Laparoscopic versus open distal pancreatectomy (LAPOP), study protocol for a single center, non-blinded randomized controlled trial

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Abstract

Background Earlier non-randomized studies have suggested that laparoscopic distal pancreatectomy (LDP) is advantageous in comparison to open distal pancreatectomy (ODP) regarding hospital stay, blood loss and recovery. Only one randomized study has been conducted showing reduced time to functional recovery after LDP compared to ODP. Methods LAPOP is a prospective randomized, non-blinded, parallel group single center superiority trial. Sixty patients with lesions in the pancreatic body or tail that are found by a multidisciplinary tumor board to need surgical resection will be randomized to LDP or ODP. The primary outcome variable is post-operative hospital stay and secondary outcomes include functional recovery (defined as no need for intravenous medications or fluids as well as ambulatory patient able to perform activities of daily live), perioperative bleeding, complications, need of pain medication and quality of life comparison. Discussion The LAPOP trial will test the hypothesis that LDP reduces post-operative hospital stay compared to ODP Registration of trial ISRCTN:26912858, date of registration 28/9 2015

Background

A laparoscopic approach was introduced for most abdominal procedures during the last 30 years, and a minimal invasive approach for these procedures has become the standard of care (1-5). The main advantage expected from laparoscopic surgery is decreased patient discomfort and faster recovery, including a shortened postoperative hospital stay. A laparoscopic approach was described for resections of the pancreatic body and tail in the mid-1990s, but the general introduction of this method has been slow (6). Before the publication of the only available randomized controlled trial comparing LDP to ODP, some cohort studies and systemic reviews suggested the benefits of the laparoscopic approach (7). The benefits commonly mentioned are a shortening of hospital stay, reduction in blood loss and complications and higher rate of spleen-preserving procedures with LDP (8). However, selection bias, such as differences in tumor size between the study groups, are commonly found in the available nonrandomized studies (8). LDP has been in use for over 20 years without a single RCT supporting its proposed advantages. The LAPOP study was designed and initiated to investigate the hypothesis that a minimally invasive approach would shorten the hospital stay in a cohort of patients undergoing standard distal pancreatectomy (9). A learning curve was passed and described prior to starting the study (10). Since the start of the LAPOP study, one RCT using a similar approach was published, and the results suggest enhanced functional recovery and a shortening of hospital stay using the laparoscopic approach (7).

Methods

Design and patients

The LAPOP study is a randomized, controlled, nonblinded parallel assignment single-center superiority trial of the effectiveness of LDP versus ODP in the settings of lesions in the pancreatic body or tail,

regardless of suspicion of malignancy. Patients who fulfill the inclusion criteria and do not satisfy any of the exclusion criteria will be randomized in a 1:1 manner to LDP or ODP.

All patients with tumors in the body or tail of the pancreas in the South-East health district in Sweden are presented to the multidisciplinary board (MDB) at the study site (Linköping University Hospital), where eligibility screening is performed.

Sample size

The sample size considerations are based on the primary endpoint hospital stay in an intention-to-treat manner. A one-sided power calculation is used because none of the previous publications indicated an inferiority for LDP. The assumed mean hospital stay is 5 and 7.5 days for LDP and ODP, respectively. The standard deviation is 3.5 with a type I error = 0.05, and 25 patients are needed in each group to achieve a 0.8 power.

Thirty patients will be included in each group to include possible drop-outs.

Inclusion and exclusion criteria

The following inclusion criteria are used for the LAPOP study:

· Patients with lesion in the body or tail of the pancreas who require surgery (indication set by multidisciplinary conference).

· Operable patient (based on the local preoperative evaluation).

· Possibility to achieve an R0-resection without resection of additional organs (besides the spleen).

· Patients with a performance status of 0-2 according to WHO scale.

· Written informed consent.

· Age > 18 years.

The following exclusion criteria will be used:

· Pregnancy and/or lactation.

· Patients unable to comply with the protocol because of language or cognitive function.

· Preoperatively defined need to resect organs other than the pancreas and spleen.

· Preoperatively defined division line of the pancreas to the right of the superior mesenteric vein.

