Pancreatic cancer: Open or minimally invasive surgery?

Yu-Hua Zhang, Cheng-Wu Zhang, Zhi-Ming Hu, De-Fei Hong

Yu-Hua Zhang, Cheng-Wu Zhang, Zhi-Ming Hu, De-Fei Hong, Division of Hepatobiliary and Pancreatic Surgery and Minimally Invasive Surgery, Zhejiang Provincial People’s Hospital, Hangzhou 310014, Zhejiang Province, China

Author contributions: Zhang YH and Hong DF designed the study; Zhang YH, Zhang CW, Hu ZM and Hong DF reviewed and analyzed the literature, and drafted and revised the manuscript; All authors approved the final version of the manuscript to be published.

Supported by the Natural Science Foundation of Zhejiang Province, China, No. LY15H160054; and the Key Project of the Science and Technology Department of Zhejiang Province, No. 2013C03046.

Conflict-of-interest statement: The authors declare that there is no potential conflict of interest related to this study.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: De-Fei Hong, Professor, Division of Hepatobiliary and Pancreatic Surgery and Minimally Invasive Surgery, Zhejiang Provincial People’s Hospital, 158 Shantang Road, Hangzhou 310014, Zhejiang Province, China. hongdefi@163.com

Telephone: +86-571-85893396

Received: March 25, 2016

Peer-review started: March 26, 2016

First decision: April 14, 2016

Revised: May 4, 2016

Accepted: May 23, 2016

Article in press: May 23, 2016

Published online: August 28, 2016

Abstract
Pancreatic duct adenocarcinoma is one of the most fatal malignancies, with R0 resection remaining the most important part of treatment of this malignancy. However, pancreatectomy is believed to be one of the most challenging procedures and R0 resection remains the only chance for patients with pancreatic cancer to have a good prognosis. Some surgeons have tried minimally invasive pancreatic surgery, but the short- and long-term outcomes of pancreatic malignancy remain controversial between open and minimally invasive procedures. We collected comparative data about minimally invasive and open pancreatic surgery. The available evidence suggests that minimally invasive pancreaticoduodenectomy (MIPD) is as safe and feasible as open PD (OPD), and shows some benefit, such as less intraoperative blood loss and shorter postoperative hospital stay. Despite the limited evidence for MIPD in pancreatic cancer, most of the available data show that the short-term oncological adequacy is similar between MIPD and OPD. Some surgical techniques, including superior mesenteric artery-first approach and laparoscopic pancreatoduodenectomy with major vein resection, are believed to improve the rate of R0 resection. Laparoscopic distal pancreatectomy is less technically demanding and is accepted in more pancreatic centers. It is technically safe and feasible and has similar short-term oncological prognosis compared with open distal pancreatectomy.

Key words: Laparoscopic; Minimally invasive; Robotic; Pancreaticoduodenectomy; Distal pancreatectomy; Pancreatic cancer

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Minimally invasive pancreaticoduodenectomy is as safe and feasible as open pancreaticoduodenectomy (OPD) and shows some superiority. The
short-term oncological results are similar between laparoscopic pancreaticoduodenectomy (LPD) and OPD. However, in some experienced hands, better prognosis is detected in the LPD group because the patients can receive adjuvant therapy faster because of the benefits of minimal invasiveness. Minimally invasive distal pancreatectomy is a well-established procedure and widely accepted. It is safe, feasible, and has similar short-term oncological results compared with open distal pancreatectomy.

Zhang YH, Zhang CW, Hu ZM, Hong DF. Pancreatic cancer: Open or minimally invasive surgery? World J Gastroenterol 2016; 22(32): 7301-7310 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i32/7301.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i32.7301

INTRODUCTION

Pancreatic cancer ranks as the 4th highest cause of cancer-related death in the United States and the 5-year survival is about 6%[1]. Surgical R0 resection is the best chance for a cure and remains the cornerstone of treatment of pancreatic malignancy[2,3]. However, pancreatic surgery is believed to be one of the most challenging procedures because of the high risks of postoperative morbidity and mortality associated with intraoperative bleeding and postoperative complications including pancreatic fistula[2,4,5]. Another key point for surgical treatment of pancreatic malignancy is oncological adequacy. R0 resection is the best chance for patients to have a good prognosis[4,6].

Minimally invasive techniques, including laparoscopic and robotic approaches, have rapidly evolved and include a variety of abdominal surgical procedures[7-10]. They provide the patients with better short-term outcomes, including smaller incisions, shorter hospital stay and less blood loss. Some surgeons in large-volume pancreatic centers have tried minimally invasive pancreatic surgery[11-16]. However, the short- and long-term outcomes of pancreatic malignancy remain controversial, especially for oncological prognosis.

Many pancreatic surgeons doubt the safety and oncological adequacy of minimally invasive pancreatic surgery. Here, we collected and analyzed the published data about minimally invasive pancreatic surgery.

LAPAROSCOPIC PANCREATICODUODENECTOMY

Background of laparoscopic pancreaticoduodenectomy

Following the first report of laparoscopic pancreaticoduodenectomy (LPD) in 1994[17], Gagner and Pomp[18] subsequently published a series of 10 patients in 1997. In Gagner’s series, the conversion rate was 40% and the operating time was 8.5 h. Dependent upon these results, the authors concluded that the minimally invasive approach was not advocated because there was no apparent advantage over traditional open approaches. After that, surgeons spent a decade improving their laparoscopic skills, until a large LPD cohort was reported in France in 2005[19] and then in India in 2009[15]. During 1994-2009, several surgeons tried to apply hybrid, laparoscopic-open approaches to avoid the complexity of a purely laparoscopic procedure[13,19]. Although these approaches may overcome some of the limitations, they may reduce the potential benefits of purely laparoscopic approaches, including less pain, improved postoperative recovery and shorter hospital stay. After Palanivelu et al[15] reported 75 cases of LPD in 2009, large cohorts of LPD have been reported in the United States[11,20,21], South Korea[16], China[22], Italy[23] and France[24]. LPD eventually gained momentum, following its 30 years’ development, and it has emerged as a well-established procedure with acceptable morbidity and mortality rates in some specialized high-volume pancreatic centers[12,15,16,20,22,23]. Although LPD has been accepted in many specialized minimally invasive pancreatic centers, the short- and long-term results remain controversial. We collected clinical reports with comparative data between minimally invasive PD (MIPD) and open PD (OPD) (Table 1).

