

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

Bergthor Björnsson

Department of Surgery and Clinical and Experimental Medicine, Linköping University
<https://orcid.org/0000-0001-9704-1260>

Per Sandström

Department of Surgery and Clinical and Experimental Medicine, Linköping University

Anna Lindhoff Larsson

Department of Surgery and Clinical and Experimental Medicine, Linköping University

Claes Hjalmarsson

Department of Surgery, Blekinge hospital

Thomas Gasslander

Department of Surgery and Clinical and Experimental Medicine, Linköping University

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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

Background

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

Methods

Design and patients

The LAPOP study is a randomized controlled non-blinded parallel assignment single-center superiority trial on the effectiveness of LDP versus ODP in the settings of lesions in the pancreatic body or tail regardless of suspicion of malignancy. Patients fulfilling inclusions criteria and not meeting any of the exclusion criteria will be randomized in a 1:1 manner to LDP or ODP.

All patients with tumors in the body and the tail of the pancreas in the South-East health district in Sweden are presented on the MDB (Multidisciplinary board) at the study site (Linköping University Hospital). Here eligibility screening is performed.

Sample size

The sample size considerations are based on the primary endpoint hospital stay in an intention to treat manner. One sided power calculation is used as none of the previous publications indicates inferiority for LDP. Assumed mean hospital stay is 5 and 7.5 days for laparoscopic respective open operations. The standard deviation is 3,5 and with type I error = 0.05 and a 0.8 power 25 patients are needed in each group.

Due to possible drop-outs 30 patients will be included in each group.

Inclusion and exclusion criteria

The inclusion criteria for the LAPOP study are set as follows:

- Patients with lesion in the body or tail of the pancreas demanding surgery (indication set by multidisciplinary conference).
- Operable patient (as the local preoperatively evaluation dictates).
- Possibility to achieve R0-resection without resection of additional organs (besides the spleen)
- Patients with performance status 0-2 according to WHO scale.
- Written informed consent.
- Age > 18 years

The following exclusion criteria apply:

- Pregnancy and/or lactation.
- Patients being unable to comply with the protocol for reasons of language or cognitive function.
- Preoperatively defined need to resect other organs than pancreas and spleen.
- Preoperatively defined division line of pancreas to the right of the superior mesenteric vein.

Randomization and inclusion

Randomisation will be performed with computer-generated random numbers in block of 10 (5:5). The randomisation is done by a research nurse that does not participate in the patient care. Study group allocation will depend upon the contents of sealed opaque envelopes generated in this manner, opened after the patient inclusion. Written and oral information about the study will be given by surgeon at the outpatient clinic and if the patient accepts to participate this is followed by signing of a written informed consent

Treatment

LDP (treatment group)

In general anaesthesia with the patient in the supine position 4 trocars are 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) stand on the patients right side.

The left colonic flexure is mobilized and the splenocolic ligament divided. Thereafter, the omental bursa is opened and the stomach 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 if found appropriate a band is placed around the pancreas between the lesion and the spleen. To the right of the lesion a band is placed around the pancreas (and the splenic vein if splenectomy is intended). Before dividing the pancreas the splenic artery is identified and secured with Hem-o-lock clips (Teleflex Medical, Weck Drive, Research Triangle Park, NC, USA). In case of spleen preserving procedure, the splenic artery is dissected from the pancreas and left intact. In order 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 linear stapler with cartridge size based on the thickness of the pancreas. A slow compression and division is applied in order to reduce risk of rupture of the pancreas along the stapling line. Following division of the pancreas the resection is carried out 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)

After a midline laparotomy and placement of retractors the resection is carried out essentially as described above. The stomach is retracted with 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 in the LDP group and drain is placed in the same way. 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 case of conversion, analysis will be done in an intention-to-treat manner.

Postoperative treatment

Both groups follow a fast track program omitting the use of nasogastric tube directly after operation (in the operating theatre) and encouraging oral intake as soon as possible. Epidural anaesthesia is allowed in the ODP group but not applied in the LDP group.

Study outcomes

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

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

Follow up and data collection

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

The questionnaires will be filled out by the study subjects at inclusion, after 4-6 weeks from surgery, at 6,12 and 24 months postoperatively. Patients not returning questionnaires will be contacted by research nurse in order to improve follow up. Survival will be followed up to 24 months postoperatively (Figure 2).