Randomization and inclusion

Randomization will be performed using computer-generated random numbers in blocks of 10 (5:5). A research nurse who will not participate in patient care will perform the randomization. Study group

allocation will depend on the contents of sealed opaque envelopes generated in the above-described manner, and envelopes will be opened after patient inclusion. A surgeon in the outpatient clinic will provide written and oral information about the study, and patients who agree to participate will sign a written informed consent

Treatment

LDP (treatment group)

Patients will receive general anesthesia in a supine position, and 4 trocars will be placed: above the umbilicus (12 mm); in the lateral part of the left rectus abdominis muscle (12 mm); to the left of the xiphoid process (5 mm); and in the left flank (5 mm). The surgeon and assisting surgeon (controlling the camera) will stand on the patient's right side.
The left colonic flexure is mobilized, and the splenocolic ligament is divided. Thereafter, the omental bursa is opened, and the stomach is completely mobilized, including the short gastric vessels. The lesion in the pancreas is identified with or without the help of ultrasonography. The inferior border of the pancreas is dissected, and a band is placed around the pancreas between the lesion and spleen if appropriate. A band is placed around the pancreas to the right of the lesion (and the splenic vein if splenectomy is intended). Before dividing the pancreas, the splenic artery is identified and secured using Hem-o-lock clips (Teleflex Medical, Weck Drive, Research Triangle Park, NC, USA). In cases of spleen-preserving procedures, the splenic artery is dissected from the pancreas and left intact. To improve visibility of the superior border of the pancreas, the stomach is sutured to the anterior abdominal wall. Depending on the preoperative assessment, lymphadenectomy is performed as indicated for pancreatic adenocarcinoma. The pancreas is divided using a linear stapler with a cartridge size based on the thickness of the pancreas. A gradual stepwise compression technique and division is used as described previously to reduce risk of rupture of the pancreas along the stapling line (11). Following division of the pancreas, the resection is performed in a medial to lateral direction. The surgical specimen is placed in a plastic bag and retrieved through enlargement of the trocar incision above the umbilicus. A 24 CH passive drain is placed through the trocar incision in the left flank with the tip in front of the pancreatic transection line.

ODP (control group)

A midline laparotomy is performed, retractors are placed, and the resection is performed essentially as described above. The stomach is retracted with the retractor instead of sutures, and the splenic artery is suture ligated instead of the use of clips. No attempt is made to dissect around the pancreas between the lesion and the spleen as antegrade resection is applied. The division of the pancreas is performed in the same manner as the LDP group, and a drain is placed in the same manner. Lymphadenectomy is performed when indicated.

Conversion to open surgery

Conversion (in the LDP group) is defined as any incision that is not for trocar placement or surgical specimen retrieval. In cases of conversion, analyses will be performed in an intention-to-treat manner.

Postoperative treatment

Both groups follow a fast track program that omits the use of a nasogastric tube directly after surgery (in the operating theatre) and encourages oral intake as soon as possible. Epidural anesthesia is allowed in the ODP group but not in the LDP group.

Study outcomes

The primary outcome variable of the LAPOP study is hospital stay, which is defined as the number of days spent in the hospital after surgery. The study hypothesis is that LDP results in shorter hospital stays than ODP.

Secondary outcomes include functional recovery (key secondary outcome), which is defined as the number of days needed to reach no need for intravenous drug administration or fluids and ambulatory patients who are able to perform ADL. These outcomes do not exclude discharge with drains or urinary catheters. Other secondary outcomes are perioperative bleeding (assessed by anesthesia nurse), use of pain medications, complications (according to Clavien Dindo classification), frequency of postoperative pancreatic fistula, quality of life, lymph node harvesting, R0 frequency and cost.

Follow up and data collection

Baseline characteristics are collected using standardized case report forms (CRFs) before randomization. Data for the outcome variables are collected on separate CRFs for surgical procedure, hospital stay, pathology report and 90-day follow up. Quality of life is assessed using the EORTC QLQ-C30 with the addition of the PAN26 module and EQ-5D.

Study subjects will complete the questionnaires at inclusion, 4-6 weeks after surgery, and 6, 12 and 24 months postoperatively. A research nurse will contact patients who do not return questionnaires to improve follow up. Survival will be followed up to 24 months postoperatively (Figure 2).

