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ORIGINAL ARTICLE

Laparoscopic Distal Pancreatectomy in Benign or Premalignant Pancreatic Lesions: Is It Really More Cost-Effective than Open Approach?

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Abstract
Background Data regarding the quality of life in patients undergoing laparoscopic distal pancreatectomy are lacking and no studies have reported a real cost-effectiveness analysis of this surgical procedure. The aim of this study was to evaluate and compare the quality of life and the cost-effectiveness of a laparoscopic distal pancreatectomy with respect to an open distal pancreatectomy.
Methods Forty-one patients who underwent a laparoscopic distal pancreatectomy and 40 patients who underwent an open distal pancreatectomy were retrospectively studied as regards postoperative results, quality of life and cost-effectiveness analysis. The Italian neutral version of the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C-30, version 3.0, was used to rate the quality of life.
Results Postoperative results were similar in the two groups; the only difference was that the first oral intake took place significantly earlier in the laparoscopic group than in the open group ($P<0.001$). Regarding quality of life, the laparoscopic approach was able to ameliorate physical functioning ($P=0.049$), role functioning ($P=0.044$) and cognitive functioning ($P=0.030$) and reduce the sleep disturbance scale ($P=0.050$). The cost-effectiveness analysis showed that the acceptability curve for a laparoscopic distal pancreatectomy had a higher probability of being more cost-effective than an open distal pancreatectomy when a willingness to pay above 5400 Euros/quality-adjusted life years (QALY) was accepted.
Conclusion Despite the limitations of the study, laparoscopic distal pancreatectomy can be considered not only safe and feasible but also permits a better quality of life and is acceptable in terms of cost-effectiveness to Italian and European health care services.

Keywords Laparoscopy · Pancreas · Cost-effectiveness

Introduction

Laparoscopic distal pancreatectomy (LDP) has become widely accepted in the treatment of benign and low-grade malignant pancreatic diseases[1]. Recent systematic reviews and meta-analyses[2–8] have demonstrated the safety and feasibility of an LDP and have reported some postoperative advantages with respect to an open approach. Recently, some studies[9–12] have compared the costs of an LDP and an open distal pancreatectomy (ODP). However, data regarding the quality of life (QoL) in patients treated with an LDP are lacking and, to our knowledge, no study has reported a real cost-effectiveness analysis. The principal aim of this study was to evaluate and compare the QoL and the cost-effectiveness of an LDP with respect to an ODP.

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Materials and Methods

Study Design

This was a retrospective study based on a prospectively collected database regarding 41 consecutive patients who were treated from January 2008 to June 2013 with an LDP for

benign or low-grade malignant lesions of the pancreatic body-tail. This group was compared with a cohort of 40 consecutive patients who underwent an ODP from January 2003 to June 2013 for benign or low-grade malignant lesions of the pancreatic body-tail.

Surgical Procedures

All procedures (both ODPs and LDPs) were carried out by the same surgical team consisting of two high-volume pancreatic surgeons (FM and RC)[13]. After 2008, patients were selected for an ODP with the following criteria: absolute contraindications for laparoscopy[14] and patients who did not consent to a laparoscopy. The surgical laparoscopic technique was the same as previously reported[15]. The following devices were used for each laparoscopic procedure: disposable 10-mm trocars (Ethicon® Endosurgery) (from minimum 3 to maximum 5), one or two disposable 10-mm graspers (endo Grasper™ Ethicon® Endosurgery), one clip applier (Endo-Clip appliers™ Ethicon® Endosurgery), one endobag (EndoBag™ Ethicon® Endosurgery) and old (Ultracision Harmonic Scalpel, Ethicon Endo-Surgery, Cincinnati, OH, USA)- or new (Harmonic Ace, Ethicon Endo-Surgery, Cincinnati, OH, USA)-generation harmonic scalpels. A pancreatic resection was usually performed using a linear stapler. The selection of the type of stapler and of the colour/size of the cartridge was at the discretion of the surgeon: a double-row Endo GIA stapler 45 mm (Ethicon® Endosurgery), a three-row Echelon Endopath™ 60 mm (Ethicon® Endosurgery) or a three-row Endo GIA Ultra Tri stapler™ 60 mm ((Covidien®)Surgical). The ODP was performed as previously reported[16], and the pancreatic stump was treated either one of two techniques, according to the preference of the surgeon: (a) stapling with a linear stapler using one of the above-mentioned staplers and (b) hand-sewing. A splenectomy was performed in both the open and the laparoscopic procedures in cases of suspicious malignant lesions or when a spleen-preserving distal pancreatectomy was impossible for technical reasons.