Safety and feasibility of LPD

PD is a complex procedure because of the dissection around important vessels and three complex reconstructions. Moreover, it is a procedure with high morbidity[25]. Although LPD has been accepted in some specialized centers, it is still a challenging operation for most pancreatic surgeons; still, there has been a rapid increase in the number of LPDs performed in different centers. Some large-volume centers have published their comparative studies between LPD and OPD[11,15,14,20,21,24,26-31], demonstrating the safety of LPD; although, long-term oncological benefits of this approach remain debatable.

Croome et al[20] reviewed their data for patients with pancreatic ductal adenocarcinoma (PDAC) undergoing LPD (n = 108) and OPD (n = 214). A significantly reduced blood loss and blood transfusion requirement and a shorter postoperative stay (6 d vs 9 d) were observed in the LPD group compared with the OPD group.

A case match study was performed by Dokmak et al[21] comparing 46 LPD and OPD procedures. Patients were matched for demographic data, associated comorbidity and underlying disease. The results suggested that a high rate of severe morbidity due to severe pancreatic fistula was detected in patients with a high risk of pancreatic fistula. In a subgroup of patients with a low risk of pancreatic fistula, the outcome of the two approaches was similar. The result of this study suggested that, in a subgroup of patients with a high risk of pancreatic fistula, LPD was associated with high
Table 1 Safety and feasibility of laparoscopic pancreaticoduodenectomy: Clinical cohorts of minimally invasive pancreaticoduodenectomy and open pancreaticoduodenectomy including comparative results

| Ref. | Year | Country | Technique | Cases | Operating time, min | EBL, mL | LHS, D | CD ≥ III | PF | DGE | Readmission rate | Mortality |
|------|------|---------|-----------|-------|---------------------|---------|--------|----------|----|-----|-----------------|-----------|
| Sharp et al | 2015 | United States | LPD | 384 | NR | NR | NR | NR | NR | NR | NR | 5.0% | 5.2% (30 D) |
| | | | OPD | 4037 | NR | NR | NR | NR | NR | NR | NR | 9.0% | 3.7% (30 D) |
| Song et al | 2015 | South Korea | LPPPD | 93 | 482.5 ± 117.6 | 609 ± 375 | 143.7 ± 7.8 | 7.5% | 6 (6.5) | 3.2% | 5 (5.4) | NR |
| | | | OPPPD | 93 | 347.9 ± 87.2 | 570 ± 448 | 192 ± 8.8 | 5.4% | 6 (6.5) | 7.5% | 3 (3.2) | NR |
| Chen et al | 2015 | China | RPDP | 60 | 410 ± 110 | 400 (200-600) | 20 ± 7.4 | 11.7% | 13.3% | 83% | NR | 1.7% |
| | | | OPD | 120 | 325 ± 80 | 500 (350-800) | 25 ± 11.2 | 13.3% | 24% | 15.0% | NR | 25% |
| Dokmak et al | 2015 | France | RPDP | 46 | 342 (240-540) | 368 (50-1200) | 25 (8-104) | 28.0% | 48.0% | 17.0% | 9.0% | 2.0% |
| | | | OPD | 46 | 264 (120-400) | 293 (50-1200) | 23 (7-115) | 20.0% | 41.0% | 15.0% | 9.0% | 0 |
| Baker et al | 2015 | United States | RPDP | 22 | 454 (294-529) | 425 ± 133 | 7 (4-25) | 13.6% | 4.6% | 13.5% | 22% | 0 |
| Tran et al | 2015 | United States | LPD | 681 | NR | NR | 12 (9-20) | NR | NR | NR | NR | 3.8% |
| | | | OPD | 14893 | NR | NR | 11 (8-16) | NR | NR | NR | NR | 5.0% |
| Tan et al | 2015 | China | LPD | 30 | 513.7 ± 56.3 | NR | 9.9 ± 3.7 | NR | 10/30 | 2/30 | NR | 0 |
| | | | OPD | 30 | 371.6 ± 85.53 | NR | 11.87 ± 5.72 | NR | 3/30 | 3/30 | NR | 1/30 |
| Adam et al | 2015 | United States | MIPD | 983 | NR | NR | NR | NR | NR | NR | NR | 4.5% |
| | | | OPPPD | 6078 | NR | NR | NR | NR | NR | NR | NR | 3.7% |
| Chalikonda et al | 2014 | United States | HPDP | 30 | 476.00 | 485 | 9.79 | 30.0% | NR | NR | NR | 4.0% |
| | | | OPD | 63 | 366.48 | 775 | 13.2 ± 43.0% | NR | NR | NR | 0 |
| Bao et al | 2014 | United States | RPDP | 28 | 431 (340-628) | 100 (50-300) | 7.4 (5.5-17.1) | NR | 29.0% | NR | 25.0% | 7.0% (30 D) |
| | | | OPD | 28 | 410 (190-621) | 300 (100-800) | 8.1 (6.5-15.3) | NR | 29.0% | NR | 25.0% | 7.0% (30 D) |
| Croome et al | 2014 | United States | LPD | 108 | 5794 ± 93.5 | 4924 ± 5193 | 6 (4-118) | 5.6% (≥ III b) | 11% (B/C) | 9% (B/C) | NR | 1.0% (1 H) |
| | | | OPD | 214 | 387.6 ± 191.8 | 866 ± 733.7 | 9.6 (7-115) | 13.6% (≥ III b) | 12% (B/C) | 8% (B/C) | NR | 2.0% (1 H) |
| Speicher et al | 2014 | United States | HPDP | 31 | 442 (386.3-496.5) | 600 (312.5-700) | 12 (8.5-18.5) | NR | 35.5% | NR | 35.5% | 3.2% (30 D) |
| | | | OPD | 84 | 425.5 (345.8-478.8) | 425 (300-700) | 10 (8-14) | NR | 22.6% | NR | 39.3% | 1.2% (30 D) |
| Asbun et al | 2012 | United States | LPD | 53 | 541.88 | 195 ± 136 | 8.0 ± 3.2 | NR | 16.7% | 11.3% | NR | 5.7% (100 D) |
| | | | OPD | 215 | 401 ± 108 | 1032 ± 1151 | 12.4 ± 8.5 | NR | 17.3% | 15.3% | NR | 8.8% (100 D) |
| Lai et al | 2012 | China | RPDP | 20 | 491.5 ± 194.0 | 247 (30-899) | 13.7 ± 6.1 | NR | 55.0% | 5% | NR | 0 |
| | | | OPD | 67 | 264.9 ± 63.7 | 774.8 (30-800) | 25.8 ± 23.1 | NR | 17.9% | 11.9% | NR | 3% |

