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# Costs and quality of life in a randomized trial comparing minimally invasive and open distal pancreatectomy (LEOPARD trial)

J. van Hilst<sup>1</sup>, E. A. Strating<sup>1</sup>, T. de Rooij<sup>1</sup>, F. Daams<sup>3</sup>, S. Festen<sup>4</sup>, B. Groot Koerkamp<sup>5</sup> , J. M. Klaase<sup>6</sup>, M. Luyer<sup>7</sup>, M. G. Dijkgraaf<sup>2</sup> and M. G. Besselink<sup>1</sup> , on behalf of the Dutch Pancreatic Cancer Group and LEOPARD trial collaborators\*

<sup>1</sup>Department of Surgery, Cancer Center Amsterdam, and <sup>2</sup>Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, University of Amsterdam, and <sup>3</sup>Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, VU University, Amsterdam, and Departments of Surgery, <sup>4</sup>OLVG, Amsterdam, <sup>5</sup>Erasmus MC, Rotterdam, <sup>6</sup>University Medical Center Groningen, Groningen and <sup>7</sup>Catharina Hospital, Eindhoven, The Netherlands

Correspondence to: Professor M. G. Besselink, Department of Surgery, Cancer Centre Amsterdam, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands (e-mail: m.g.besselink@amc.nl)

**Background:** Minimally invasive distal pancreatectomy decreases time to functional recovery compared with open distal pancreatectomy, but the cost-effectiveness and impact on disease-specific quality of life have yet to be established.

**Methods:** The LEOPARD trial randomized patients to minimally invasive (robot-assisted or laparoscopic) or open distal pancreatectomy in 14 Dutch centres between April 2015 and March 2017. Use of hospital healthcare resources, complications and disease-specific quality of life were recorded up to 1 year after surgery. Unit costs of hospital healthcare resources were determined, and cost-effectiveness and cost-utility analyses were performed. Primary outcomes were the costs per day earlier functional recovery and per quality-adjusted life-year.

**Results:** All 104 patients who had a distal pancreatectomy (48 minimally invasive and 56 open) in the trial were included in this study. Patients who underwent a robot-assisted procedure were excluded from the cost analysis. Total medical costs were comparable after laparoscopic and open distal pancreatectomy (mean difference €-427 (95 per cent bias-corrected and accelerated confidence interval €-4700 to 3613;  $P = 0.839$ ). Laparoscopic distal pancreatectomy was shown to have a probability of at least 0.566 of being more cost-effective than the open approach at a willingness-to-pay threshold of €0 per day of earlier recovery, and a probability of 0.676 per additional quality-adjusted life-year at a willingness-to-pay threshold of €80 000. There were no significant differences in cosmetic satisfaction scores (median 9 (i.q.r. 5.75–10) versus 7 (4–8.75);  $P = 0.056$ ) and disease-specific quality of life after minimally invasive (laparoscopic and robot-assisted procedures) versus open distal pancreatectomy.

**Conclusion:** Laparoscopic distal pancreatectomy was at least as cost-effective as open distal pancreatectomy in terms of time to functional recovery and quality-adjusted life-years. Cosmesis and quality of life were similar in the two groups 1 year after surgery.

\*The LEOPARD trial collaborators are also co-authors of this article and can be found under the heading Collaborators

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## Introduction

Minimally invasive distal pancreatectomy has gained popularity in recent years. Meta-analyses<sup>1,2</sup> of non-randomized, mostly single-centre and/or retrospective studies have suggested a decreased length of hospital stay after minimally invasive compared with open distal

pancreatectomy. Recently, the multicentre randomized LEOPARD trial<sup>3</sup> showed a 2-day reduction in time to functional recovery and duration of hospital stay in favour of minimally invasive distal pancreatectomy compared with the open approach. Despite these positive results, the costs associated with minimally invasive surgery could be a barrier to further implementation<sup>4</sup>.

Data on the costs of minimally invasive distal pancreatectomy are limited. One systematic review<sup>5</sup> combined data from 12 small retrospective studies, and showed that intraoperative costs were higher for minimally invasive distal pancreatectomy. In eight of these studies, the higher costs were compensated for by lower postoperative costs. Health economic data on minimally invasive distal pancreatectomy are even scarcer. Tax and colleagues<sup>6</sup> proposed a decision analytical model, which estimated minimally invasive distal pancreatectomy to be more cost-effective than the open approach with a willingness-to-pay threshold of €80 000 for each quality-adjusted life-year (QALY) gained. In this study, the probabilities of complications were derived from the literature and expert opinion. Gurusamy and co-workers<sup>7</sup> reported a probability of 0.70–0.80 that laparoscopic distal pancreatectomy was cost-effective (willingness-to-pay threshold €23 163–34 744; £20 000–30 000, exchange rate 10 March 2019); however, this analysis included only patients with pancreatic cancer, whereas a large proportion of patients undergoing distal pancreatectomy have other conditions such as pancreatic cysts.

Data on disease-specific quality of life (QoL) after minimally invasive distal pancreatectomy are also limited. The LEOPARD trial<sup>3</sup> showed improved disease-specific QoL after minimally invasive distal pancreatectomy from day 3 to day 30 after surgery. Quality-of-life outcomes after minimally invasive distal pancreatectomy beyond this time point and data on more specific measures, such as cosmetic satisfaction, are not currently available.

Therefore, the aim of the present study was to undertake an economic evaluation, and to analyse QoL after minimally invasive *versus* open distal pancreatectomy using data from the multicentre LEOPARD trial up to 1 year after surgery.

## Methods

### LEOPARD trial

This economic evaluation was performed alongside the multicentre patient-blinded randomized LEOPARD trial which was approved by the institutional review board of Amsterdam UMC, location AMC, University of Amsterdam (NTR5188). The rationale and design of this trial<sup>8</sup> and the 90-day follow-up<sup>3</sup> have been reported previously. In summary, patients with a benign, premalignant or malignant tumour of the pancreatic tail were randomized to undergo either minimally invasive (laparoscopic or robot-assisted) or open distal pancreatectomy. In accordance with the protocol, costs of robot-assisted procedures were not included, so patients whose procedure

was robot-assisted were excluded from the cost analysis<sup>8</sup>. Postoperative outcomes of patients randomized in 14 centres in the Netherlands were assessed. The primary clinical endpoint was time to functional recovery, defined as all of the following: independently mobile to the preoperative level, sufficient pain control with only oral medication, ability to maintain more than 50 per cent daily required calorie intake, no intravenous fluid administration and no clinical signs of infection. Median time to functional recovery in the LEOPARD trial<sup>3</sup> was 4 (i.q.r. 3–6) days after minimally invasive distal pancreatectomy compared with 6 (5–8) days after open distal pancreatectomy ( $P < 0.001$ ).