Definitions

Operative time was defined as the time interval from incision to the suturing of the skin. Postoperative morbidity included all complications following surgery up to the day of discharge, according to the Clavien-Dindo classification[17]. A postoperative pancreatic fistula (POPF) was defined according to the definition proposed by the International Study Group of Pancreatic Fistula (ISGPF; grades A, B and C)[18]. Postpancreatectomy haemorrhage (PPH) was defined as intraabdominal or intestinal bleeding according to the criteria of the International Study Group of Pancreatic Surgery (ISGPS)[19]. Reoperation was defined as any surgical procedure carried out in the first 30 postoperative days or before discharge from the hospital. Postoperative mortality was defined as all deaths occurring during the hospital stay or within 90 days from surgery. The hospital stay was defined as the interval from the day of surgery to discharge.

Patients Characteristics and Clinical Outcomes of Interest

The groups were compared as regards sex, age, comorbidities, body mass index (BMI), size of lesions, previous abdominal surgery, type of surgery (splenectomy, pancreatic stump management and extension of resection), characteristics of the pancreatic stump (texture and Wirsung dilatation), operative time and final histological diagnosis. Postoperative results, such as mortality, overall complications, POPF, PPH, reoperation rate, first oral intake, hospital stay and pathological data, were also evaluated.

Quality of Life

Data regarding patient quality of life were obtained from the database of the patients who underwent pancreatic resection. All patients who underwent pancreatic resection in our institution were asked to respond to two different questionnaires 1 year after surgery: a condition-specific questionnaire (European Organization for Research and Treatment of Cancer Quality of-Life Questionnaire C-30 (EORTC QLQ C30)) and a generic questionnaire (EuroQOL five dimensions (EQ-5D)). The Italian neutral version of the EORTC QLQ C-30, version 3.0, was used. The EORTC QLQ C-30 consists of one global domain (global health [GH]); five functional domains exploring physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF) and social functioning (SF) as well as eight symptom scales (fatigue [FA], pain [PA], nausea-vomiting [NV], dyspnea [DY], appetite loss [AP], sleep disturbance [SL], constipation [CO], diarrhoea [DI]); and 1 item concerning the financial impact (FI) of the disease. Scoring of the EORTC QLQ C-30 was carried out according to published methods[20]; all scales were transformed to scores between 0 and 100. For the functional scales and the global health status, higher scores reflected a higher level of functioning. In the symptom scales or single items, higher scores reflected increasing level of symptoms or difficulty. The interpretation of the scores was carried out according to the EORTC QLQ C-30 Scoring Manual[21]. Moreover, the presence of an incisional hernia at the time of interview was evaluated. The results of the QoL questionnaire and the incisional hernia rate between the two groups were compared. Multivariate analysis was also carried out to establish which factors independently influenced patients: QoL as well as age, comorbidities, pathological data (malignant or benign), postoperative course (complicated or uncomplicated), type of surgery (a laparoscopic or an

open approach, standard or extended resection) and other chronic or acute diseases occurring during the 1-year follow-up. Data derived from EORTC QLQ C30 are unable to directly calculate quality-adjusted life years (QALYs). Thus, data regarding QALYs were derived from the values of generic preference-based measures, such as the EuroQoL five dimension questionnaire[22].