CD: Clavien-Dindo; DGE: Delayed gastric emptying; EBL: Estimated blood loss; HPD: Hybrid pancreaticoduodenectomy; LHS: Length of hospital stay; LPD: Laparoscopic pancreaticoduodenectomy; LPPPD: Laparoscopic pylorus-preserving pancreaticoduodenectomy; MIPD: Minimally invasive pancreaticoduodenectomy; NR: Not reported; OPD: Open pancreaticoduodenectomy; OPPPD: Open pylorus-preserving pancreaticoduodenectomy; PF: Pancreatic fistula; RPDP: Robotic pancreaticoduodenectomy.

morbidity. Thus, it should be considered only in patients with a dilated pancreatic duct and a hard pancreas texture, who have been believed to have a low risk of pancreatic fistula.

Adam et al reviewed patients undergoing PD from the National Cancer Database between 2010 and 2011, including 983 MIPDs and 6078 LPDs. Their results suggested that, for patients with PDAC, no difference was detected in number of lymph nodes (LNs) removed, rate of R0 resection, length of hospital stay or readmission. However, the 30-d mortality was lower in the OPD group than in the MIPD group. The authors suggested that the widespread adoption of the technique should be paused. MIPD is a complex procedure that needs comprehensive protocols outlining criteria for implementation.

Asbun and Stauffer presented retrospective clinical data from Mayo Clinic of 215 OPD and 53 LPD patients. They also showed significantly better results in LPD...
groups, such as less blood loss ($P < 0.001$) and blood transfusion requirements ($P < 0.001$), and a shorter postoperative hospital stay ($P < 0.001$). While a significantly longer operating time was observed in LPD ($P < 0.001$), the LPD patients had a greater number of LNs removed than the OPD patients ($P = 0.007$). This series also demonstrated that LPD is safe and feasible and showed some benefits for patients.

Results from another cohort with PDAC in the United States treated with LPD were presented at the Western Surgical Association 122nd Scientific Session[21]. The researchers compared 4037 OPDs with 384 LPDs and showed significant differences favoring LPD for length of hospital stay and unplanned readmission. A lower risk of 30-d mortality was found in high-volume centers and in centers with experience of performing more than 10 LPDs; moreover, the 30-d mortality for LPD was similar to that for OPD. Finally, the researchers demonstrated that there is a learning curve for LPD.

Song et al[16] compared 137 laparoscopic pylorus-preserving PDs (LPPPDs) with 2055 open PPPDs (OPPPDs) in South Korea. They found that operating time was longer for LPPPD than for OPPPD, and the perioperative complications were similar in both groups. Fewer analgesic injections were administrated in the LPPPD group ($P < 0.001$). The oncological results were similar between the two groups, including number of LNs removed and long-term survival.

In addition to LPD, a few studies have compared robotic PD (RPD) with OPD. Chalikonda et al[21] from the Cleveland Clinic reviewed the results of 30 matched laparoscopic RPD (LRPD) and OPD procedures. LRPD and OPD groups were matched with demographics. A similar estimated blood loss and rate of reoperation were found in the two groups. However, there was a significant increase in operating time and shorter hospital stay for the LRPD group.

We found that most of the clinical studies showed that LPD is as safe and feasible as OPD technically, and has some of the superiority associated with minimally invasive surgery, such as less estimated blood loss and shorter hospital stay. However, some authors have suggested that MIPD should be advocated in a subgroup of patients with lower risk of pancreatic fistula. In our opinion, LPD is as safe as OPD. However, due to the complexity of LPD, it is a technically demanding procedure with a learning curve. In small clinical cohorts of LPD at the beginning of the learning curve, there might be higher morbidity and mortality for LPD than for OPD. The problem now is how to reduce the risks of LPD at the beginning of the learning curve. Apart from technical feasibility, the major arguments against LPD are oncological adequacy, especially for patients with PDAC.

**Oncological adequacy of LPD for pancreatic malignancy**

Pancreatic cancer still has a high fatality rate. Radical resection is required for a good prognosis. Many clinical studies have reported LPD; however, most of those studies have included a variety of diseases requiring LPD. To the best of our knowledge, few studies have compared the oncological prognosis of PDAC treated with LPD or OPD (Table 2).

Song et al[16] compared the oncological results of pancreatic cancer treated with OPPPD ($n = 261$) and LPPPD ($n = 11$). TMN stage, R0 resection rate, in-hospital stay and the overall survival were similar between the two groups. In a case-control study from France[24], the results for LPD ($n = 15$) in patients with PDAC were similar to those with OPD ($n = 14$) with regard to tumor size, number of LNs harvested and rate of R0 resection. Croome et al[20] reported a large single center study of pancreatic carcinoma treated with LPD. Clinical data of 108 cases of LPD were reviewed retrospectively and compared with 214 cases of OPD performed in the same period at their center. The short-term oncological results, including tumor size, LN positivity, R0 resection and overall survival, were similar between the two groups, and significantly longer progression-free survival was found in the LPD group. The authors thought that this difference might have been because the patients who underwent LPD had the advantage of minimal invasiveness and recovered faster from the operation. This allowed the patients to receive adjuvant therapy in a timely manner and probably led to better prognosis.

A large LPD cohort study[21] from the National Cancer Data Base involved 384 LPDs and 4039 OPDs. The results showed no difference between the LPD and OPD groups with regard to length of stay, margin-positive resection, LN count and readmission rate.