### Type of economic evaluation, perspective and time horizon

The economic evaluation was performed as cost-effectiveness and cost-utility analyses from a hospital healthcare perspective in a secondary care setting, with a time horizon of 1 year. The cost-effectiveness endpoint was the cost per day reduction in duration of postoperative functional recovery. The cost-utility endpoint was the cost per QALY. The results are reported in accordance with CHEERS guidelines<sup>9,10</sup>.

### Hospital resources, unit costing and costs

During the 12 months after randomization, use of hospital healthcare resources was collected from case report forms, and electronic hospital information systems: initial duration of hospital admission (general ward and ICU) and readmission, surgical (distal pancreatectomy and reoperations), radiological (X-ray, ultrasound imaging, CT, MRI, interventions) and endoscopic (gastroscopy, feeding tube placement, endoscopic retrograde cholangiopancreatography) procedures, outpatient clinic visits and emergency room visits. The 2015 Dutch manual for costing in healthcare research<sup>11</sup> was used to obtain the unit costs of hospital admissions, and outpatient and emergency room visits. The unit costs of radiological and endoscopic procedures (including personnel, material and overhead costs) were based on the Amsterdam UMC, location AMC, tariffs ledger. Unit costs of laparoscopic and open distal pancreatectomy were calculated from costs of operating theatre use, personnel (specialists' fees for the surgeon (total duration of surgery), anaesthetist (estimated involvement for 1 h) and theatre room personnel (total duration of surgery)), purchase of disposable materials used and overhead costs. All distal pancreatectomies were planned electively and were therefore done during office hours. A fraction of the reoperations were possibly undertaken - outside office hours, but prices were not adjusted as no

**Table 1** Unit costs of major resources used

	Unit	Unit costs in 2016 (€)	Source
<b>Surgery</b>			
Personnel and theatre costs	Minute	12.22	DCM – 2015 <sup>11</sup> /Silver Cross Price finder 2017 <sup>12</sup>
Anaesthetist	Procedure	114.01	DCM – 2015 <sup>11</sup>
Laparoscopy tools	Procedure	251.77	Provider/expert opinion
Epidural	Procedure	559.49	Hospital ledger 2014
Wound catheters	Procedure	60.0	Expert opinion
Reoperation	Procedure	1591.90	Hospital ledger 2014
<b>Hospital stay</b>			
General ward	Day	577.50	DCM – 2015 <sup>11*</sup>
ICU	Day	2033.14	DCM – 2015 <sup>11*</sup>
<b>Diagnostic procedures</b>			
CT	Procedure	189.08	Hospital ledger 2014
MRI	Procedure	435.66	Hospital ledger 2014
Ultrasound imaging	Procedure	142.81	Hospital ledger 2014
Radiography of thorax/abdomen	Procedure	48.75	Hospital ledger 2014
<b>Therapeutic procedures</b>			
ERCP or drainage	Procedure	689.54	Hospital ledger 2014
Radiological drainage	Procedure	902.67	Hospital ledger 2014
Vascular embolization	Procedure	1822.42	Hospital ledger 2014
Endoscopic feeding tube	Procedure	302.84	Hospital ledger 2014
Diagnostic endoscopy	Procedure	288.39	Hospital ledger 2014
Peripherally inserted central catheter	Procedure	546.79	Hospital ledger 2014

\*Adjusted for academic or non-academic hospital admissions. DCM, Dutch cost manual; ERCP, endoscopic retrograde cholangiopancreatography.

differences between minimally invasive and open procedures were expected for this. Unit costs were calculated for the reference year 2016, after price indexing with general consumer price indices if original sources from other base years were used (<https://www.cbs.nl/>; accessed 1 December 2017) (Table 1). Costs were calculated as the product of the numbers of hospital resources used and their respective unit costs. All costs are presented in euros.

### Postoperative outcomes

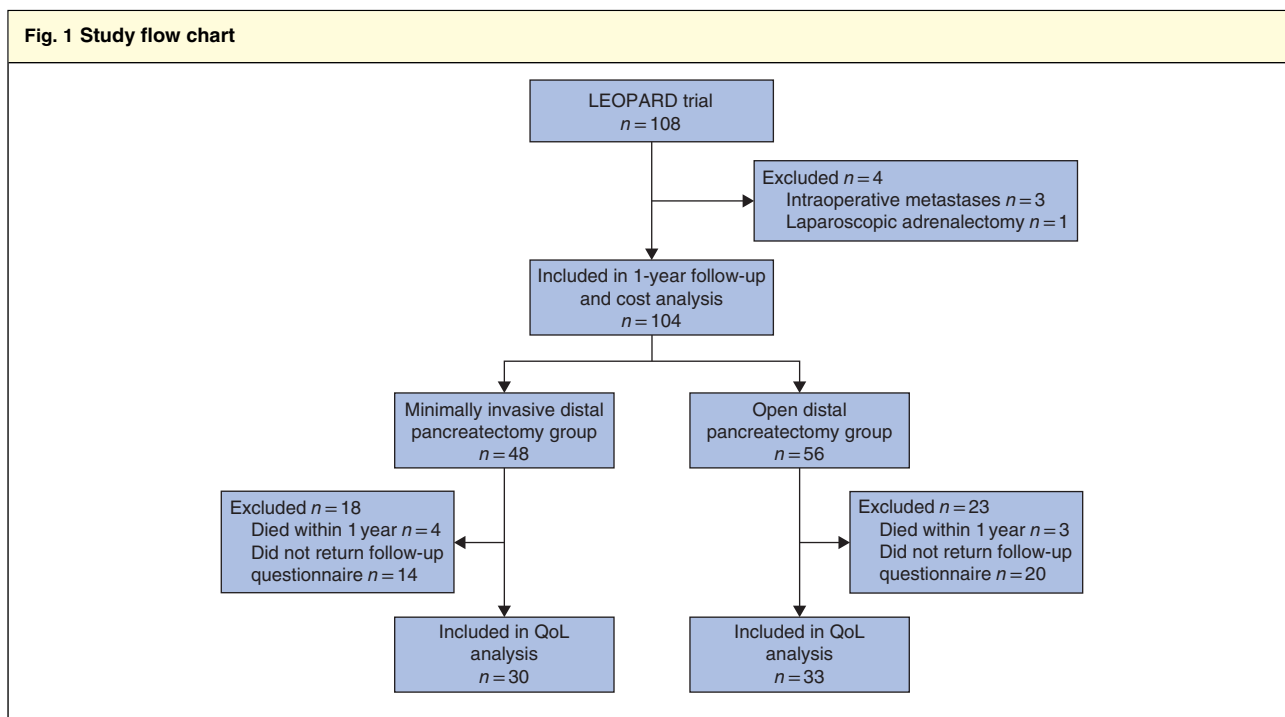
All postoperative outcomes up to 1 year after surgery were registered on a standard case report form. Complications were classified according to the Clavien–Dindo classification<sup>13</sup> and those of grade III or higher were considered clinically relevant. Pancreatic surgery-specific complications (delayed gastric emptying, postoperative pancreatic fistula and postpancreatectomy haemorrhage) were classified according to International Study Group of Pancreatic Surgery definitions<sup>14–16</sup>.

