; LDPS, laparoscopic distal pancreatectomy; BMI, body mass index; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; SPN, solitary pseudopapillary neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; POPF, postoperative pancreatic fistula; CR-POPF, clinically relevant POPF.

*Statistically significant.

Data are presented as mean±standard deviation, n (%), or number only.

Table 3. Clinical Characteristics and Surgical Outcomes of Two Groups in Era 2

	LSpDP (n=40)	LDPS (n=75)	p value
Clinical characteristics			
Age (yr)	49.18±15.08	53.11±15.65	0.196
Sex, male	13 (32.5)	27 (36.0)	0.707
BMI (kg/m ²)	22.55±3.44	24.07±3.60	0.031*
Diagnosis			0.098
IPMN	5	14	
NET	10	18	
SPN	8	11	
MCN	11	6	
SCN	1	5	
Metastatic cancer	1	4	
Chronic pancreatitis	3	5	
Other benign	1	10	
Other cancer	0	2	
Tumor size (cm)	3.68±2.82	3.69±2.26	0.980
Surgical outcomes			
Operation time (min)	216.8±65.5	216.2±88.7	0.973
Hospital stay (days)	8.7±4.6	9.1±3.8	0.684
Estimated blood loss (mL)	104.3±112.1	144.5±161.7	0.121
Transfusion	0 (0.0)	0 (0.0)	-
Complication	9 (22.5)	30 (40.0)	0.059
G1+G2	8 (20.0)	27 (36.0)	>0.999
G3+G4	1 (2.5)	3 (4.0)	
POPF	15 (37.5)	28 (37.3)	0.986
CR-POPF	0 (0.0)	2 (2.7)	0.542

LSpDP, laparoscopic spleen-preserving distal pancreatectomy; LDPS, laparoscopic distal pancreatectomy; BMI, body mass index; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; SPN, solitary pseudopapillary neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; POPF, postoperative pancreatic fistula; CR-POPF, clinically relevant POPF.

*Statistically significant.

Data are presented as mean±standard deviation, n (%), or number only.

not differ, except for BMI. The BMI in LDPS group was higher than that in LSpDP group (24.07 kg/m² vs. 22.55 kg/m², $p=0.031$). However, the surgical outcomes showed no statistical differences between the two groups (Table 3).

Long-term follow-up of immunologic function between LDPS and LSpDP

To evaluate immunologic functions according to spleen preservation, we compared the immunologic profiles, such as IgG, IgA, IgM, and Kappa and Lambda chain, between the two groups. Among the patients in Era 2, 28 patients (70%) in LSpDP group and 53 patients (70.7%) in LDPS group were enrolled in the immunologic marker follow-up. The duration of the follow-up periods of the immunologic profiles ranged from 3 to 51 months, and the mean duration between the operation and measurement of immunologic profiles was 14.12±14.52 months in LSpDP group and 11.68±12.10 months in LDPS

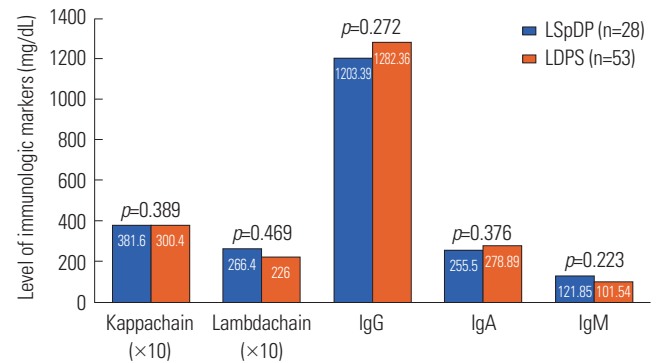


Fig. 3. Immunologic profile following distal pancreatectomy. The two groups showed no significant differences in all of the immunologic markers. LSpDP, laparoscopic spleen-preserving distal pancreatectomy; LDPS, laparoscopic distal pancreatectomy.

group, without significant change ($p=0.434$). Immunologic parameters were well-preserved in patients with LDPS. We also observed no significant differences in all of the immunologic markers between the two groups (Fig. 3).

DISCUSSION

The treatment of choice for benign and borderline malignant pancreatic tumor in pancreas body and tail is DP, and recently, most operations are conducted using the laparoscopic approach.⁶⁻⁹ However, due to the technical complexity and anatomical proximity, combined splenectomy is occasionally conducted without any relation to oncologic outcomes.¹⁰ In this study, we planned concomitant splenectomy preoperatively, if any of the following findings were found on the preoperative image study: the tumor abuts splenic hilum or splenic vessels; the splenic vessel is tortuous and has multiple branch; or the pancreas tail abuts splenic hilum, so vessel preserving or Warshaw's procedure is difficult and complicated. In addition, we conducted completion of splenectomy in case of total splenic ischemia after Warshaw's procedures.

The impact of splenectomy on surgical outcomes still remains controversial, since the function of spleen is not well-known, excluding immunological functions.¹¹ A few decades ago, severe complications, such as overwhelming post-splenectomy infection, were occasionally observed;¹² however, due to the advance in postoperative care, most recent patients do not experience complications after splenectomy.