Chen et al[25] compared the oncological results of pancreatic cancer treated with RPD ($n = 19$) and OPD ($n = 38$). There was no difference in the R0 resection rate, number of LNs resected, cancer stage, overall survival and disease-free survival between the two groups.

All the results above show that in most of the experienced minimally invasive pancreatic centers, LPD has similar short-term oncological results as OPD. However, Croome et al[20] reported the long-term prognostic benefit in the LPD group because of the advantages of minimal invasiveness. Furthermore, Croome et al[20] presented the largest cohort with pancreatic cancer treated with LPD, thus, we can probably form the hypothesis that, if surgeons acquire enough experience of LPD, LPD can yield the benefits of minimal invasiveness as well as long-term oncological benefit, compared with OPD. To obtain oncological adequacy, some technical tips are suggested for application during the operation.

**Surgical technique to improve rate of R0 resection**

**Superior mesenteric artery-first approach:** To improve the long-term prognosis of patients with
PDAC; curative (R0) resection is required initially. Many reports have discussed the value of R0 resection in prognosis of PDAC. The consensus among pancreatic surgeons is that positive surgical margins are associated with poor survival[35-38]. The primary site of positive margins is from the right side of the superior mesenteric artery (SMA) (N14) to the right side of the celiac trunk (N9), including the mesopancreas[39]. To improve R0 resection, the SMA-first approach was advocated in OPD. The artery-first approach has been proven as effective in reducing the risk of bleeding and improving the rate of R0 resection in pancreatic cancer. However, few publications have reported the SMA-first approach in LPD. To the best of our knowledge, only two publications have described laparoscopic SMA-first approaches[40,41]. Pittau et al[40] reported the right posterior approach. The authors performed this procedure exactly like the Pessaux procedure in OPD[42], and they dissected the SMA after complete kocherization, including mobilization of the right colon. Cho et al[41] described the left posterior SMA-first approach. They dissected the SMA at the ligament of Treitz without mobilization of the duodenum or right colon[43]. In our center, we perform the right posterior SMA-first approach, as described by Pittau et al[40]. We expose the SMA from the right side after complete kocherization (Figure 1). After exposure of the SMA, it would be easy to decide the resectability of the tumor. Another benefit is that this approach makes resection of the uncinate process from the SMA easier, and warrants complete removal of the neuro laminar tissue at the right side of the SMA up to the celiac axis (Figure 2).

**Major vein resection:** Involvement of the portal vein in locally advanced tumor is no longer a contradiction for surgical resection of pancreatic malignancy using traditional open procedures. A lot of data from larger pancreatic centers have provided evidence indicating that en bloc resection of tumor with involved vessels is safe and feasible, and can improve the rate of R0 resection[44-51]. Patients who have en bloc resection with the involved vein have similar long-term oncological prognosis compared with patients who do not have vascular involvement.[44,45,48-50].

### Table 2  Oncological results of pancreatic cancer in minimally invasive pancreaticoduodenectomy and open pancreaticoduodenectomy: Clinical trials including comparative results of pancreatic ductal adenocarcinoma between minimally invasive pancreaticoduodenectomy and open pancreaticoduodenectomy

| Ref.        | Year | Country   | Technique | No. of PDAC cases | Rate of R0 resection | No. of LN | Positive LN | Tumor size, cm |
|-------------|------|-----------|-----------|-------------------|----------------------|----------|-------------|----------------|
| Sharp et al[21] | 2015 | United States | LPD       | 384               | 80.0%                | 18 ± 9.7 | NR          | 3.2 ± 1.3     |
| Song et al[16] | 2015 | South Korea | LPPPD     | 11                | 72.7%                | 15 ± 10  | 0.8 ± 1.2   | 2.8 ± 0.6     |
| Dokmak et al[24] | 2015 | France    | LPD       | 15                | 60.0%                | 20 (8-59)| 4.7 (4-32)  | 2.4 (1.5-4)   |
| Chen et al[34] | 2015 | China     | RPD       | 19                | 94.7%                | 18.1 ± 6.6| NR          | 3.0 ± 0.9     |
| Croome et al[21] | 2014 | United States | LPD       | 108               | 77.8%                | 21.4 ± 8.1| 73.1%       | 3.3 ± 1.0     |

LN: Lymph node; LPD: Laparoscopic pancreaticoduodenectomy; LPPPD: Laparoscopic pylorus-preserving pancreaticoduodenectomy; MIPD: Minimally invasive pancreaticoduodenectomy; OPD: Open pancreaticoduodenectomy; OPPPD: Open pylorus-preserving pancreaticoduodenectomy; PDAC: Pancreatic duct adenocarcinoma; NR: Not reported.

**Figure 1**  Superior mesentery artery was exposed from the right posterior side after complete kocherization. D: Duodenum; IVC: Inferior vena cava; LRV: Left renal vein; PUP: Pancreatic uncinate process; SMA: Superior mesenteric artery.

**Figure 2**  Local vision after removal of the specimen. CT: Celiac trunk; IVC: Inferior vena cava; PV: Portal vein; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein; SPV: Splenic vein.
RPD has since been proven to be feasible and safe, with the minimally invasive advantages compared with open procedures \cite{30,31,33,34,55,56}. It is believed that the robotic surgical system provides surgeons with enhanced dexterity, superior magnified high-resolution 3D visualization, and greater precision and ergonomic comfort. This approach enables surgeons to control the surgical instruments with accuracy, flexibility and a wide range of motion, which is suggested for procedures that require complicated resection and reconstruction, such as prostatectomy, coronary surgery and PD. In our opinion, the application of robotic systems in PD with major vein resection can improve the quality of vein reconstruction, and we advocate them if possible.

**LAPAROSCOPIC DP**

**Background**

DP is widely accepted as an option for PDAC located in the distal pancreas. However, in past decades, laparoscopic DP (LPD) has been accepted increasingly with evidence of minimally invasive benefits. Compared with LPD, LDP is less technically demanding because there is limited dissection around the vessels and no reconstruction is required \cite{57,58}. So, more surgeons accept LDP than LPD.