Statistical analysis

The analyses will be based on the intention to treat principle. Primary outcome and key secondary outcome will be tested with t-test. Demography, treatment and clinical data will be reported.

Quality of life as measured by the EORTC QLQ-C30, EORTC PAN26 and EQ-5D will be analysed.

Cost-benefit analysis will be performed with regards to the operation, postoperative complications and interventions, days in hospital, need for postoperative outpatient treatment, readmissions for complications, tumor recurrence. Cost for sick leave will be included.

The study is done without 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 including 108 patients after a structured nationwide implementation of the method (7, 11). Although the results from the LEOPARD trial support the hypothesis that LDP shortens hospital stay this needs to be further investigated in different settings in order to increase the generalizability of the high level evidence available. Due to the structure of the Swedish health care system all patients from the South-east health district (about 1 million inhabitants) will be eligible for the study and evaluated at the same tumour board. As the study includes all types of tumors in adult patients and no upper limit of tumour size as long as standard distal pancreatectomy can be applied the results will be useful in general for decisionmaking. The secondary outcomes will provide information about health economic aspects as well as quality of life.

Conclusion

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

Trial status

The current protocol version is 1.1 and the date 2015-09-13,

The randomisation started (recruitment) on 5/11 2015 and at the time of manuscript submission (31/10 2018) 53 (88%) of 60 patients have been randomized. The trial is therefore ahead of schedule and expected end of recruitment is May 2019.

Declarations

Ethical approval and consent to participate

The LAPOP trial has been reviewed by the ethical board at Linköping University in concordance with Swedish law and permitted (dnr. 2015/39-31). Date for ethical permission: June 10th 2015. A 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

Due to the ongoing recruitment datasets are unavailable.

Competing interests

None

Funding

The LAPOP study is investigator initiated, 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, interpretation of the data, or decision to submit results.

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

Authors' contribution

BB initiated the study, 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 analysis. BB wrote the manuscript, PS, ALL, CH and TG have critically reviewed the manuscript and are fully aware of the publication.

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None

References

1. Gagner M, Lacroix A, Bolte E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *N Engl J Med.* 1992;327(14):1033.
2. Hashizume M, Sugimachi K, Ueno K. Laparoscopic splenectomy with an ultrasonic dissector. *N Engl J Med.* 1992;327(6):438.
3. Gagner M, Pomp A, Heniford BT, Pharand D, Lacroix A. Laparoscopic adrenalectomy: lessons learned from 100 consecutive procedures. *Ann Surg.* 1997;226(3):238-46; discussion 46-7.
4. Jacobs JK, Goldstein RE, Geer RJ. Laparoscopic adrenalectomy. A new standard of care. *Ann Surg.* 1997;225(5):495-501; discussion -2.
5. Katkhouda N, Hurwitz MB, Rivera RT, Chandra M, Waldrep DJ, Gugenheim J, et al. Laparoscopic splenectomy: outcome and efficacy in 103 consecutive patients. *Ann Surg.* 1998;228(4):568-78.
6. Gagner M, Pomp A, Herrera MF. Early experience with laparoscopic resections of islet cell tumors. *Surgery.* 1996;120(6):1051-4.
7. de Rooij T, van Hilst J, van Santvoort H, Boerma D, van den Boezem P, Daams F, et al. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded Randomized Controlled Trial. *Ann Surg.* 2018.

8. Mehrabi A, Hafezi M, Arvin J, Esmailzadeh M, Garoussi C, Emami G, et al. A systematic review and meta-analysis of laparoscopic versus open distal pancreatectomy for benign and malignant lesions of the pancreas: it's time to randomize. *Surgery*. 2015;157(1):45-55.
9. Hartwig W, Vollmer CM, Fingerhut A, Yeo CJ, Neoptolemos JP, Adham M, et al. Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS). *Surgery*. 2014;156(1):1-14.
10. Hasselgren K, Halldestam I, Fraser MP, Benjaminsson Nyberg P, Gasslander T, Bjornsson B. Does the Introduction of Laparoscopic Distal Pancreatectomy Jeopardize Patient Safety and Well-Being? *Scand J Surg*. 2016;105(4):223-7.
11. de Rooij T, van Hilst J, Boerma D, Bonsing BA, Daams F, van Dam RM, et al. Impact of a Nationwide Training Program in Minimally Invasive Distal Pancreatectomy (LAELAPS). *Ann Surg*. 2016;264(5):754-62.