Cost-Effectiveness Analysis

The cost-effectiveness analysis was carried out in accordance with the EVEREST guidelines[23]. The total costs of the two surgical procedures regarded hospital stay, and instrumental and operative room costs, and were obtained from the economic office of our hospital. All costs were discounted at a real annual rate to adjust for the relative value of the Euro at present. The crude costs of both groups were compared separately considering hospital stay costs, intraoperative costs (surgical instrument costs, operative room costs) and total costs.

The mean differential cost and mean differential QALY were calculated and plotted on a cost utility plane. The horizontal axis represented the differences in QALYs and the vertical axis the differences in costs. The incremental cost-effectiveness ratio (ICER) was properly computed as cost per QALY gained and reported as mean values. The ICER slope and 95 % confidence intervals (CI 95 %) were plotted. The Italian gross domestic product (GDP) per capita (24,048 Euros) was considered as a reference value assuming an ICER of 1xGDP to define an intervention as cost-effective[24,25]. Uncertainty regarding cost-effectiveness was also explored using the cost-effectiveness acceptability curve (CEAC) which shows the probability that an intervention is cost-effective as compared with the alternative, given the observed data, for a range of monetary values that a decision-maker might be willing to pay for a particular unit change in outcome (willingness to pay (WTP))[26]. The incremental net monetary benefit (INMB) was calculated to obtain a confidence interval for producing the cost-effectiveness analysis acceptability curve. Finally, a sensitivity analysis was carried out to assess the impact of disposable instruments (trocars, graspers, clip appliers). In this hypothetical scenario, we considered that surgeons used only harmonic scalpels for the dissection and the least expensive linear stapler available in our hospital.

Statistical Analysis

Data were analysed on an intention-to-treat basis, including a group of LDP patients in whom a conversion to a laparotomic procedure was needed. Means, medians, standard deviations, ranges and frequencies were used to describe the data. The Fisher's exact test and Pearson chi square test were applied to discrete variables. Continuous variables were compared using the Student's *t* test. Multivariate analysis was carried out using linear regression. The results and costs were reported as mean difference and interval confidence (CI 95 %). Two-tailed *P* values less than 0.05 were considered statistically significant. A confidence interval for the costs per QALY ratio was obtained using the non-percentile bootstrap method, based on 2000 replications. Fieller's method was used to establish the confidence interval[27]. Data analyses were carried out by running the Statistical Package for Social Science (SPSS, Chicago, IL), version 13. Cost-effectiveness analyses were carried out using Stata™ 5.0 software (Stata Corporation, College Station, Texas, USA).

Results

Table 1 shows the results comparing the ODP and the LDP groups. There were no differences in sex, age, presence of comorbidities, BMI index, previous abdominal surgery, size of lesions, splenectomy rate, characteristics of the pancreatic stump (texture and Wirsung dilatation), extension of resection and operative time. In the LDP group, the pancreatic stump was closed more frequently with a linear stapler than in the ODP group (82.9 vs. 47.5 %; $P=0.001$). No postoperative mortality was reported and five (12.2 %) procedures in the LDP group were converted. Of the 81 patients included in the analysis, 39.6 % ($n=32$) had well-differentiated endocrine tumours, 22.3 % ($n=18$) intraductal papillary mucinous neoplasms (4 patients with high-grade dysplasia and 14 with mild-moderate dysplasia), 11.2 % ($n=9$) serous cystic neoplasms, 9.8 % ($n=8$) mucinous cystic neoplasms with mild-moderate dysplasia, 4.8 % ($n=4$) solid cystic papillary neoplasms, 3.7 % ($n=3$) non-Hodgkin's lymphoma and 8.6 % ($n=7$) other non-neoplastic lesions. The number of benign and low-grade malignant lesions was similar in the two groups. The postoperative outcomes of interest are shown in Table 2. Complications, POPF, PPH and reoperation rates were similar between the two groups. The first oral intake was significantly earlier in the LDP group than in the ODP group (4 vs. 5 days; $P<0.001$). Overall hospital stay was similar in the LDP and ODP groups ($P=0.754$), but it shows a trend toward statistical significance when the postoperative course was uneventful (8 vs. 9 days; $P=0.059$).