**Safety and feasibility of LDP**

A recently published meta-analysis \cite{59-63} indicated that LDP was a safe and feasible option in terms of operating time and postoperative mortality and morbidities, such as postoperative bleeding and pancreatic fistula. Moreover, minimally invasive superiority was found in LDP, including significantly decreased estimated blood loss, time to first oral intake and length of hospital stay \cite{59-63}. These results clearly show that LDP is as safe and feasible as ODP.

**Short-term oncological results**

Microscopically, R0 resection is the most important part of treatment of resectable pancreatic cancer. Some non-comparative cohorts have shown that R0 resection of pancreatic cancer can be achieved by laparoscopic resection \cite{64,65}. Most of the comparative studies have shown that there is no difference in the rate of R0 resection in the final pathological results between LPD and ODP \cite{58,66,67}. To the best of our knowledge, only DiNorcia et al. \cite{68} have reported a decrease in R1 resection in the laparoscopic group; however, their series had mixed pathology, including neuroendocrine tumor and pancreatic adenocarcinoma. Another important short-term oncological marker is LN retrieval. A minimum of 12 LNs is required for resection of pancreatic adenocarcinoma \cite{69,70}. N0 patients with > 12 LNs have better survival than N0 patients with < 12 LNs (P < 0.001) \cite{70}. Most studies have found that the number of LNs harvested in laparoscopic and open procedures is similar \cite{58,66-68,71}.
The data here demonstrate that most of the minimally invasive pancreatic surgeons have a consensus that LDP has the same short-term oncological results as ODP.

Long-term oncological outcomes of LDP

Only a few studies have described long-term prognosis after LDP, and few comparative data are reported. Mabrut et al.\(^1\) reported 16 patients with pancreatic malignancy, 4 of whom had pancreatic adenocarcinoma, and 23% of these patients had recurrence during 15 mo. Fernández-Cruz et al.\(^2\) reported 10 cases of laparoscopic radical antegrade modular pancreatosplenectomy (RAMPs), with 3 having died within a year and a median survival period of 14 mo. Rehman et al.\(^3\) found a similar 3-year overall survival between 8 LDP and 14 ODP procedures for PDAC. Kooby et al.\(^4\) reported similar median survival (16 mo) after LDP and ODP in a matched study. Kim et al.\(^5\) reported 11 LDPs with diagnosis of malignancy in their postoperative pathological results, including 5 cases of PDCA; only 1 patient died of cancer during the follow-up period (3-60 mo). The results to date suggest that the long-term prognosis of LDP for adenocarcinoma is similar to that for open procedures. It was also found that there was no difference in short-term oncological markers, including tumor size, radiological stage, margin-negative resection, power of LN retrieval and LN metastasis between the two groups. The authors concluded that LDP is acceptable for patients with pancreatic malignancy. However, further larger studies are required to give solid evidence of the long-term oncological benefit of LDP.

CONCLUSION

After initial reports of LPD and LDP in the 1990s, laparoscopic pancreatectomy finally became a well-established procedure following 30 years' development of laparoscopic skills and equipment. The data here suggest that minimally invasive pancreatectomy is safe and feasible and has adequate evidence of good short-term outcome. However, randomized controlled trials and long-term oncological results are still lacking. The long-term oncological results should be further addressed by randomized controlled trials. Another problem now is how to generalize this procedure from experienced hands to other centers.

ACKNOWLEDGMENTS

We wish to thank Tang Wei and Song Peipei from Tokyo University for their kind help and critical review of the manuscript.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30 [PMID: 26742998 DOI: 10.3322/ caac.21332]
2. Gao JJ, Song PP, Tamura S, Hasegawa K, Sugawara Y, Kokudo N, Uchida K, Oriri R, Qi FH, Dong JH, Tang W. Standardization of perioperative management on hepatobiliary-pancreatic surgery. Drug Discov Ther 2012; 6: 108-111 [PMID: 22622021]
3. Hidalgo M. Pancreatic cancer. N Engl J Med 2010; 362: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMra0901557]
4. Shimoda M. Upon completing the 7th Sino-Japanese Symposium on Hepato-Pancreato-Biliary Disease. Biosci Trends 2008; 2: 96 [PMID: 20103909]
5. Yamashita S, Sakamoto Y, Kaneko J, Tamura S, Aoki T, Sugawara Y, Hasegawa K, Kokudo N. Resection of the second portion of the duodenum sacrificing the minor papilla but preserving the pancreas for a recurrent duodenal adenocarcinoma: report of a case. Biosci Trends 2012; 6: 44-47 [PMID: 22426103 DOI: 10.5582/bst.2012.v6.1.44]
6. Flattet Y, Yamaguchi T, Andrejevic-Blant S, Hallik N. Pancreatic adenocarcinoma: the impact of neoplastic lesion pattern on survival. Biosci Trends 2015; 9: 402-406 [PMID: 26781798 DOI: 10.5582/bst.2015.01163]
7. Hong D, Cheng J, Wang Z, Shen G, Xie Z, Wu W, Zhang Y, Zhang Y, Liu X. Comparison of two laparoscopic splenectomy plus pericardial devascularization techniques for management of portal hypertension and hypersplenism. Surg Endosc 2015; 29: 3819-3826 [PMID: 25783835 DOI: 10.1007/s00464-015-4147-4]
8. Hong D, Liu Y, Peng S, Sun X, Wang Z, Cheng J, Shen G, Zhang Y, Huang D. Binding pancreaticoastrogastricostomy in laparoscopic central pancreatectomy: a novel technique in laparoscopic pancreatic surgery. Surg Endosc 2016; 30: 715-720 [PMID: 26123326 DOI: 10.1007/s00464-015-4265-9]
9. Hong DF, Gao M, Bryner U, Cai XJ, Mou YP. Intraoperative endoscopic sphincterotomy for common bile duct stones during laparoscopic cholecystectomy. World J Gastroenterol 2000; 6: 448-450 [PMID: 11819626]
10. Hong DF, Xin Y, Chen DW. Comparison of laparoscopic cholecystectomy combined with intraoperative endoscopic sphincterotomy and laparoscopic exploration of the common bile duct for cholecystocholedocholithiasis. Surg Endosc 2006; 20: 424-427 [PMID: 16955359 DOI: 10.1007/s00464-004-8248-8]
11. Asbun HJ, Staufier JA. Laparoscopic vs open pancreaticoduodenectomy: overall outcomes and severity of complications using the Accordion Severity Grading System. J Am Coll Surg 2012; 215: 810-819 [PMID: 22999327 DOI: 10.1016/j.jamcollsurg.2012.08.006]
12. Dulucq JL, Wintringer P, Mahajna A. Laparoscopic pancreaticoduodenectomy for benign and malignant diseases. Surg Endosc 2006; 20: 1045-1050 [PMID: 16756311 DOI: 10.1007/s00464-005-0474-1]
13. Kimura Y, Hirata K, Mukaiya M, Mizuguchi T, Koiito K, Katsuramaki T. Hand-assisted laparoscopic pylorus-preserving pancreaticoduodenectomy for pancreas head disease. Am J Surg 2005; 189: 734-737 [PMID: 15910728 DOI: 10.1016/j.amjsurg.2005.03.017]
14. Lee SH, Kang CM, Hwang HK, Choi SH, Lee WJ, Chi HS. Minimally invasive RAMPS in well-selected left-sided pancreatic cancer within Yonsei criteria: long-term (>median 3 years) oncologic outcomes. Surg Endosc 2014; 28: 2848-2855 [PMID: 24853839 DOI: 10.1007/s00464-014-3537-3]
15. Palanivelu C, Rajan PS, Ragparajan M, Vaithiswaran V, Senthilnathan P, Parthasarathi R, Praveen Raj P. Evolution in techniques of laparoscopic pancreaticoduodenectomy: a decade long experience from a tertiary center. J Hepatobiliary Pancreat Surg 2009; 16: 731-740 [PMID: 19652900 DOI: 10.1007/s00534-009-0157-8]
16. Song KB, Kim SC, Hwang DW, Lee JH, Lee DJ, Lee JW, Park KM, Lee YJ. Matched Case-Control Analysis Comparing Laparoscopic and Open Pylorus-preserving Pancreaticoduodenectomy in Patients With Pancreatitis. Ann Surg 2015; 262: 146-155 [PMID: 25563866 DOI: 10.1097/SLA.00000000000001079]
17. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreateo-
Pomp A. Laparoscopic pancreatic resection: Is it worthwhile? J Gastrointest Surg 1997; 1: 20-25; discussion 25-26