Statistical analysis

Analyses will be based on the intention-to-treat principle. Primary outcome and key secondary outcomes will be tested using t-tests. Demography, treatment and clinical data will be reported.

Quality of life will be measured using the EORTC QLQ-C30, EORTC PAN26 and EQ-5D for analyses.

Cost-benefit analysis will be performed for the surgery, postoperative complications and interventions, days in hospital, need for postoperative outpatient treatment, readmissions for complications, and tumor recurrence. The costs for sick leave will be included.

The study is performed without a data monitoring committee (DMC), and no interim analysis is planned.

Discussion

Despite its increasing use, LDP has only been compared to ODP in a single randomized trial of 108 patients after a structured nationwide implementation of the method (7, 12). The results from the LEOPARD trial support the hypothesis that LDP shortens hospital stay, but this finding must be further investigated in different settings to increase the generalizability of the high level evidence available. Functional recovery may be a more reliable end point than hospital stay in multicenter studies, and particularly multinational studies, but it remains partially subjective. Our study is performed in a homogenous population that represents approximately 10% of the Swedish nation. Therefore, differences in routines should not influence the results, and other factors that can influence the length of stay should be equally distributed between the groups due to the randomized nature of the study. Therefore, the more robust endpoint of hospital stay is more suitable as the primary endpoint rather than functional recovery. Due to the structure of the Swedish health care system, all patients from the South-east health district (approximately 1 million inhabitants) will be eligible for the study and evaluated at the same tumor board. The study includes all types of tumors in adult patients and no upper limit of tumor size as long as standard distal pancreatectomy may be used. Therefore, the results will be useful for general decision-making. The secondary outcomes will provide information on health economic aspects and quality of life.

This study has several limitations that should be acknowledged. Blinding is impractical and will not be used because Swedish patients have access to their health records, including operation notes, and the unit performing the study is small in size. The lack of blinding may be a limitation, but the importance of blinding in surgical studies is largely unknown. The use of fixed size blocks for randomization makes it theoretically possible to know beforehand the allocation of every 10th patient randomized. However, the practical implications of this limitation are minor because of the organization, where the decision to offer participation is made at a multidisciplinary conference based on rigid inclusion and exclusion criteria, and a research nurse informs the patients at the outpatient clinic prior to randomization.

Conclusion

The LAPOP trial will provide level-1 evidence on hospital stay after LDP vs. ODP and increase the level of evidence for guidelines on the use of LDP in the future.

Trial status

The current protocol version is 1.1 and the date 9-13-2015.

The randomization began (recruitment) on 5/11/2015, and 53 (88%) of 60 patients were randomized at the time of manuscript submission (10/31/2018). Therefore, the trial is ahead of schedule, and recruitment is expected to end in May 2019.

Declarations

Ethical approval and consent to participate

The LAPOP trial was reviewed by the ethical board at Linköping University in concordance with Swedish law and permitted (dnr. 2015/39-31). Date for ethical permission: June 10, 2015. Part of this process involves reviewing the written informed consent that must be signed by the patient prior to inclusion in the trial.

Consent for publication

Not applicable

Availability of data and materials

Datasets are not available due to the ongoing recruitment.

Competing interests

None.

Funding
The LAPOP study is investigator initiated, and a grant was received from the Medical Research Council of Southeast Sweden. The funding source had no role in the design of this study and will not have any role during its execution, analyses, data interpretation, or decision to submit the results.

The primary sponsor of the LAPOP trial is The County Counicil of Östergötland (Region Östergötland, c/o dr. Bärbel Jung, Linköping University Hospital Surgical clinic. Garnesonvägen 58185 Linköping, Sweden.

Authors' contributions
BB initiated the study and drafted the protocol and the manuscript. BB, PS, ALL, CH and TG contributed to the final design of the study. BB performed sample size calculations. BB, PS, ALL, CH and TG will contribute to data sampling and analyses. BB wrote the manuscript. PS, ALL, CH and TG critically reviewed the manuscript and are fully aware of the publication contents.

Acknowledgments

None.

