Laparoscopic distal pancreatectomy is more cost-effective than open resection: results from a Swedish randomized controlled trial

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Abstract

Background: Laparoscopic distal pancreatectomy is being implemented worldwide. The aim of this study was to perform a cost-effectiveness analysis from a health care perspective.

Methods: This cost-effectiveness analysis was based on the randomized controlled trial LAPOP, where 60 patients were randomized to open or laparoscopic distal pancreatectomy. For the follow-up of two years, resource use from a health care perspective was recorded, and health-related quality of life was assessed using the EQ-5D-5L. The per-patient mean cost and quality-adjusted life years (QALYs) were compared using nonparametric bootstrapping.

Results: Fifty-six patients were included in the analysis. The mean health care costs were lower, €3863 (95% CI: -€8020 to €385), for the laparoscopic group. Postoperative quality of life improved with laparoscopic resection and resulted in a gain in QALYs of 0.08 (95% CI: -0.09 to 0.25). The laparoscopic group had lower costs and improved QALYs in 79% of bootstrap samples. With a cost-per-QALY threshold of €50 000, 95.4% of the bootstrap samples were in favour of laparoscopic resection.

Conclusion: Laparoscopic distal pancreatectomy is associated with numerically lower health care costs and improvements in QALYs compared with the open approach. The results support the ongoing transition from open to laparoscopic distal pancreatectomies.

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Introduction

Minimally invasive pancreatic surgery is rapidly increasing worldwide. The safety and efficacy of minimally invasive distal pancreatectomy have been established by two separate randomized controlled trials1,2 as well as the pan-European propensity score-matched DIPLOMA study.3 While the remaining question of the oncological safety of minimally invasive pancreatic surgery is under investigation in two ongoing randomized controlled studies,4,5 current guidelines conclude that based on the available evidence, it also seems to be an equivalent approach for malignant lesions, such as pancreatic ductal adenocarcinoma.6

Although the results of minimally invasive distal pancreatectomy are relatively well elucidated, the cost-effectiveness of the procedure is less explored. The LEOPARD trial based in the Netherlands compared costs of laparoscopic and open distal pancreatectomy one year after the operation from a hospital perspective and reported a probability of 0.676 of the laparoscopic approach being cost-effective at a willingness to pay €80 000 for each quality adjusted life year (QALY) gained.7 Apart from the relatively short follow-up period, this analysis was also restricted to hospital costs. One systematic review on the
subject reported overall lower hospital costs for laparoscopic distal pancreatectomy but advocated further cost-effectiveness studies, in particular those incorporating long-term quality of life.\(^8\)

In the LAPOP trial based in Linköping, Sweden, 60 patients were randomized to open or laparoscopic distal pancreatectomy. The group undergoing laparoscopic resection had a significantly shorter hospital stay, shorter time to recovery and less blood loss than their counterparts who underwent open resection while having a comparable complication rate.\(^1\)

The aim of this study was to perform a cost-effectiveness analysis of laparoscopic compared to open distal pancreatectomy based on the 2-year follow-up data from the LAPOP trial, including all costs from primary, secondary and tertiary health care, as well as health-related quality of life.

**Methods**

**Study design**

The design of the LAPOP trial has been described elsewhere, along with details of operative and postoperative management.\(^1\) Briefly, it was a singlecentre, randomized, nonblinded superiority trial based in Linköping, Sweden, performed between 2015 and 2019. The 60 patients included were randomized 1:1 to laparoscopic or open distal pancreatectomy and compared on an intention-to-treat basis regarding the length of stay and time to functional recovery. A 2-year follow-up of health-related quality of life and an accompanying cost-effectiveness analysis was included in the protocol. The analysis was performed on a modified intention-to-treat basis, where patients who were not able to undergo the operation were excluded. The protocol was approved by the ethics board in the South-East health care region of Sweden with the decision number 2015/39–31.

**Resource use**

The resources used within two years following surgery were acquired from patients’ medical records. All resources related to the procedures and their consequences were collected, while those solely pertaining to the underlying diagnosis were excluded. Hence, costs related to a malignant diagnosis such as chemotherapy treatment, re-admissions because of the malignancy itself and not the index operation, re-operations for recurring disease or follow-up control exams were not included. The recording was started at the time of surgery, with the exception of vaccinations due to splenectomy that were collected both pre- and postoperatively. Diabetes controls and procedures such as retinal screening were included for patients who developed diabetes within two years of the operation but not for patients with a preoperative diabetes diagnosis. Five main categories of resource use were identified and recorded.