Ammori BJ. Laparoscopic hand-assisted pancreaticoduodenectomy: initial UK experience. Surg Endosc 2004; 18: 717-718 [PMID: 15214369]

Croome KP, Farnell MB, Que FG, Reid-Lordardo KM, Truty MJ, Nagorney DM, Kendall MC. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches. Ann Surg 2014; 260: 633-638, discussion 638-640 [PMID: 25203880 DOI: 10.1097/SLA.0b013e3182e69057]

Sharpe SM, Talamonti MS, Wang CE, Prinz RA, Roggin KK, Bentrem DJ, Winchester DJ, Marsh RD, Stocker SJ, Baker MS. Early National Experience with Laparoscopic Pancreatoduodenectomy for Ductal Adenocarcinoma: A Comparison of Laparoscopic Pancreatoduodenectomy and Open Pancreaticoduodenectomy from the National Cancer Data Base. J Am Coll Surg 2015; 221: 175-184 [PMID: 26095569 DOI: 10.1016/j.jamcollsurg.2015.04.021]

Wang M, Zhang H, Wu Z, Zhang Z, Peng B. Laparoscopic pancreatectomy: single-surgeon experience. Surg Endosc 2015; 29: 3783-3794 [PMID: 25783837 DOI: 10.1007/s00464-015-4154-5]

Corcione F, Pirozzi F, Cucurullo D, Piccolboni D, Caracino V, Galante F, Cusano D, Sciuto A. Laparoscopic pancreaticoduodenectomy: experience of 22 cases. Surg Endosc 2013; 27: 2131-2136 [PMID: 23355144 DOI: 10.1007/s00464-012-2728-y]

Dokmak S, Fièrse FS, Aussilhou B, Bensafta Y, Lévy P, Ruszniewski P, Belghiti J, Sauvanet A. Laparoscopic pancreaticoduodenectomy should not be routine for resection of periampullary tumors. J Am Coll Surg 2015; 220: 831-838 [PMID: 25840531 DOI: 10.1016/j.jamcollsurg.2014.12.052]

Weihui W, Wei B, Zheng Z, Huang Y, Huang J, Fang J. Comparative study of outcomes after laparoscopic versus open pancreaticoduodenectomy. Zhonghua Wai chang Zaike Zhi 2014; 17: 465-468 [PMID: 24859956]

Langan RC, Graham JA, Chin AB, Rubinstein AJ, Oza K, Nusbach JA, Smirniotopoulos J, Ryder S, Jha R, Haddad N, Al-kawas F, Carroll J, Hanna J, Parker A, Al-Refaie WB, Johnson LB. Laparoscopic-assisted versus open pancreaticoduodenectomy: favorable early favorable physical-quality-of-life measures. Surgery 2014; 156: 379-384 [PMID: 24680859 DOI: 10.1016/j.surg.2014.03.018]

Lai EC, Yang GP, Tang CN. Robot-assisted laparoscopic versus open pancreaticoduodenectomy-a comparative study. Int J Surg 2012; 10: 475-479 [PMID: 22732431 DOI: 10.1016/j.ijsu.2012.06.003]

Hakeem AR, Verbeke CS, Cairns A, Aldouri A, Smith AM, Menon KV. A matched-pair analysis of laparoscopic versus open pancreaticoduodenectomy: oncological outcomes using Leeds Pathology Protocol. Hepatobiliary Pancreat Dis Int 2014; 13: 435-441 [PMID: 25010330]

Buchs NC, Addio P, Bianco FM, Ayloo S, Benedetti E, Giulianotti P. Robotic versus open pancreaticoduodenectomy: a comparative study at a single institution. World J Surg 2011; 35: 2739-2746 [PMID: 21947494 DOI: 10.1007/s00268-011-1276-3]