List Of Abbreviations

LDP: Laparoscopic distal pancreatectomy; ODP: Open distal pancreatectomy; WHO: World health organisation; CRF: Case report form

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Figures

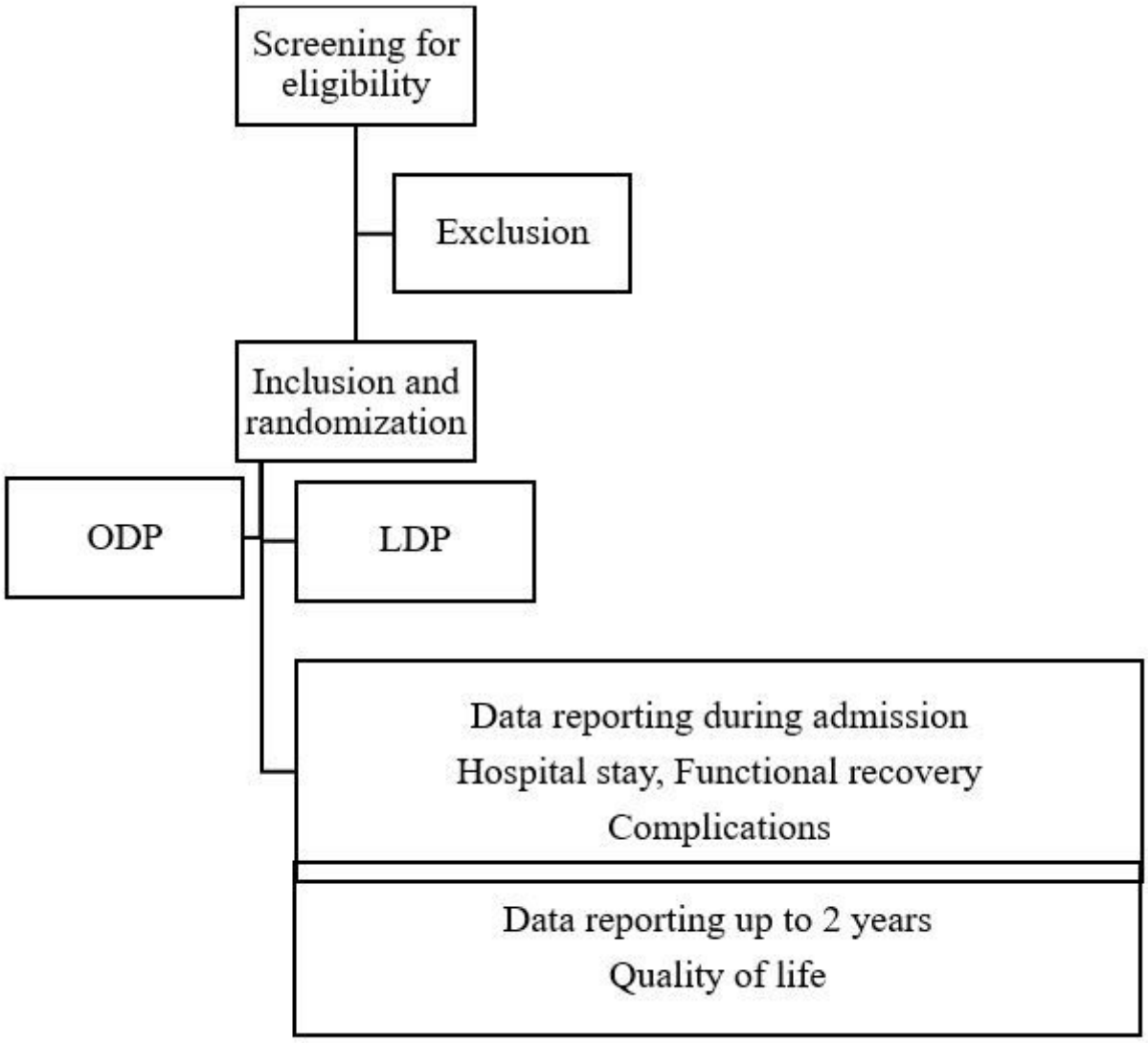

Figure 1

Trial flow diagram. OPD: open distal pancreatectomy, LDP: laparoscopic distal pancreatectomy