**Hospital stay.** The time spent at the hospital in connection to the operation included the subsequent stay in a secondary care hospital or readmissions due to complications. The time spent at hospital was categorized into days spent in an intensive care unit, days spent in an ordinary ward and hours spent in the recovery room.

**Operations** included minutes in the operation theatre, hours of senior consultant and specialist surgeons, and materials used for both the index operation and any reoperations. The initial cost for buying equipment for laparoscopic and open surgery were not included in the analysis.

**Interventions and tests.** All procedures and tests (endoscopic procedures, radiological interventions and exams, blood samples and cultures) were included, regardless of whether they were performed in the hospital, the emergency room, an outpatient clinic or a primary care facility. Ultrasonic cardiograms were included when performed for postoperative complications such as pulmonary embolism or postoperative atrial fibrillation.

**Medications** included intravenous drugs, liquids and blood products administered during the index hospitalization, visits to the emergency room or any subsequent hospital stays. Oral drugs related to the operation or its complications were included. Drugs taken habitually preoperatively or related to a separate condition were excluded. Drug prescriptions within two years of the operation were recorded in the same manner. Splenectomy vaccinations were included, as well as medications administered for patient-controlled or epidural analgesia.

**Health care contacts.** Visits and telephone contacts with doctors, nurses, dieticians, podiatrists and health care counsellors in all levels of health care were recorded. Multidisciplinary conferences were recorded when they were associated with complications and not the diagnosis only. Visits to the emergency room were recorded as the number of visits.

**Unit costs**

Unit costs to value resource use were obtained from various sources, which are listed in Table 1 and Supplementary data 1. Unit costs are reported in 2021 Euros, which were converted from Swedish kronor using the average exchange rate of 2021.\(^1\)

Resource cost for each patient was multiplied by the appropriate unit cost to arrive at a total cost per patient in the study. As the study was based on the two-year follow-up data from the LAPOP trial, costs remained undiscounted. As splenectomy vaccinations were unreliably recorded in the medical records, a fixed cost was also calculated. A fixed cost was also calculated for the operation materials generally used in the different operations.

**Health-related quality of life**

Health-related quality of life was assessed with the EQ-5D-5L questionnaire preoperatively and at 5–6 weeks, 6 months, 12 months, and 24 months postoperatively. The EQ-5D is a well-
established questionnaire consisting of the five dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, as well as a visual analogue scale of perceived health scored from 0 (worst health) to 100 (best health). Each dimension has 3 or 5 levels of severity, depending on which version is used. The current study employed the 5-level version. Value sets have been developed to establish a quality-of-life weight for each health state defined by the 5 dimensions and 5 levels of severity, where 1 corresponds to full health and 0 to death. A Swedish value set was used, and based on the 5 measurements of health-related quality of life, QALYs for each patient in the study were calculated using the area under the curve approach. Therefore, patients could accrue a total of 2 QALYs corresponding to being in full health during the entire study period. For patients who died during follow-up, the area under the curve until death was calculated by carrying the last

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<th>Table 1 Overall costs and major resource use in both treatment arms</th>
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\(^a\) Includes podiatrist, physiotherapist, dietician and health care counsellors.

\(^b\) Detailed costs and sources are outlined in Supplementary data 1.

\(^c\) Estimations are described in Supplementary data 4.
observed health-related quality of life value forward until the date of death.

Statistical analysis
All analyses were performed using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY) and R version 4.2.0 (R Core Team, Vienna, Austria).

Missing EQ-5D data were imputed using the multiple imputation by chained equations (MICE) package in R. Ten datasets were imputed, and predictive mean matching was used for all imputed variables. In imputation modelling, EQ-5D measurements from other time points were included, as well as total cost, American Society of Anaesthesiology score, Eastern Cooperative Oncology Group performance status and Charlson Comorbidity Index. The EQ-5D index was computed after imputation. Rubin’s rule was used to pool standard errors from the imputed EQ-5D index to construct 95% confidence intervals for health-related quality of life. Nonparametric bootstrapping with 10,000 samples was performed to establish per patient mean costs and QALYs for each treatment group. We used the percentile method to construct 95% confidence intervals for costs and QALYs. For QALYs, an uneven baseline distribution was adjusted using a multiple regression analysis that included baseline health-related quality of life as a parameter. Based on these estimates, the cost-effectiveness analysis compared the mean difference in costs with the mean difference in QALYs for laparoscopic and open pancreatectomy, by observing the confidence intervals of the difference. The incremental cost-effectiveness ratio (ICER) describes the additional cost required to produce an additional QALY if laparoscopic surgery was provided instead of open surgery. The ICER was then compared with a cost per QALY threshold indicating the maximum cost a decision-maker would accept for a gained QALY. In the case of incremental costs being negative and QALYs positive, the treatment is deemed dominant, and no ICER is calculated.