### Quality-adjusted life-years and quality-of-life analysis

The EuroQol Five dimensions (EQ-5D<sup>TM</sup>; EuroQol Group, Rotterdam, the Netherlands)<sup>17</sup> and European

Organization for Research and Treatment of Cancer (EORTC) core Quality of Life Questionnaire QLQ-C30<sup>18</sup> were completed by patients before surgery (baseline), and 1, 3, 5, 14, 30, 90 and 365 days after operation. An extensive follow-up questionnaire was sent on day 365 after surgery. This questionnaire concerned patient characteristics (current height and weight), wound complications, wound complaints and satisfaction regarding the cosmetic result. This questionnaire also included the EORTC QLQ-PAN26 questionnaire. The EQ-5D<sup>TM</sup> was used to derive QALYs, whereas the QLQ-C30 and QLQ-PAN26 described disease-specific QoL. QoL outcomes during the first 90 days after surgery have been reported previously<sup>3</sup>.

Each patient was asked to score five aspects of health status using the EQ-5D<sup>TM</sup> questionnaire: mobility, self-care, usual activities, pain/complaints and mood (anxiety/depression). A patient could indicate for each dimension whether they experienced no, some or serious problems. During the study, the EuroQol Group presented the EQ-5D-5L<sup>TM</sup> questionnaire as the improved version of the EQ-5D-3L<sup>TM</sup>, with five instead of three response levels for each item. Therefore, at 1 year after surgery patients received the EQ-5D-5L<sup>TM</sup> questionnaire. Cross-walk value sets were used to map EQ-5D-5L<sup>TM</sup> scores to EQ-5D-3L<sup>TM</sup> scores. EQ-5D-3L<sup>TM</sup> health status scoring profiles were converted into health utilities by



QoL, quality of life.

applying an existing health valuation algorithm based on a time trade-off technique to elicit preferences from the Dutch general population<sup>19</sup>. Where EQ-5D™ health status scoring profiles were missing at any time point, health utilities were derived by taking the mean of ten imputations following predictive mean matching before calculation of QALYs. Patients who died were assigned a health utility of zero for the remainder of follow-up. QALYs were calculated from the area under the curve of health utility values during the first year following interpolation between successive measurements over time.

The QLQ-C30 questionnaire is a cancer-specific measurement instrument focusing on several aspects of QoL, including physical, emotional and social functioning. The global health score was reported for the present study. The QLQ-PAN26 is a pancreatic cancer-specific extension to the QLQ-C30 focusing on specific symptoms related to pancreatic disease (pancreatic pain, digestive problems, altered bowel habit, hepatic pain, body image, health-care satisfaction and sexuality). Missing QLQ-C30 and QLQ-PAN26 data were imputed ten times after predictive mean matching.

**Statistical analysis**

Analyses were performed according to modified intention-to-treat principles, excluding patients who did not undergo

**Table 2 Baseline characteristics**

	MIS (n = 48)	Open (n = 56)	P†
Age (years)*	61(13)	63(12)	0.495‡
Sex ratio (F : M)	19 : 29	29 : 27	0.213
BMI (kg/m) <sup>2</sup> *	27(6)	26(4)	0.825‡
History of abdominal surgery	20 (42)	27 (48)	0.504
History of diabetes mellitus	5 (10)	10 (18)	0.282
History of pancreatitis	3 (6)	3 (5)	1.000§
<b>ASA physical status grade</b>			0.571
I	12 (25)	9 (16)	
II	29 (60)	37 (66)	
III	7 (15)	10 (18)	

Values in parentheses are percentages unless indicated otherwise; \*values are mean(s.d.). MIS, minimally invasive distal pancreatectomy; open, open distal pancreatectomy. †χ<sup>2</sup> test, except ‡independent-samples *t* test and §Fisher's exact test.

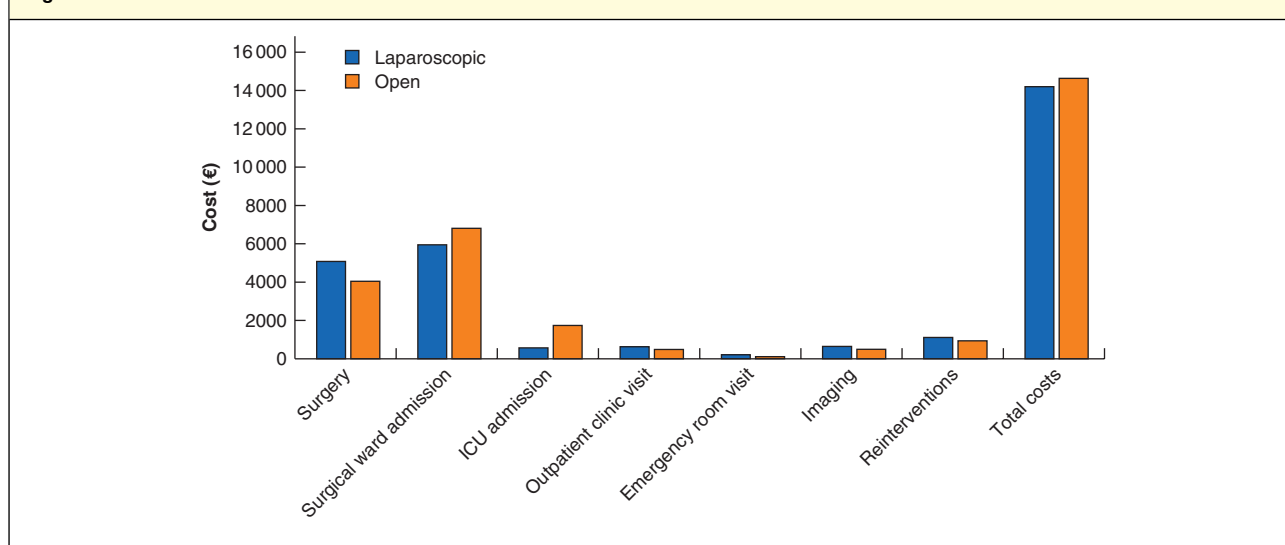
distal pancreatectomy owing to metastases or tumour location. Categorical variables were compared using the χ<sup>2</sup> or Fisher's exact test, as appropriate. Independent-samples *t* test was used for analysis of normally distributed continuous variables and the Mann–Whitney *U* test for those with a skewed distribution.