Analysis of the Quality of Life

Analysis of the quality of life was available in only 54 patients (34 treated with LDP and 20 with ODP) because the other patients refused QoL questionnaires or were lost at the follow-up. The complication rate in LDP and ODP groups remains similar after exclusion of the patients without QoL questionnaires (32.4 vs. 35.5 %; $P=1.000$, respectively).

The QoL was similar between the two groups regarding global health and some functional domains (EF, CF and SF).

Table 1 Open distal pancreatectomy and laparoscopic distal pancreatectomy groups compared as regards demographic, clinical, surgical, intraoperative and pathological data

Characteristics	ODP (n=40) N (%)	LDP (n=41) N (%)	P value
Sex			
Male	21 (52.5)	14 (34.1)	0.119[a]
Female	19 (47.5)	27 (65.9)	
Age (years)	67 (2582)	58 (1582)	0.912[b]
Comorbidities			
None	14 (35)	17 (41.5)	0.649[a]
One or more	26 (65)	24 (58.5)	
BMI (kg/m^2)	26.6 (1745)	25.3 (1840)	0.912[b]
Previous abdominal surgery			
No	12 (30)	18 (43.9)	0.252[a]
Yes	28 (70)	23 (56.1)	
Size of lesions (cm)	3 (8–15)	2.5 (0.5–15)	0.292[b]
Splenectomy			
No	12 (30)	11 (26.8)	0.809[a]
Yes	28 (80)	30 (73.2)	
Texture of the pancreatic stump			
Soft	30 (75)	34 (82.9)	0.424[a]
Hard	10 (25)	7 (17.1)	
Wirsung >3 mm			
No	38 (95)	39 (95.1)	1.000[a]
Yes	2 (5)	2 (4.9)	
Pancreatic stump management			
Hand closure	21 (52.5)	7 (17.1)	0.001[a]
Linear stapler	19 (47.5)	34 (82.9)	
Extended resection			
No	36 (90)	38 (92.7)	0.712[a]
Yes	4 (10)	3 (7.3)	
Operative time (minutes)	217.5 (135–385)	210 (150–400)	0.760[b]
Pathological diagnosis			
Benign disease	18 (45)	23 (56.1)	0.377[a]
Low-grade malignant disease	22 (55)	18 (43.9)	

ODP open distal pancreatectomy, *LDP* laparoscopic distal pancreatectomy, *BMI* body mass index

[a] Fischer's exact test

[b] Student's t test

Table 2 Comparison of postoperative outcomes between open distal pancreatectomy and laparoscopic distal pancreatectomy

Postoperative results	ODP (n=40) N (%)	LDP (n=41) N (%)	P value
Complications			
No	20 (50)	26 (63.4)	0.226[a]
Yes	20 (50)	15 (36.6)	
POPF			
No	32 (80)	30 (73.2)	0.352[b]
Grade A	3 (7.5)	3 (7.3)	
Grade B	5 (12.5)	7 (17.1)	
Grade C	0	1 (2.4)	
PPH			
No	34 (85)	37 (90.2)	0.444[b]
Grade A	1 (2.5)	1 (2.4)	
Grade B	5 (12.5)	3 (7.3)	
Grade C	0	0	
Reoperation			
No	40 (100)	39 (95.1)	0.494[a]
Yes	0	2 (4.9)	
First oral intake (days; median; range)	5 (3–12)	4 (2–8)	<0.001[c]
Hospital stay in uncomplicated patients (days; median; range)	9 (7–14)	8 (6–12)	0.059[c]
Hospital stay in complicated patients (days; median; range)	11 (7–22)	10 (7–24)	0.754[c]
Hospital stay in all patients (days; median; range)	10 (7–22)	9 (6–24)	0.640[c]

ODP open distal pancreatectomy, *LDP* laparoscopic distal pancreatectomy, *POPF* postoperative pancreatic fistula, *PPH* postpancreatectomy haemorrhage