Baker EH, Ross SW, Seshadri R, Swan RZ, Iannitti DA, Vrochides D, Martinie JB. Robotic pancreaticoduodenectomy: comparison of complications and cost to the open approach. Int J Med Robot 2015; Epub ahead of print [PMID: 26202591 DOI: 10.1002/rcs.1688]

Adam MA, Choudhury K, Dinan MA, Reed SD, Scheri RP, Blazer DG, Roman SA, Sosa JA. Minimally Invasive Versus Open Pancreatoduodenectomy for Cancer: Practice Patterns and Short-term Outcomes Among 7061 Patients. Ann Surg 2015; 262: 372-377 [PMID: 26158612 DOI: 10.1097/SLA.0000000000001055]

Challikonda S, Aguilar-Saaavedra JR, Walsh RM. Laparoscopic robotic-assisted pancreaticoduodenectomy: a case-matched comparison with open resection. Surg Endosc 2012; 26: 2397-2402 [PMID: 22439474 DOI: 10.1007/s00464-012-2207-6]

Chen S, Chen JZ, Zhan Q, Dong XX, Shen BY, Peng CH, Li HW. Robot-assisted laparoscopic versus open pancreaticoduodenectomy: a prospective, matched, mid-term follow-up study. Surg Endosc 2015; 29: 3698-3711 [PMID: 25761559 DOI: 10.1007/s00464-015-4140-y]

Konstantinidis IT, Warshaw AL, Allen JN, Blaszkowsky LS, Castillo CF, Deshpande V, Hong TS, Kwak EL, Lauwers GY, Ryan DP, Wargo JA, Lillemoe KD, Ferrone CR. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a “true” R0 resection? Ann Surg 2013; 257: 731-736 [PMID: 22968073 DOI: 10.1097/SLA.0b013e318263d2a2]

Neoptolemos JP, Stocken DD, Dunn JA, Almond J, Beger HG, Pедерзоли P, Bassi C, Dervenis C, Fernandez-Cruz L, Lacaine F, Buckels J, Deakin M, Adab FA, Sutton R, Imrie C, Илне I, Tihanу T, Olah A, Pedrazzoli S, Spooner D, Kerr D, Fiiess H, Biihler MW. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. Ann Surg 2004; 239: 758-768 [PMID: 11729382]

Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hubran RH, Riiil TS, Schulicld RD, Choti M, Lillemoe KD, Yeо J. Margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon’s contribution to long-term survival in pancreatic cancer. J Gastrointest Surg 2006; 10: 133-1345; discussion 1345-1346 [PMID: 17175452 DOI: 10.1016/j.jgas.2006.09.008]

Gaedecke J, Gunawan B, Grade M, Sозке R, Liersch T, Becker H, Ghadimi BM. The mesopancreas is the primary site for R1 resection in pancreatic head cancer: relevance for clinical trials. Langenbeck’s Arch Surg 2010; 395: 451-458 [PMID: 19418067 DOI: 10.1007/s00423-009-0494-8]

Pittau G, Sanchez-Cabuis S, Laurenzi A, Gellli M, Cunha AS. Laparoscopic Pancreatoduodenectomy: Right Superior Mesenteric Artery “First” Approach. Ann Surg Oncol 2015; 22 Suppl 3: S345-S348 [PMID: 26471492 DOI: 10.1245/s10434-015-4913-5]

Cho A, Yamamoto H, Kainuma O. Tips of laparoscopic pancreatoduodenectomy: superior mesenteric artery first approach (with video). J Hepatobiliary Pancreat Sci 2014; 21: E19-E21 [PMID: 24307512 DOI: 10.1002/jhbp.54]

Pessaux P, Varma D, Arnaud JP. Pancreatoduodenectomy: superior mesenteric artery first approach. J Gastrointest Surg 2006; 10: 607-611 [PMID: 16627229 DOI: 10.1016/j.jgss.2005.05.001]

Kurosaki I, Minagawa M, Takano K, Takizawa H, Hatakeyama K. Left posterior approach to the superior mesenteric vascular pedicle in pancreatoduodenectomy for cancer of the pancreatic head. JOP 2011; 12: 220-229 [PMID: 21546696]

Tseng JF, Raut CP, Lee JE, Pisters PW, Vauthney JN, Adallaba EK, Gomez H, Sun CC, Crane CH, Wolfll RA, Evans DB. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg 2004; 8: 935-49; discussion 949-50 [PMID: 15585381 DOI: 10.1016/j.jgss.2004.09.046]

Takahashi S, Ogata Y, Tsuchi Z. Combined resection of the pancreas and portal vein for pancreatic cancer. Br J Surg 1994; 81: 1190-1193 [PMID: 7953357]

Shibata C, Kobari M, Tsuchiya T, Arai K, Anzai R, Takahashi M, Uzuki M, Sawai T, Yamazaki T. Pancreatoduodenectomy combined with superior mesenteric-portal vein resection for adenocarcinoma in
pancreas. World J Surg 2001; 25: 1002-1005 [PMID: 11571964]

47 Nakao A, Takeda S, Sakai M, Kaneko T, Inoue S, Sugimoto H, Kanazumi N. Extended radical resection versus standard resection for pancreatic cancer: the rationale for extended radical resection. Pancreas 2004; 28: 209-292 [PMID: 15064973]

48 Müller SA, Hartel M, Mehrabi A, Welsch T, Martin DJ, Hinz U, Schmied BM, Büchler MW. Vascular resection in pancreatic cancer surgery: survival determinants. J Gastrointest Surg 2009; 13: 784-792 [PMID: 19137380 DOI: 10.1001/annals.2009.027-091-1]

49 Martin RC, Scoggins CR, Egnatashvili V, Staley CA, McMasters KM, Kooby DA. Arterial and venous resection for pancreatic adenocarcinoma: operative and long-term outcomes. Arch Surg 2009; 144: 154-159 [PMID: 19221327 DOI: 10.1001/ archsurg.2008.547]

50 Kaneko Y, Yamaguchi A, Isogai M. Portal or superior mesenteric vein resection for pancreatic head adenocarcinoma: prognostic value of the length of venous resection. Surgery 2009; 145: 417-425 [PMID: 19303991 DOI: 10.1016/j.surg.2008.12.009]