Differences in QLQ-C30 and QLQ-PAN26 scores between minimally invasive and open distal

**Table 3** Resource utilization and mean costs per patient, indexed for 2016

	Unit	Laparoscopic distal pancreatectomy (n = 43)		Open distal pancreatectomy (n = 56)		Difference in costs (€)
		Mean units	Costs (€)*	Mean units	Costs (€)*	
<b>Surgery</b>	Procedure	1	5081 (4666, 5497)	1	4043 (3778, 4307)	1038 (527, 1531)
<b>Admission</b>			6517 (4868, 8363)		8549 (6242, 11692)	-2032 (-5840, 1130)
Surgical ward	Days	11.4	5950 (4486, 7671)	12.1	6806 (5419, 8394)	-857 (-3206, 1547)
ICU	Days	1.7	567 (144, 1147)	4	1743 (489, 3681)	-1175 (-3796, 435)
<b>After discharge</b>			841 (680, 1002)		600 (481, 724)	239 (28, 438)
Outpatient clinic	Visit	4.7	628 (524, 736)	3.6	489 (410, 571)	139 (3, 275)
Emergency room	Visit	0.8	213 (131, 305)	0.4	112 (62, 170)	101 (-6, 208)
<b>Imaging</b>	Procedures	3.5	647 (473, 829)	3.2	500 (390, 618)	147 (-82, 359)
<b>Reinterventions</b>	Procedures	1.4	1118 (507, 1853)	1.3	938 (504, 1478)	181 (-648, 1010)
<b>Total costs</b>			14 204 (11 992, 16 714)		14 631 (11 694, 18 508)	-427 (-4700, 3616)

\*Values are mean (95 per cent bias-corrected and accelerated confidence intervals) costs estimated by non-parametric bootstrapping.

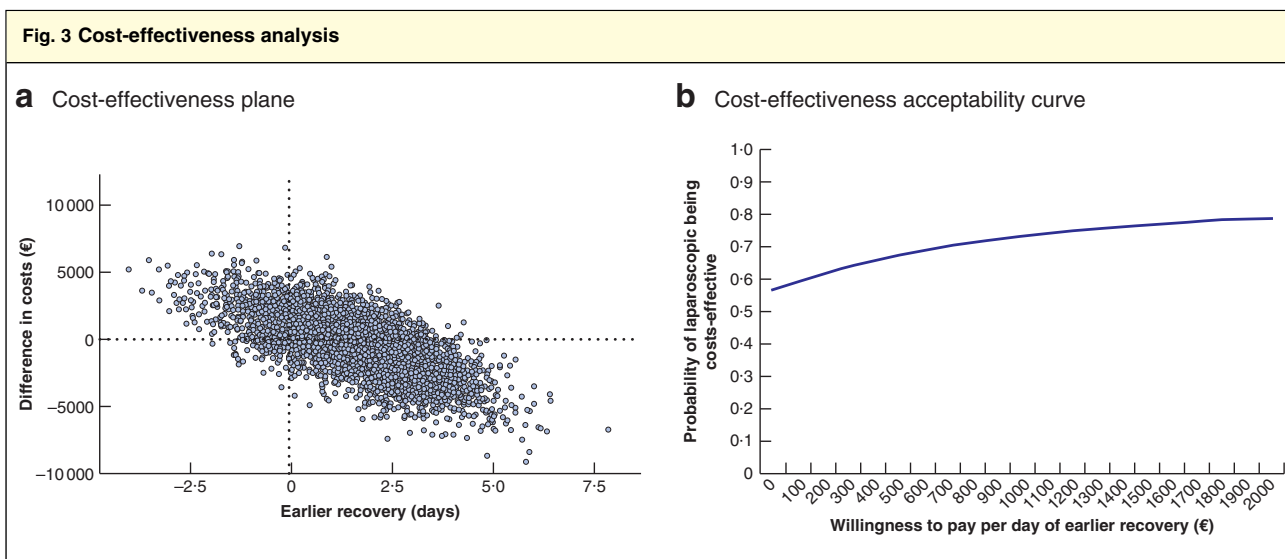
**Fig. 2** Distribution of costs

pancreatectomy groups over time, adjusted for baseline values, were assessed using a generalized linear mixed model with pooling of data from the imputation sets.

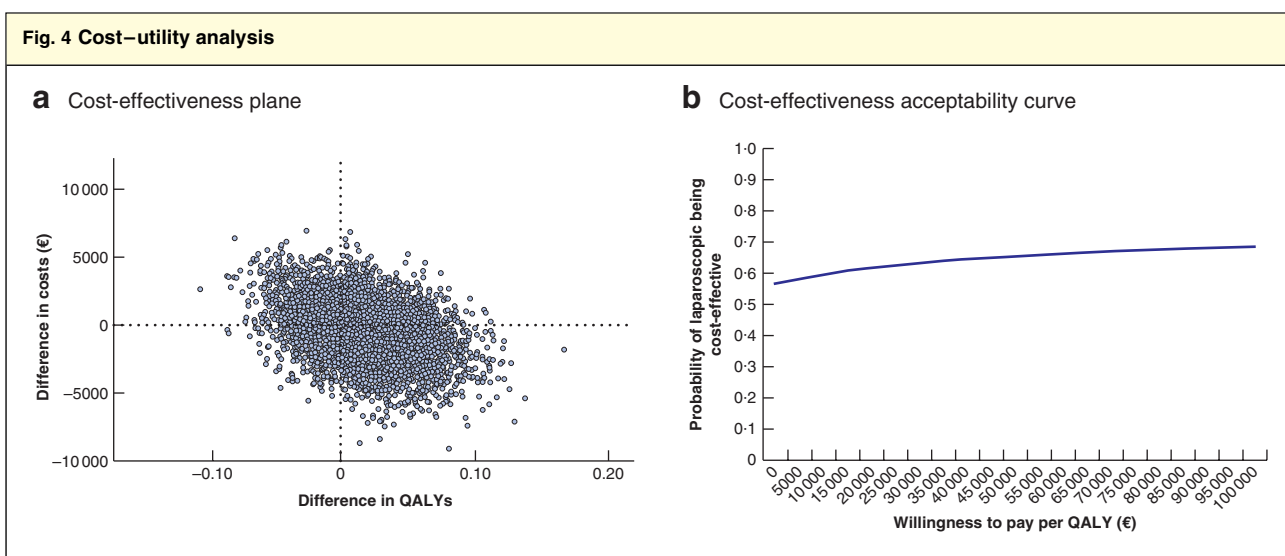
Differences in health economic outcomes between laparoscopic and open distal pancreatectomy were analysed by means of non-parametric bootstrapping, drawing 5000 samples of the same sizes as the original samples, with replacement<sup>20</sup>. Mean differences are reported with corresponding 95 per cent bias-corrected and accelerated confidence intervals (BCaCI); mean rather than median values are considered appropriate in health economic evaluations. The incremental cost-effectiveness ratio for laparoscopic *versus* open distal pancreatectomy was

calculated as the difference in mean costs per patient divided by the mean gain per patient in reduction in time to functional recovery measured in days. The incremental cost-utility ratio was calculated as the difference in mean costs per patient divided by the difference in mean QALYs per patient. Results were visualized in a cost-effectiveness plane. Cost-effectiveness acceptability curves were prepared showing the probability of laparoscopic distal pancreatectomy being cost-effective for various levels of societal willingness to pay per day reduction in time to functional recovery and per QALY gained.