[a] Fischer's exact test

[b] Pearson chi square test

[c] Student's t test

At 12 months, in the group of patients treated with LDP, the PF (88.1±19.2 vs. 72.7±29.5; P=0.046) and RF (81.8±25.1 vs. 62.5±34.1; P=0.035) functional domains were more significantly improved than in the ODP group. Some symptom scales, such as FA, PA, NV, DY, AP and CO, were comparable. On the contrary, the ODP patients presented a significantly higher SL scale (26.7±25.6 vs. 12.7±21.7; P=0.049) while LDP patients presented a significantly higher (5.9±15.3 vs. 0; P=0.032) DI scale (Fig. 1). Finally, there was no difference concerning the FI scale. The rate of postoperative incisional hernia was similar (5.0 vs. 5.9 %; P=0.694) in both the ODP and the LDP groups, respectively. Multivariate analysis of the possible factors influencing the QoL scores (Table 3) showed that the laparoscopic approach was an independent factor capable of ameliorating the PF (P=0.049), RF (P=0.044) and CF (P=0.030) functional domains. It moreover confirmed that patients treated with an LDP presented a lower SL scale (P=0.050).

Cost-Effectiveness Analysis

Comparison of crude health service costs (Table 4) showed that postoperative stay costs were similar (5194 vs. 5520 Euros; P=0.628) while total and intraoperative costs were significantly higher in the LDP group than in the ODP group (6869 vs. 4076 Euros; P<0.001). In particular, the ODP

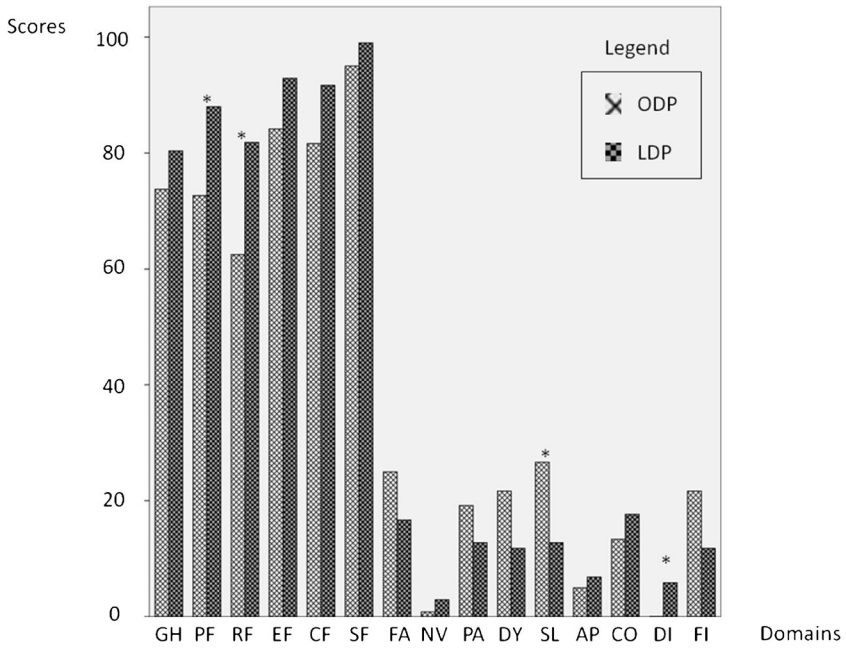

Fig. 1 EORTC QLQ C-30 domains and symptoms evaluated 12 months after surgery in the 54 patients undergoing open or laparoscopic distal pancreatectomy. The data are reported as mean (±SD). *ODP* open distal pancreatectomy, *LDP* laparoscopic distal pancreatectomy, *GH* global health, *PF* physical functioning, *RF* role functioning, *EF* emotional functioning, *CF* cognitive functioning, *SF* social functioning, *FA* fatigue, *PA* pain, *NV* nausea-vomiting, *DY* dyspnea, *AP* appetite loss, *SL* sleep disturbance, *CO* constipation, *DI* diarrhoea, *FI* financial impact of the disease. *P* values were computed by means of ANOVA. **P* value <0.05

procedures were less expensive regarding surgical instruments (177 vs. 2172 Euros; $P<0.001$). Finally, an LDP was more expensive than ODP regarding total costs (11,058 vs. 8038 Euros; $P<0.001$).