51 Harrison LE, Klimstra DS, Brennan MF. Isolated portal vein resection and its clinical significance. J Am Coll Surg 2009; 205: 572-578 [PMID: 20011005 DOI: 10.1016/j.jamcollsurg.2009.05.010]

52 Venkataratnam R, Edjl BH, Schulick RD, Lidor AO, Makary MA, Wolfgang CL. Laparoscopic distal pancreatectomy is associated with significantly less overall morbidity compared to the open technique: a systematic review and meta-analysis. J Gastrointest Surg 2015; 19: 770-781 [PMID: 25561051 DOI: 10.1007/s11605-014-2721-z]

53 Venkat R, Edjl BH, Schulick RD, Lidor AO, Makary MA, Wolfgang CL. Laparoscopic distal pancreatectomy is associated with significantly less overall morbidity compared to the open technique: a systematic review and meta-analysis. J Gastrointest Surg 2012; 16: 1048-1059 [PMID: 22531003 DOI: 10.1007/s11605-011-1869-7]

54 Mabrut JY, Fernández-Cruz L, Azagara JS, Bassi C, Delvaux G, Weerts J, Fabre JM, Boulez J, Baulieux J, Peil JL, Gigot JP. Hepatobiliary and Pancreatic Section (HBPS) of the Royal Belgian Society of Surgery; Belgian Group for Endoscopic Surgery (BGES); Club Coelio. Laparoscopic pancreatic resection: results of a multicenter European study of 127 patients. Surgery 2005; 137: 597-605 [PMID: 15962401]

55 Manoung KH, Buunes T, Rosok BL, Kazaryan AM, Rosseland AR, Grzyb KV, Villanger O, Mathisen O, Gladhaug IP, Edwin B. Laparoscopic resection of exocrine carcinoma in central and distal pancreas results in a high rate of radical resections and long postoperative survival. Surgery 2012; 151: 717-723 [PMID: 22284762 DOI: 10.1016/j.surg.2011.12.016]

56 Jayaraman S, Gonen M, Brennan MF, D’Angelica MI, DeMatteo RP, Fong Y, Jarnagin WR, Allen PJ. Laparoscopic distal pancreatectomy: evolution of a technique at a single institution. J Am Coll Surg 2010; 211: 503-509 [PMID: 20868976 DOI: 10.1016/j.jamcollsurg.2010.06.010]

57 Mehta SS, John SK, Lochan R, Jaques BC, Manas DM, Charney RM, French JJ, White SA. Oncological feasibility of laparoscopic distal pancreatectomy for adenocarcinoma: a single-institution comparative study. World J Surg 2014; 38: 476-483 [PMID: 24081543 DOI: 10.1007/s00268-013-2268-2]

58 DiNocia J, Schrøe BA, Lee MK, Reavley PL, Rosen SJ, Lee JA, Chabot JA, Allendorf JD. Laparoscopic distal pancreatectomy offers shorter hospital stays with fewer complications. J Gastrointest Surg 2010; 14: 1804-1812 [PMID: 20589466 DOI: 10.1007/s11605-010-1264-1]

59 House MG, Gonen M, Jarnagin WR, D’Angelica M, DeMatteo RP, Fong Y, Brennan MF, Allen PJ. Prognostic significance of pathologic nodal status in patients with resected pancreatic cancer. J Gastrointest Surg 2007; 11: 1549-1555 [PMID: 17786531 DOI: 10.1007/s11605-007-0243-7]

60 Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, Choti MA, Pawlik TM. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. Ann Surg Oncol 2008; 15: 165-174 [PMID: 17896141 DOI: 10.1245/s10434-007-9587-1]

61 Mehta SS, Doumane G, Mura T, Nocca D, Fabre JM. Laparoscopic versus open distal pancreatectomy: a single-institution case-control study. Surg Endosc 2012; 26: 402-407 [PMID: 21909859 DOI: 10.1007/s00464-011-1887-7]

62 Fernández-Cruz L, Cosa R, Blanco L, Levi S, López-Boado MA, Navarro S. Curative laparoscopic resection for pancreatic neoplasms: a critical analysis from a single institution. J Gastrointest Surg 2007; 11: 1607-1621; discussion 1621-1622 [PMID: 17896167 DOI: 10.1007/s11605-007-0266-0]

63 Kim J, Han HS, Yoon YS, Cho JY, Ahn KS, Kwon Y. Outcomes of the patients who were postoperatively diagnosed as malignancy after laparoscopic distal pancreatectomy. Surg Laparosc Endosc Percutan Tech 2012; 22: 467-470 [PMID: 23074359 DOI: 10.1097/SLQ.0b013e3182632833]

64 Tran TB, Dua MM, Worhunsky DJ, Poultisides GA, Norton JA, Visser BC. The First Decade of Laparoscopic Pancreaticoduodenectomy in the United States: Costs and Outcomes Using the Nationwide Inpatient Sample. Surg Endosc 2016; 30: 1778-1783 [PMID: 26257542 DOI: 10.1007/s00464-015-4444-y]

65 Tan CL, Zhang H, Feng B, Li KZ. Outcome and costs of laparoscopic pancreaticoduodenectomy during the initial learning
curve vs laparotomy. World J Gastroenterol 2015; 21: 5311-5319 [PMID: 25954105 DOI: 10.3748/wjg.v21.i17.5311]

76 **Bao PQ**, Mazirka PO, Watkins KT. Retrospective comparison of robot-assisted minimally invasive versus open pancreaticoduodenectomy for periampullary neoplasms. *J Gastrointest Surg* 2014; 18: 682-689 [PMID: 24234245 DOI: 10.1007/s11605-013-2410-3]

77 **Speicher PJ**, Nussbaum DP, White RR, Zani S, Mosca PJ, Blazer DG, Clary BM, Pappas TN, Tyler DS, Perez A. Defining the learning curve for team-based laparoscopic pancreaticoduodenectomy. *Ann Surg Oncol* 2014; 21: 4014-4019 [PMID: 24923222 DOI: 10.1245/s10434-014-3839-7]

P- Reviewer: Kleeff J  S- Editor: Ma YJ  L- Editor: Filipodia  E- Editor: Ma S