$P < 0.050$  was considered statistically significant. All analyses were performed in SPSS® Windows® version 24.0 (IBM, Armonk, New York, USA).



**a** Cost-effectiveness plane showing differences in hospital healthcare costs and in time until recovery between laparoscopic and open distal pancreatectomy. There are four possible outcomes: the laparoscopic approach is more costly and more effective (upper right quadrant), more costly and less effective (upper left), cheaper and less effective (lower left), or cheaper and more effective (lower right). **b** Cost-effectiveness acceptability curve showing the probability of laparoscopic distal pancreatectomy being cost-effective for different values of willingness to pay per day of earlier recovery.



**a** Cost-effectiveness plane showing differences in hospital healthcare costs and in quality-adjusted life-years (QALYs) between laparoscopic and open distal pancreatectomy. There are four possible outcomes: the laparoscopic approach is more costly and more effective (upper right quadrant), more costly and less effective (upper left), cheaper and less effective (lower left), or cheaper and more effective (lower right). **b** Cost-effectiveness acceptability curve showing the probability of laparoscopic distal pancreatectomy being cost-effective for different values of willingness to pay per additional QALY.

**Results**

In total, 104 patients underwent distal pancreatectomy in the LEOPARD trial and were included in the present analysis (*Fig. 1*). One patient in the minimally invasive distal pancreatectomy group underwent an open procedure. This patient was analysed in the minimally invasive group

according to the intention-to-treat principle. Baseline characteristics were comparable in the two groups (*Table 2*).

**Cost analysis and cost-effectiveness**

Five patients who had robot-assisted surgery were excluded from the analyses of cost and cost-effectiveness, according



	Minimally invasive distal pancreatectomy (n = 48)	Open distal pancreatectomy (n = 56)	P†
<b>Clavien–Dindo grade ≥ III</b>	18 (38)	21 (38)	1.000‡
IIIa + IIIb	16 (33)	16 (29)	
IVa + Vb	2 (4)	5 (9)	
<b>Reintervention</b>	18 (38)	21 (38)	1.000‡
Surgical	2 (4)	3 (5)	1.000
<b>Postoperative pancreatic fistula grade B/C</b>	21 (44)	14 (25)	0.044‡
Grade B	18 (38)	13 (23)	
Grade C	3 (6)	1 (2)	
<b>Percutaneous catheter drainage</b>	12 (25)	12 (21)	0.667‡
<b>Endoscopic drainage</b>	6 (13)	6 (11)	1.000
<b>Drainage &gt; 90 days after surgery</b>	4 (8)	2 (4)	0.411
<b>Delayed gastric emptying grade</b>	4 (8)	11 (20)	0.101
<b>Postpancreatectomy haemorrhage grade B/C</b>	2 (4)	2 (4)	1.000
<b>Readmission</b>	17 (35)	15 (27)	0.342‡
<b>Total duration of hospital stay (days)*</b>	6 (5–14)	8 (6–14)	0.055§
<b>Death within 1 year</b>	4 (8)	3 (5)	0.701
<b>Symptomatic incisional hernia</b>	0 (0)	2 (4)	0.498
<b>New-onset diabetes mellitus</b>	12 (25)	6 (11)	0.070
<b>Pancreatic enzyme supplementation</b>	9 (19)	6 (11)	0.275

Values in parentheses are percentages unless indicated otherwise; \*values are median (i.q.r.). †Fisher's exact test, except ‡ $\chi^2$  test and §Mann–Whitney *U* test.

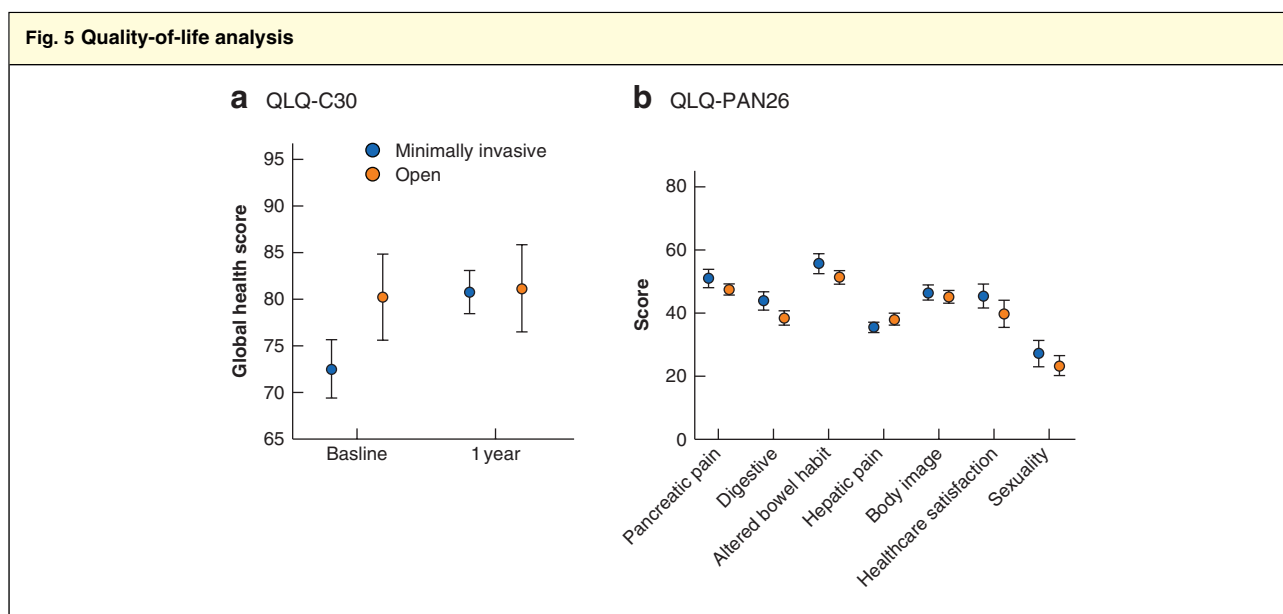
	Minimally invasive distal pancreatectomy (n = 30)	Open distal pancreatectomy (n = 33)	P‡
<b>Satisfaction with cosmetic result*</b>	9 (5.5–10)	7 (4–8.75)	0.056
<b>No. of patients visiting physician owing to problems with scar</b>	5	4	0.728§
<b>Chronic pain associated with scar†</b>			
At rest	0 (0–0)	0 (0–1)	0.433
During movement	0 (0–1)	0 (0–1.75)	0.993
During coughing/lifting heavy objects	0 (0–0.5)	0 (0–2.75)	0.259
Effect on daily activities	0 (0–0.25)	0 (0–0)	0.426