A cost-effectiveness analysis was carried out in only 61 patients (35 treated with LDP and 26 with ODP) in which we obtained information regarding the quality of life using the EQ-5D. When comparing the LDP and the ODP groups, the mean difference in QALYs was 0.2±0.08 ($P=0.005$) and in costs was 1379±919 Euros ($P<0.001$). The ICER was 5622 Euros for additional QALY gain. Figure 2 (panel A) shows the cost utility plane: from 2000 bootstrapped replications, 1944 observation (97.2 %) were found to be in the "uncertain quadrant" (northeast), 46 (2.3 %) in the "accept quadrant" (southeast) and 10 (0.5 %) in the "reject quadrant" (northwest).

In Fig. 2 (panel B), the ICER slope with a 95 % confidence interval is reported. The mean ICER slope was 16,108 Euros per QALY gained (-390; 18,922 Euros per QALY; CI 95 %). Figure 3 shows the incremental net monetary benefit (INMB) with a 95 % confidence interval (panel A) and the cost-effectiveness acceptability curve (panel B). The acceptability curve shows that an LDP had a higher probability of being more cost-effective than an ODP when a WTP more than 5400 Euros/QALY was accepted.

The sensitivity analysis showed that the use of some reusable laparoscopic equipment (trocars, graspers, clip appliers), and the use of the least expensive linear stapler available reduced the mean differential cost to 808±957 Euros ($P=0.001$), with an LDP still remaining significantly more expensive. The ICER was 3293 Euros per additional QALY gain. The acceptability curve showed that an LDP had a higher probability of being more cost-effective than an ODP when a WTP more than 3240 Euros/QALY was accepted.

Discussion

Recent systematic reviews and meta-analyses[2–8] have demonstrated that the laparoscopic approach is a reasonable and safe alternative to the open technique in performing a distal pancreatectomy. Some advantages regarding postoperative course as well as the complication rate and hospital stay have been described, but several limitations in the study designs (no randomised trials, different classification systems for detecting complications, no intention-to-treat analyses) rendered it impossible to state that LDP was clearly superior to ODP. To our knowledge, our study is the first in which LDP and ODP were compared as regards not only the postoperative results but also for QoL, crude costs and cost utility.

Patients were similar as regards age, sex, BMI, size of lesions, presence of comorbidities, previous abdominal surgery, splenectomy rate, characteristics of the pancreatic stump (texture and Wirsung dilatation), extension of the resection and operative time. The closure of the pancreatic stump was carried out using a linear stapler more frequently in the

Table 3 Multivariate analysis of factors influencing the quality of life (QoL) according to the Italian neutral version of the European Organization for Research and Treatment of Cancer Quality of-Life Questionnaire C-30 (EORTC QLQ C-30), version 3.0