Figures

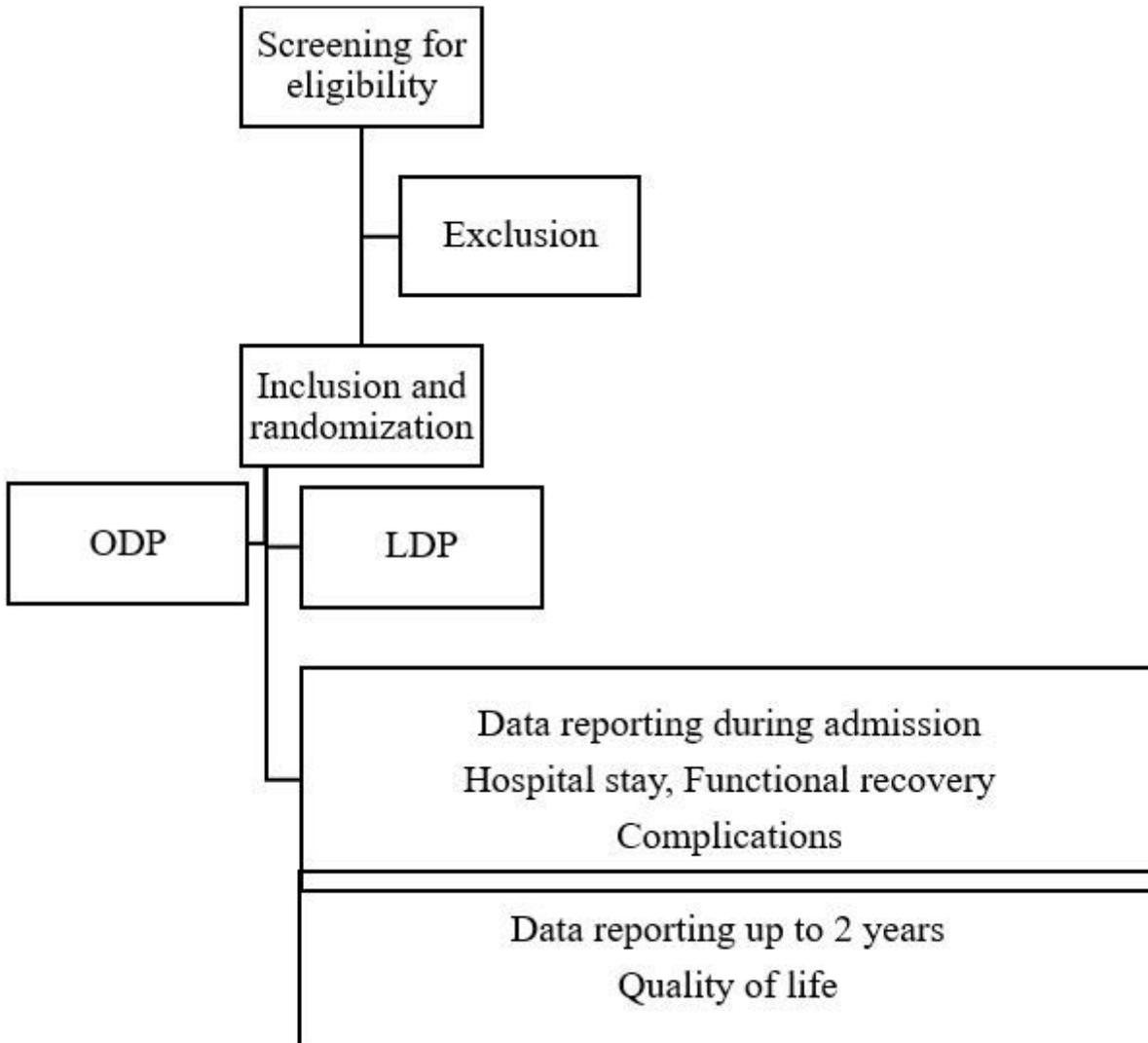


Figure 1

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

	MTB	Outpatient clinic	Surgery	POD1	POD2	POD3...	Discharge	4-6 weeks postop	POD90	6 months postop	12 months	24 months
Screening for eligibility	x											
Informed consent		x										
Randomisation		x										
Baseline characteristics		x										
Intraop outcomes			x									
Post op outcomes				x	x	x	x		x			
QOL assessment		x						x		x	x	x

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](#)