One patient in the open group experienced a large number of complications, reoperations and readmissions, resulting in a total cost that was approximately seven times higher than the average for the group (details are provided in Supplementary data 2). This patient was excluded from the base case analysis. The effect of this exclusion was investigated in an additional analysis including the patient.

The results were visualized on a cost-effectiveness plane illustrating the joint distribution of incremental costs and QALYs for laparoscopic compared with open distal pancreatectomy.

Results
Patients
Of the 60 patients who were randomized, two were excluded from the LAPOP analyses, one patient in the laparoscopic group due to preoperative dissemination of cancer and one patient in the open group who was operated on at another hospital. In addition to the patient with extreme costs, another patient with disseminated disease at the time of operation was excluded from the open group (Fig. 1).

Baseline characteristics indicating that the groups were relatively well balanced have been published previously along with complication rates. The proportion of pancreatic adenocarcinoma was unevenly distributed, with one patient in the open group and six in the laparoscopic group. Additional complications and mortality from the two-year follow-up are presented in Supplementary data 3. One patient in the laparoscopic group underwent reoperation due to nonradicality and two in the open group underwent reoperation due to incision hernia. Eight patients in the laparoscopic group and ten in the open group were readmitted due to complications from the initial surgery. In the laparoscopic group, five patients developed new-onset diabetes, one impaired glucose tolerance, and seven exocrine pancreatic insufficiency, while the
corresponding numbers in the open group were four, one, and ten patients, respectively.

**Costs**

Resource use and main cost categories are presented in Table 1 (references 18–24) and Fig. 2. Additional details are provided in Supplementary data 1 and Supplementary data 4.

The per-patient mean costs were €14 454 and €18 317 for the laparoscopic and open groups, respectively. The difference in costs was €3863 (95% CI: −385 to 8020). The mean costs were higher for the open group in all subcategories except for operation costs.

**Health-related quality of life**

The mean QALY weights from the 5 EQ-5D measurements are shown in Fig. 3. The first panel includes all patients with complete follow-up data, and the second panel shows the results obtained after imputation.

The difference in QALYs between the laparoscopic and open pancreatectomy groups was 0.08 (95% CI: −0.09 to 0.25) when controlling for baseline QALY weights.

**Cost effectiveness**

The incremental costs and QALYs were €3863 and 0.08, respectively, for the laparoscopic group compared with the open group, indicating that laparoscopic pancreatectomy was a dominant strategy. The uncertainty around the joint distribution of incremental costs and QALYs is illustrated in the cost-effectiveness plane in Fig. 4. In 79% of the bootstrap samples, laparoscopic pancreatectomy was the dominant strategy used (lower right quadrant). After applying a commonly used Swedish cost-per-QALY threshold of €50 000, 95.4% of the bootstrap samples were in favour of the laparoscopic intervention.

When including the one patient with extreme costs in the analyses, 81% of bootstrap samples were located in the lower right quadrant (dominant strategy), and using a cost-per-QALY threshold of €50 000, 98% of the samples were in favour of the laparoscopic method. The difference in costs was €7695 (95% CI: −3388 to 30 373), with higher costs for the open group.

**Discussion**

This cost-effectiveness analysis, which was based on a randomized controlled trial comparing laparoscopic with open distal pancreatectomy, provides an important addition to the one previous study performed worldwide. With a longer follow-up time than its predecessor, as well as providing a more comprehensive evaluation of all health care costs, the higher costs of laparoscopic equipment were outweighed by a lower resource use in all other categories, resulting in a nominal reduction in health care costs at the 2-year follow-up of €3863. Furthermore, the estimated (not statistically significant) gain in QALYs with laparoscopic pancreatectomy at the 2-year follow-up was 0.08, indicating that laparoscopic treatment is a dominant strategy in the cost-effectiveness analysis with lower health care costs and improved QALYs. Laparoscopic pancreatectomy was the dominant strategy in 79% of the bootstrap samples, a figure that increased to 95% when applying a cost-effectiveness threshold of €50 000.