Some recent studies reported equivalent surgical outcomes between LDPS and LSpDP. In 2014, Dumitrascu, et al.¹³ reported that spleen removal during DP was not associated with a higher morbidity but with an increased blood loss and the need for intraoperative transfusions. Although the postoperative systemic inflammatory response was higher when the splenectomy was performed, the number of postoperative infectious complications was not influenced. In 2016, Kwon, et al.¹⁴ reported that LDPS was associated with more fluid collec-

tions and LSpDP with more vascular complications, all with a minimal clinical impact. Both methods showed similar functional outcomes. They concluded that either LDPS or LSpDP could be performed depending on the indication and surgeon's experiences, considering the comparable results.

In this study, we divided the patient groups into Era 1 and Era 2, and found no statistical differences in clinical characteristics between the two groups. In surgical outcomes, LSpDP group showed superior results in Era 1; however, in Era 2, LDPS group showed equivalent surgical outcomes to LSpDP group. These results suggest that the potential benefit of spleen preservation in surgical outcomes has diminished as time passes, as a result of advances in laparoscopic techniques and postoperative care. In technical aspect, we developed a modified lasso technique for LDPS,¹⁵ which was reported to be feasible, easy, and safe for improving perioperative outcomes in LDPS. Recently, Early Recovery After Surgery¹⁶ has suggested early drain removal, early diet build-up, and early discharge after pancreatic surgery; and in line with these changes, postoperative management at our institution has changed to the use of open drain, early drain removal, and early diet build-up. We cautiously assume that the improvement in POPF rate is due to the change in postoperative management. CR complication (Clavien-Dindo classification grade II or IV) accounted for only 4.0% (3 of 75 patients) of LDPS group in Era 2. The CR complications of three patients were two cases of reoperation due to the peritonitis of unknown origin and one case of reoperation due to the wound dehiscence. As a result, the ratio of LDPS at our institution gradually increased compared to LSpDP, as the time passed from Era 1 to Era 2.

Several studies used immunoglobulin levels to evaluate immunologic function after splenectomy, such as IgG, IgA, and IgM.¹⁷⁻¹⁹ These studies reported that the level of IgG and IgA increased normally and the level of IgM was normal or decreased after splenectomy.¹⁷ In the present study, similar tendency was observed; however there was no statistical differences in immunologic markers between LSpDP and LDPS groups. Among the patients who underwent LDPS and were followed up for immunologic markers, five patients were re-admitted due to infectious disease. Three patients were admitted due to pneumonia, one patient due to herpes zoster, and the other one patient due to unknown origin. However, in additional analysis comparing the immunologic markers between patients re-admitted due to infectious disease and the others, we failed to find differences in immunologic markers. We carefully conclude that splenectomy does not affect immunologic markers, and that low immunologic markers do not make them more susceptible to infection. Further studies on spleen and immunology should be performed in the future.

In the past, in consideration of the clinical usefulness of spleen preserving,²⁰⁻²² robots were used to maximize the success rate of spleen preservation.²³ However, according to recent meta-analyses,^{24,25} the usefulness of robots in spleen pres-

ervation was reported to be similar to that of laparoscopy, and we authors also confirmed this in previous research.²⁶ Rather, it was thought that the robots would be more useful in performing single-site plus one port DP,²⁷⁻³⁰ a concept of reduced port, in well-selected patients during DP requiring concomitant splenectomy. Further research is required regarding the application of robotic surgery on DP.

This study was mainly limited by its retrospective design, which can limit interpretation of the results. Also, there is a possibility that the surgeon factor may have influenced the surgical outcomes of LDPS. The patients enrolled in this study were operated on by four surgeons at a single institution; therefore, the development of learning curve for the surgeons may have affected the surgical outcomes of LDPS and acted as a confounding factor. Alternatively, multicenter retrospective data with propensity score matching analysis could be an option to overcome these issues.

Based on the results, we carefully conclude that during laparoscopic DP, combined splenectomy can be equivalent to spleen preserving in surgical and immunological outcomes, and inevitable splenectomy can be safely conducted.

AUTHOR CONTRIBUTIONS

Conceptualization: Chang Moo Kang and Ho Kyoung Hwang. **Data curation:** Seung Soo Hong and Sung Whan Cha. **Formal analysis:** Seung Soo Hong and Sung Whan Cha. **Investigation:** Seung Soo Hong. **Methodology:** Ho Kyoung Hwang. **Project administration:** Chang Moo Kang and Woo Jung Lee. **Resources:** Seung Soo Hong. **Software:** Seung Soo Hong. **Supervision:** Chang Moo Kang and Woo Jung Lee. **Validation:** Chang Moo Kang. **Visualization:** Ho Kyoung Hwang. **Writing—original draft:** Seung Soo Hong and Sung Whan Cha. **Writing—review & editing:** Seung Soo Hong. **Approval of final manuscript:** all authors.

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