Values are median (range) unless indicated otherwise. \*Scored on a scale from 0 (completely unsatisfied) to 10 (completely satisfied); †scored on a scale from 0 (no pain) to 10 (severe pain). ‡Mann–Whitney *U* test, except §Fisher's exact test.

to the protocol. Mean use of hospital resources and costs per patient for laparoscopic and open distal pancreatectomy, as well as mean cost differences, are shown in Table 3 and Fig. 2. Mean total costs were €14204 (95 per cent BCaCI €11992 to 16714) for laparoscopic and €14631 (11694 to 18508) for open distal pancreatectomy; the mean difference was €–427 (–4700 to 3613) ( $P = 0.839$ ). Mean time to functional recovery was 6.37 (95 per cent BCaCI 4.72 to 8.52) days after laparoscopic and 8.05 (6.57 to 9.87) days after open distal pancreatectomy, with a mean difference of –1.68 (–4.40 to 1.29) days ( $P = 0.271$ ). Fig. 3a shows the differences in hospital healthcare costs according to days of earlier recovery of the 5000 bootstrap samples. In 54.9 per cent of bootstraps,

costs of laparoscopic distal pancreatectomy were lower and the laparoscopic approach reduced the time to functional recovery (lower right quadrant). In 11.5 per cent, the laparoscopic procedure was more expensive and resulted in a longer time to functional recovery (upper left quadrant). In 1.7 per cent, laparoscopic distal pancreatectomy was cheaper, but resulted in a longer time to functional recovery, whereas in 31.8 per cent it was more expensive but resulted in earlier recovery. Fig. 3b shows the probability of laparoscopic distal pancreatectomy being cost-effective for different values of societal willingness to pay per day reduction in time to recovery; at a willingness-to-pay threshold of €0, the probability was 0.566, and at €2000 it was 0.786.





**a** QLQ-C30 global health score at baseline and 1 year after surgery, and **b** QLQ-PAN26 scores after 1 year, in minimally invasive and open distal pancreatectomy groups. Values are mean scores, with 95 per cent confidence intervals, on a scale from 0 to 100. **a** Overall estimated mean difference 0.39 (95 per cent c.i. -6.02 to 6.80) in favour of the open group ( $P=0.905$ ); **b**  $P=0.216$  (pancreatic pain),  $P=0.153$  (digestive),  $P=0.258$  (altered bowel habit),  $P=0.324$  (hepatic pain);  $P=0.607$  (body image);  $P=0.433$  (healthcare satisfaction),  $P=0.480$  (sexuality) (generalized linear mixed model).

### Quality-adjusted life-years and cost-utility

The five patients who underwent robot-assisted surgery were also excluded from the cost-utility analysis. The mean number of QALYs generated was 0.810 (95 per cent BCaCI 0.766 to 0.850) for laparoscopic and 0.792 (0.736 to 0.839) for open distal pancreatectomy, with a mean difference of 0.018 (-0.046 to 0.082) ( $P=0.609$ ). Fig. 4a shows the differences in hospital healthcare costs according to QALYs in the 5000 bootstrap samples. In 45.2 per cent of bootstraps, laparoscopic distal pancreatectomy decreased costs and increased QALYs (lower right quadrant). In 18.4 per cent, laparoscopy was more expensive and decreased QALYs (upper left quadrant). In 11.4 per cent, costs of laparoscopic distal pancreatectomy were lower, but laparoscopy resulted in fewer QALYs, whereas in 25.0 per cent laparoscopic distal pancreatectomy was more expensive but resulted in more QALYs. Fig. 4b shows the probability of laparoscopic distal pancreatectomy being cost-effective for different values of societal willingness to pay per additional QALY; at a willingness-to-pay threshold of €80 000, the probability was 0.676.

### Postoperative complications

Postoperative complications up to 1 year after minimally invasive or open distal pancreatectomy are shown in Table 4. Complications of at least Clavien-Dindo grade

III, reinterventions and readmissions were all comparable between groups. Twenty-one patients (44 per cent) developed a grade B/C pancreatic fistula in the minimally invasive group, compared with 14 (25 per cent) in the open group ( $P=0.044$ ); this included one late grade B/C pancreatic fistula (more than 90 days after surgery) in each group. In contrast, rates of percutaneous (12 (25 per cent) versus 12 (21 per cent);  $P=0.667$ ) and endoscopic (6 (13 per cent) versus 6 (11 per cent);  $P=1.000$ ) catheter drainage for pancreatic fistula were comparable between groups. The total duration of hospital stay, including readmissions during 1 year after surgery, was 6 (i.q.r. 5–14) and 8 (6–14) days after minimally invasive and open distal pancreatectomy respectively ( $P=0.055$ ). The mortality rate was comparable in the two groups. During 1-year follow-up, four patients (8 per cent) died in the minimally invasive group and three (5 per cent) in the open group ( $P=0.701$ ). One patient in the minimally invasive group died from ventricular fibrillation which caused cerebral ischaemia; the others all had a malignant tumour and died from recurrent disease or metastasis. Asymptomatic incisional hernia did not occur after minimally invasive distal pancreatectomy, but was diagnosed in two patients (4 per cent) after an open procedure ( $P=0.498$ ). Surgical hernia repair was not performed. New-onset diabetes was diagnosed in 12 patients (25 per cent) after minimally invasive and six (11 per cent) after open pancreatectomy ( $P=0.070$ ). Nine

(19 per cent) and six (11 per cent) patients respectively used oral pancreatic enzyme supplements after pancreatectomy ( $P = 0.275$ ).

### Oncological outcomes

Of all included patients, 20 (19.2 per cent) were diagnosed with a pancreatic ductal adenocarcinoma: 11 (23 per cent) in the minimally invasive group and nine (16 per cent) in the open group. Five of these patients died from local recurrence or metastasis within 1 year of surgery (minimally invasive 2 of 11, open 3 of 9;  $P = 0.617$ ). Six of 11 patients received chemotherapy after minimally invasive and five of nine after open distal pancreatectomy ( $P = 1.000$ ).