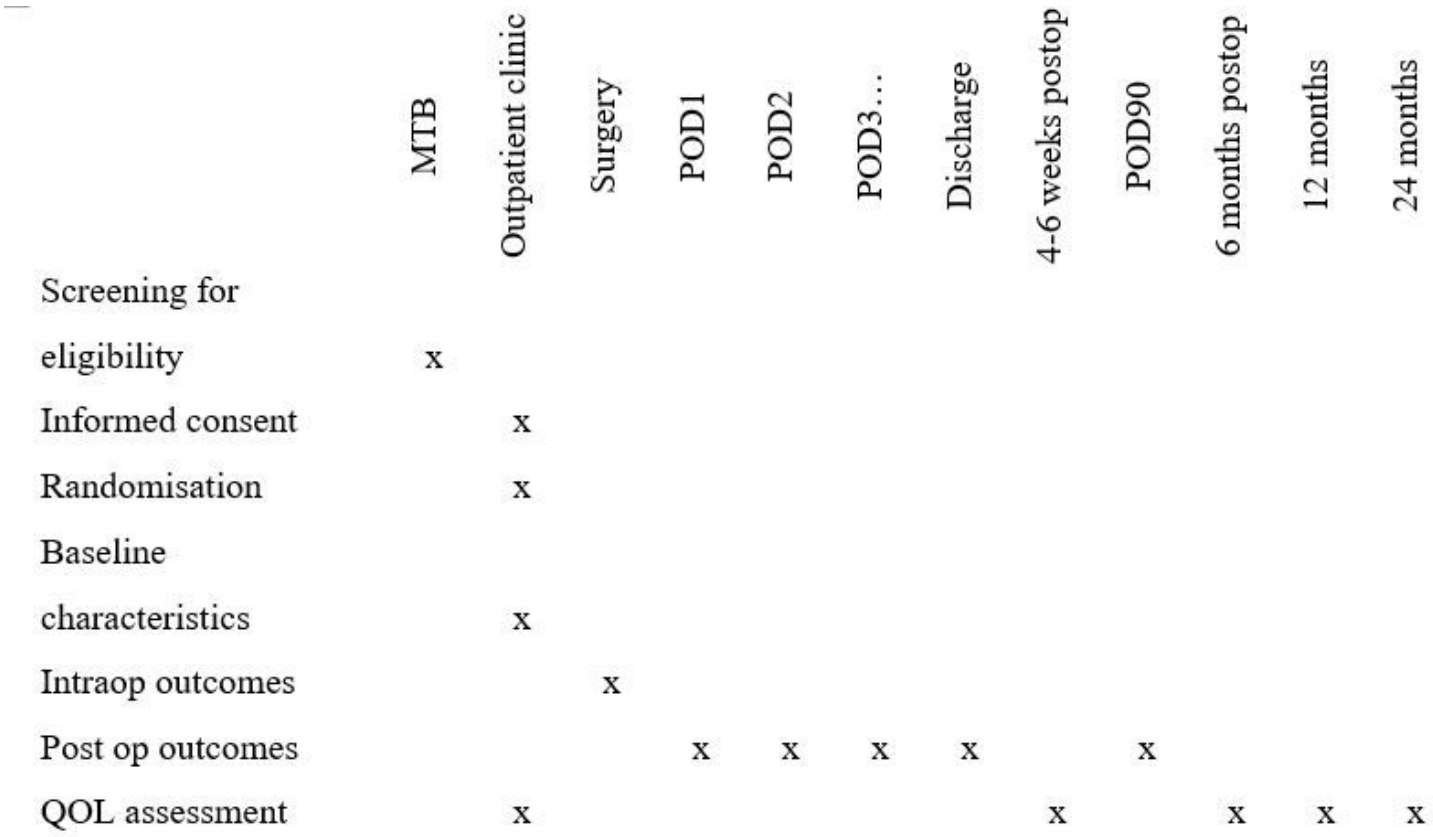

Figure 2

Schedule of enrolment, interventions, and assessments MTB: multidisciplinary tumour board, POD: Postoperative day, QOL: quality of life

Supplementary Files

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- supplement1.docx