QoL scales	Factors	Multivariate effect (C.I. 95 %)	*P* value
GH	Other acute or chronic disease during follow-up (yes vs. no)	−17.1 (−28.9; −5.1)	0.006[a]
PF	Other acute or chronic disease during follow-up (yes vs. no)	−19.1 (−32.3; −5.9)	0.005[a]
	Surgical procedures (LDP vs. ODP)	12.6 (0.1–25.3)	0.049[a]
RF	Other acute or chronic disease during follow-up (yes vs. no)	−20.4 (−36.8; −4.1)	0.016[a]
	Surgical procedures (LDP vs. ODP)	16.2 (0.4–32)	0.044[a]
EF	Type of pathology (benign vs. malignant)	−9.9 (−19.3; −0.5)	0.039[a]
	Other acute or chronic disease during follow-up (yes vs. no)	−15.5 (−25.5; −5.5)	0.003[a]
CF	Surgical procedures (LDP vs. ODP)	10.7 (1.1; 20.4)	0.030[a]
	POPF (yes vs. no)	−13.00 (−25.4; −2.4)	0.007[a]
SF	POPF (yes vs. no)	−7.1 (−14.1; −0.3)	0.040[a]
FA	Presence of comorbidities	13.5 (2.1; 25.1)	0.021[a]
NV	[b]	[b]	[b]
PA	Other acute or chronic disease during follow-up (yes vs. no)	16.3 (3.3; 29.3)	0.015[a]
DY	Other acute or chronic disease during follow-up (yes vs. no)	14.4 (1.7; 27.1)	0.027[a]
SL	Surgical procedures (LDP vs. ODP)	−12.9 (−25.9; −0.19)	0.050[a]
AP	Presence of comorbidities	10.1 (0.5; 19.6)	0.039[a]
CO	POPF	16.9 (0.2; 33.8)	0.048[a]
DI	[b]	[b]	[b]
FI	Other acute or chronic disease during follow-up (yes vs. no)	14.4 (1.7; 27.1)	0.027[a]

QoL quality of life, *ODP* open distal pancreatectomy, *LDP* laparoscopic distal pancreatectomy, *CI 95%* confidence interval, *GH* global health, *PF* physical functioning, *RF* role functioning, *EF* emotional functioning, *CF* cognitive functioning, *SF* social functioning, *FA* fatigue, *PA* pain, *NV* nausea-vomiting, *DY* dyspnea, *AP* appetite loss, *SL* sleep disturbance, *CO* constipation, *DI* diarrhoea, *FI* financial impact of the disease, *POPF* postoperative pancreatic fistula

[a] ANOVA

[b] No independent factors associated

laparoscopic approach than in the open approach (P=0.001). Diener MK et al.[28] recently reported, in the DISPACT trial, that stapler closure in distal pancreatectomies did not reduce the rate of pancreatic fistula or total complications as compared with hand-sewn closures. In our experience, the postoperative course was similar in the two groups without any differences in complications, POPF, PPH and reoperation rate. Nevertheless, in the seven meta-analyses[2–8] available in the English language which compared LDP to ODP, only four were able to demonstrate a reduction in complication rate;[2,5,7,9] one out of seven showed a reduction in the POPF rate,[2] and none reported differences in PPH and reoperation rate. In our study, only the first oral intake was significantly earlier in the LDP group with respect to the ODP group (P<0.001), confirming the results reported by five meta-analyses. The length of hospital stay was significantly shorter in patients with an uneventful postoperative course but, when complicated patients were included in the analyses, no differences were found. Pancreatic surgery, even if performed in high-volume centres, is characterised by a high risk of a

Table 4 Comparison of costs (hospital stay, intraoperative and total costs) between open distal pancreatectomy and laparoscopic distal pancreatectomy

Costs	ODP (n=40) *N* (%)	LDP (n=41) *N* (%)	*P* value
Hospital stay costs (mean±SD; Euro)	5520±2756	5194±3273	0.628[a]
Intraoperative cost (mean±SD; Euro)			
Instruments	177±179	2172±136	<0.001[a]
Operating theatre	4529±1075	4697±1264	0.521[a]
Total	4076±1070	6869±1263	<0.001[a]
Total costs (mean±SD; Euro)	8038±4159	11,058±2667	0.001[a]