These results are consistent with those from the LEOPARD trial, although the present study shows a more marked
difference between groups that is to a large extent based on the higher costs documented for the open group. This difference is most likely the result of following patients for a longer time, as well as a more detailed documentation of associated resource use that was undertaken in this study. This result highlights the need to examine the procedure from an overall health care perspective, accounting for follow-up visits and reoperations.

While few other randomized controlled trials are available to evaluate cost-effectiveness, a recent study using decision-analytical modelling to compare open to laparoscopic distal pancreatectomy found that laparoscopic treatment was a dominant strategy with a per-patient mean cost savings of €287 when including the risk of reoperations and other complications in the model. Our results are more favourable for laparoscopic

Figure 3 Index values from the EQ-5D measurements before and after imputation with 95% confidence intervals. Complete data were available for 16 patients in the open group and 18 in the laparoscopic group.

Figure 4 Results of the nonparametric bootstrap analysis with 10,000 samples on the cost-effectiveness plane.
treatment compared to this modelling study. This difference may primarily be because the modelling study was performed before any randomized controlled studies were available and was based on data from nonrandomized trials.

Apart from these studies, there is also cost-effectiveness evidence regarding minimally invasive distal pancreatectomy available from non-randomised studies based on large cohorts of patients. Interestingly, these studies have indicated that the minimally invasive approach is cost-saving already from a 90-day perspective; a fact that might be connected to the considerably larger number of subjects in these studies. However, as these were not randomized there is a risk that patients were selected differently into the groups, with for example healthier patients or easier resections selected to undergo minimally-invasive operations. Further differences between these and the present study, apart from the study type and sample size, are the time span of follow-up and the inclusion of quality-of-life data in the analysis of the present study. How these differences in study design contributed to observed differences in the results is difficult to assess but they should be considered carefully when making comparisons.

Based on these results, laparoscopic pancreatectomy appears better in terms of health outcomes and health care resource savings. Hence, from a clinical practice perspective, no objections for the continuing transition of distal resections into laparoscopic surgery should be noted. As of the latest report from the Swedish pancreatic and periampullary registry 2020, approximately 40% of distal resections in Sweden were performed laparoscopically. As the transition continues to robot-assisted surgery, the health-related outcomes and health care resource implications of this transition must continue to be evaluated.

This study had some limitations. First, only costs within the health care sector were assessed. Hence, consequences outside health care, such as productivity losses due to operations or illness, were not considered. Notably, these costs are often correlated with health care costs and health outcomes, and a large proportion of patients in the study were retired. We therefore propose that including productivity losses would not have had a substantial effect on the results. Second, the operation conceivably produces results spanning beyond two years postoperatively, which would not be captured in our analysis, most notably in terms of incisional hernias. However, the inclusion of long-term effects in a decision-analytic modelling approach would most likely result in larger cost and QALY differences in favour of the laparoscopic group than those reported from our study. Third, only a small proportion of patients had a diagnosis of pancreatic adenocarcinoma, which made it difficult to specifically study this subgroup of patients.

Resource use data were collected retrospectively from medical records. We believe this is a reliable source when it comes to capturing all relevant healthcare resources used for patients in a publicly funded healthcare system. However, this does not rule out that some relevant resources were excluded in our data extraction, or that some irrelevant ones were included. These analytical choices may have impacted the cost estimates. Given the granularity of the data extraction we believe this impact is minor, however. Furthermore, it is unclear to what extent the results of the study are transferrable to other centres and countries. As noted above, the estimation of costs is based on detailed scrutiny of patient medical records and should be transferable to centres or countries with a similar healthcare setting as a Swedish university hospital. For transparency and the possibility to apply our results in other settings, the physical resource use and corresponding unit costs to value them are comprehensively reported.

Lastly, it is important to interpret the results of this study in light of the relatively small study sample. This adds to the uncertainty of the results, and was further highlighted by the change seen in the bootstrap analysis when including the one outlier that was initially excluded.

The strength of this study to balance the limitations is that it is a two-year follow-up of a randomized controlled trial with a thorough and detailed documentation of resource use and costs, providing a solid evidence base for cost-effectiveness.

In conclusion, laparoscopic distal pancreatectomy is associated with numerically lower health care costs and improvements in QALYs compared with the open approach based on 2-year follow-up data. The results support the ongoing transition from open to laparoscopic distal pancreatectomies in clinical practice.

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The original LAPOP study was preregistered with a plan to perform a follow-up cost-effectiveness analysis, but the actual cost-effectiveness analyses to be used were not described in detail in the study plan. The registration is found in ISRCTN, study no. 26912858, and was registered on 28 September 2015.

Conflicts of interest
None declared.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.04.021.