### Quality of life

Disease-specific QoL questionnaires were completed by 63 of 97 patients (65 per cent) who were still alive. The median cosmetic satisfaction score regarding scars was 9 (i.q.r. 5.5–10) after minimally invasive and 7 (4–8.75) after open distal pancreatectomy ( $P = 0.056$ ), on a scale from 0 to 10. Self-reported chronic pain scores associated with the scar were low and comparable between groups (Table 5). The QLQ-C30 global health score and the seven categories scored using the PAN-26 questionnaire were all comparable 1 year after minimally invasive and open distal pancreatectomy (Fig. 5).

### Discussion

In the LEOPARD trial, laparoscopic distal pancreatectomy had a probability of 0.566 of being more cost-effective than the open procedure at a willingness-to-pay threshold of €0 per day earlier functional recovery. The probability per additional QALY was 0.676 at a willingness-to-pay threshold of €80 000. Measures of disease-specific QoL were comparable for minimally invasive and open distal pancreatectomy. Follow-up of complications showed more grade B/C pancreatic fistula in the minimally invasive group than the open group, whereas the rates of endoscopic and catheter drainage were similar. Wound complications (incisional hernia, infections, pain) were rare after minimally invasive and open distal pancreatectomy, and comparable between groups.

The findings of the present study are largely in line with the available data on costs and cost-effectiveness in laparoscopic *versus* open distal pancreatectomy, but also in other types of laparoscopic surgery<sup>6,7,21</sup>. To be able to interpret the cost-effectiveness probabilities, more information regarding the societal willingness-to-pay threshold for

earlier recovery is needed. The cost-effectiveness acceptability curve (Fig. 3b) shows that, if society were not willing to pay for earlier recovery, laparoscopic distal pancreatectomy would be cost-effective in only slightly more than half of all patients undergoing this procedure. Therefore, strategies to improve identification of patients who will benefit most should be investigated, and further studies should also focus on the cost-effectiveness of robot-assisted distal pancreatectomy.

Although minimally invasive distal pancreatectomy may be the preferable treatment option from a health economic perspective, the higher rate of grade B/C pancreatic fistula in the minimally invasive group is concerning, and has not been reported previously. In the LEOPARD trial<sup>3</sup>, during the first 90 days after surgery, there was a trend towards a higher rate of grade B/C pancreatic fistula in the minimally invasive compared with the open group, whereas the rates of increased drain amylase levels on day 3 and number of percutaneous catheter drainage procedures were similar. These findings could be explained by more patients being discharged home with the surgical drain still in place after minimally invasive distal pancreatectomy (owing to faster postoperative recovery), resulting in drain removal being delayed for more than 21 days after surgery. A higher rate of grade B/C pancreatic fistula could lead to more reinterventions and outpatient clinic visits, and a longer hospital stay, with increased costs; however, this was not observed in the present analysis, strengthening the abovementioned hypothesis. It should be noted that the LEOPARD trial was not powered to show differences in postoperative complications and that studies including 1-year follow-up of complications after distal pancreatectomy are limited. The DISPACT 2 trial<sup>22</sup>, which is currently in progress, is comparing laparoscopic and open distal pancreatectomy with the comprehensive complication index as primary outcome and may give more insight.

Improved QoL and cosmetic satisfaction are often mentioned as a benefit of minimally invasive surgery<sup>23–26</sup>. The present study, however, found that QoL and cosmetic satisfaction were comparable after minimally invasive and open distal pancreatectomy. During the first 30 days after surgery in the LEOPARD trial<sup>3</sup>, superior QoL outcomes were reported after minimally invasive procedures. The benefits of minimally invasive over open distal pancreatectomy are apparently most prominent during the early phase after surgery (in terms of pain and mobility). Regarding cosmetic satisfaction, the overall score was non-significantly higher in the minimally invasive group, so a type II error cannot be excluded. No standardized and validated body image questionnaire or cosmetic scale was

used to assess cosmetic satisfaction. During 2- and 5- year follow-up, a standardized body image questionnaire was added to the follow-up questionnaires.

Use of smaller incisions and therefore better preservation of the abdominal wall is one advantage of minimally invasive surgery. In another study<sup>27</sup>, the hernia rate after a median follow-up of 53 months was 5 per cent after minimally invasive and 17.4 per cent after open distal pancreatectomy ( $P = 0.050$ ). A systematic review<sup>28</sup> of RCTs comparing laparoscopic and open abdominal surgery showed a lower incisional hernia rate in the laparoscopic group after at least 1 year (4.3 *versus* 10.1 per cent). In the present study, the 1-year rate of incisional hernia was low in both groups. This could either be related to the lack of a standardized method for detection of incisional hernias (self-reported or as a finding during routine physical examination), the short duration of follow-up, or type (midline *versus* transverse subcostal) and length of incision. Scar length was not measured in all patients in the LEOPARD trial, but the specimens were extracted through a Pfannenstiel incision in all minimally invasive procedures. Another systematic review<sup>29</sup> specifically described an increase in hernia rates after midline laparotomy from 12.6 per cent in the first year after surgery to 22.4 per cent in the third year. Results of 2- and 5-year follow-up are awaited, and future cost-effectiveness analyses should include the cost of incisional hernia repairs.

The present study has some limitations which should be kept in mind when interpreting the results. First, the sample size was not designed to detect a difference in complication rates. A much larger sample is needed to analyse differences in overall complications and pancreatic fistula rates between groups. Second, no standardized follow-up at the outpatient clinic was performed, for instance for hernia detection using standard examination or imaging. This could have led to under-reporting of postoperative complications such as incisional hernia. Third, the QLQ-C30 and PAN-26 questionnaires were designed and validated for use in patients with cancer, but not all patients included in this study were diagnosed with cancer, which could have influenced outcomes. Fourth, the health economic evaluation was performed alongside an RCT, and restricted to a hospital healthcare perspective. Although all major cost components were included in the analysis, more attention should normally be paid to potential gains from earlier return to work for patients in employment owing to a quicker recovery following minimally invasive surgery. Finally, for resource use that did not differ between groups (such as postsplenectomy vaccinations), costs were not measured owing to the limited study funding.

Minimally invasive distal pancreatectomy is a promising healthcare intervention, both from a clinical and a health economic perspective. Continued follow-up and additional studies are needed to further analyse long-term complications and the financial implications for the healthcare insurer.

### Collaborators

LEOPARD trial collaborators are: H. C. van Santvoort (Department of Surgery, St Antonius Hospital, Nieuwegein, and University Medical Centre Utrecht, Utrecht, the Netherlands); M. T. de Boer (Department of Surgery, University Medical Centre Groningen, Groningen, the Netherlands); D. Boerma (Department of Surgery, St Antonius Hospital, Nieuwegein, the Netherlands); P. B. van den Boezem (Department of Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands); R. M. van Dam, C. H. Dejong (Department of Surgery, Maastricht University Medical Centre, Maastricht, the Netherlands, and Universitätsklinikum Aachen, Aachen, Germany); E. B. van Duyn (Department of Surgery, Medisch Spectrum Twente, Enschede, the Netherlands); C. H. van Eijck (Department of Surgery, Erasmus University Medical Centre, Rotterdam, the Netherlands); M. F. Gerhards (Department of Surgery, OLVG, Amsterdam); I. H. de Hingh (Departments of Surgery, Catharina Hospital, Eindhoven, and Netherlands Comprehensive Cancer Organisation, Utrecht, the Netherlands); G. Kazemier (Department of Surgery, Cancer Centre Amsterdam, Amsterdam UMC, VU University, Amsterdam, the Netherlands); R. H. de Kleine (Department of Surgery, University Medical Centre Groningen, Groningen, the Netherlands); C. J. van Laarhoven (Department of Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands); G. A. Patijn, P. Steenvoorde (Department of Surgery, Isala Clinics, Zwolle, the Netherlands); M. Suker (Department of Surgery, Erasmus University Medical Centre, Rotterdam, the Netherlands); M. Abu Hilal (Department of Surgery, Southampton University Medical Centre NHS Foundation Trust, Southampton, UK).

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## References

- Venkat R, Edil 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. *Ann Surg* 2012; **255**: 1048–1059.
- de Rooij T, Klompaker S, Abu Hilal M, Kendrick ML, Busch OR, Besselink MG. Laparoscopic pancreatic surgery for benign and malignant disease. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 227–238.
- de Rooij T, van Hilst J, van Santvoort H, Boerma D, van den Boezem P, Daams F et al.; Dutch Pancreatic Cancer Group. Minimally invasive versus open distal pancreatectomy (LEOPARD): a multicenter patient-blinded randomized controlled trial. *Ann Surg* 2019; **269**: 2–9.
- van Hilst J, de Rooij T, Abu Hilal M, Asbun HJ, Barkun J, Boggi U et al. Worldwide survey on opinions and use of minimally invasive pancreatic resection. *HPB (Oxford)* 2017; **19**: 190–204.
- Conlon KC, de Rooij T, van Hilst J, Abu Hilal M, Fleshman J, Talamonti M et al.; Minimally Invasive Pancreatic Resection Organizing Committee. Minimally invasive pancreatic resections: cost and value perspectives. *HPB (Oxford)* 2017; **19**: 225–233.
- Tax C, Govaert PHM, Stommel MWJ, Besselink MGH, Gooszen HG, Rovers MM. The value of decision analytical modeling in surgical research: an example of laparoscopic versus open distal pancreatectomy. *Ann Surg* 2019; **269**: 530–536.
- Gurusamy KS, Riviere D, van Laarhoven CJH, Besselink M, Abu-Hilal M, Davidson BR et al. Cost-effectiveness of laparoscopic versus open distal pancreatectomy for pancreatic cancer. *PLoS One* 2017; **12**: e0189631.
- de Rooij T, van Hilst J, Vogel JA, van Santvoort HC, de Boer MT, Boerma D et al.; Dutch Pancreatic Cancer Group. Minimally invasive versus open distal pancreatectomy (LEOPARD): study protocol for a randomized controlled trial. *Trials* 2017; **18**: 166.
- Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D et al.; ISPOR Health Economic Evaluation Publication Guidelines–CHEERS Good Reporting Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) – explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* 2013; **16**: 231–250.
- Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D et al.; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ* 2013; **346**: f1049.
- Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. *PLoS One* 2017; **12**: e0187477.
- Dutch Healthcare Authority. *Silver Cross Price Finder*. [https://puc.overheid.nl/nza/doc/PUC\\_13010\\_22/](https://puc.overheid.nl/nza/doc/PUC_13010_22/) [accessed 18 March 2019].
- Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187–196.
- Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M et al.; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery* 2017; **161**: 584–591.
- Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007; **142**: 761–768.
- Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007; **142**: 20–25.
- EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199–208.
- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365–376.
- Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. *Ned Tijdschr Geneesk* 2005; **149**: 1574–1578.
- Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. *Stat Med* 2000; **19**: 3219–3236.
- Fretland ÅA, Dagenborg VJ, Bjørnelv GMW, Kazaryan AM, Kristiansen R, Fagerland MW et al. Laparoscopic versus open resection for colorectal liver metastases: the OSLO-COMET randomized controlled trial. *Ann Surg* 2018; **267**: 199–207.
- WHO International Clinical Trials Registry Platform. *Distal Pancreatectomy – A randomised controlled trial to compare open versus laparoscopic resection (DISPACT 2-TRIAL)*. <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00014011> [accessed 20 April 2018].
- Canda AE, Sucullu I, Ozsoy Y, Filiz AI, Kurt Y, Demirbas S et al. Hospital experience, body image, and cosmesis after laparoscopic or open splenectomy. *Surg Laparosc Endosc Percutan Tech* 2009; **19**: 479–483.
- Eshuis EJ, Slors JF, Stokkers PC, Sprangers MA, Ubbink DT, Cuesta MA et al. Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease. *Br J Surg* 2010; **97**: 563–568.
- Dunker MS, Stiggelbout AM, van Hogezaand RA, Ringers J, Griffioen G, Bemelman WA. Cosmesis and body image after

laparoscopic-assisted and open ileocolic resection for Crohn's disease. *Surg Endosc* 1998; **12**: 1334–1340.

- 26 Dunker MS, Bemelman WA, Slors JF, van Duijvendijk P, Gouma DJ. Functional outcome, quality of life, body image, and cosmesis in patients after laparoscopic-assisted and conventional restorative proctocolectomy: a comparative study. *Dis Colon Rectum* 2001; **44**: 1800–1807.
- 27 Butturini G, Partelli S, Crippa S, Malleo G, Rossini R, Casetti L *et al*. Perioperative and long-term results after left pancreatectomy: a single-institution, non-randomized,

comparative study between open and laparoscopic approach. *Surg Endosc* 2011; **25**: 2871–2878.

- 28 Kössler-Ebs JB, Grummich K, Jensen K, Hüttner FJ, Müller-Stich B, Seiler CM *et al*. Incisional hernia rates after laparoscopic or open abdominal surgery – a systematic review and meta-analysis. *World J Surg* 2016; **40**: 2319–2330.
- 29 Fink C, Baumann P, Wente MN, Knebel P, Bruckner T, Ulrich A *et al*. Incisional hernia rate 3 years after midline laparotomy. *Br J Surg* 2014; **101**: 51–54.