ODP open distal pancreatectomy, *LDP* laparoscopic distal pancreatectomy

[a] Student's *t* test

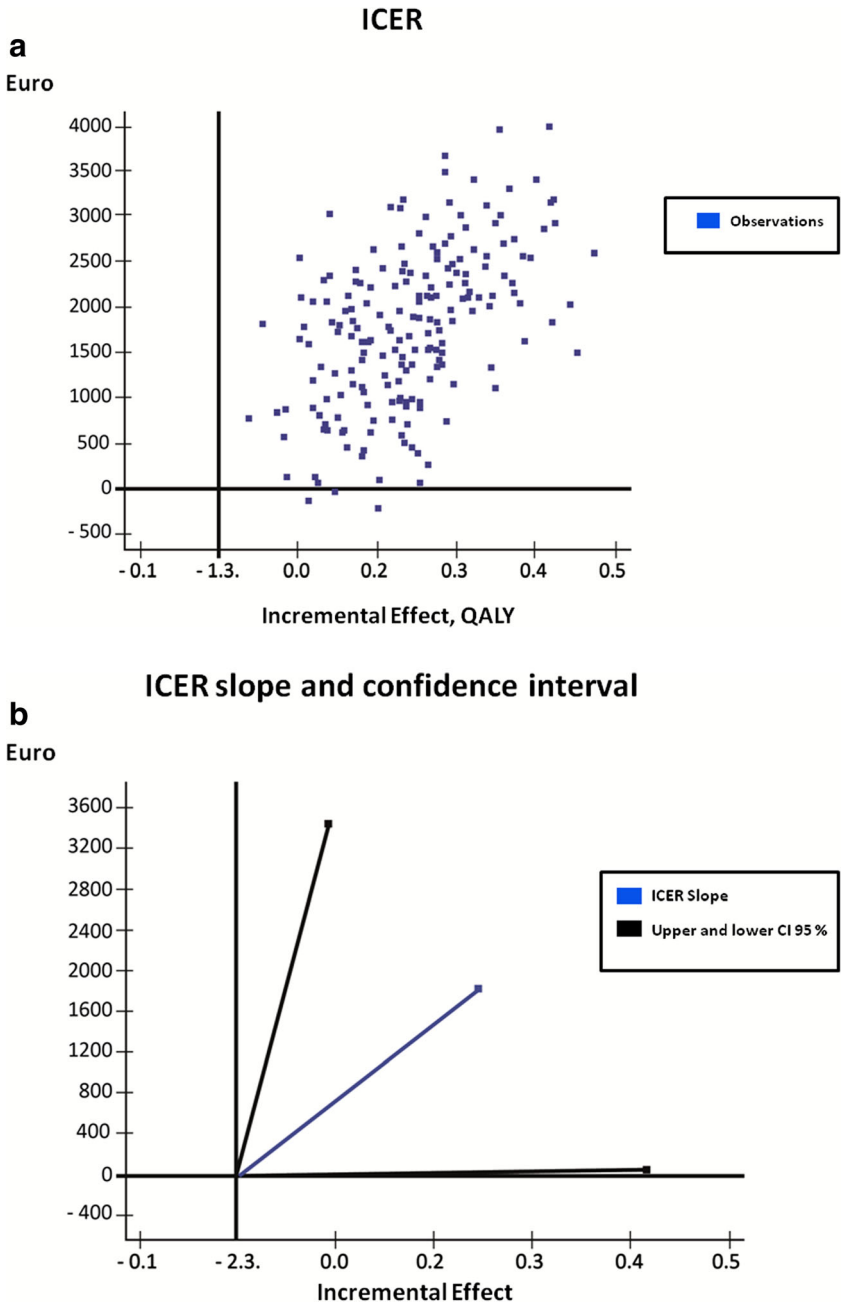

Fig. 2 **a** The cost utility plane. In 2000 bootstrapped replications, 1944 observations (97.2 %) were found to be in the northeast (NE) quadrant, 46 (2.3 %) in the southeast (SE) quadrant and 10 (0.5 %) in the northwest (NW) quadrant. *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life years. **b** The incremental cost-effectiveness ratio (ICER) slope with 95 % confidence interval. The mean ICER slope was 16,108 Euros per quality-adjusted life year (QALY) gained. Fieller's method was used to calculate the confidence intervals (CI 95 %)

complicated (up to 45 %) postoperative course[28] which can eclipse the typical advantages of the laparoscopic approach as well as a short hospital stay.

To our knowledge, data regarding the QoL after LDP are lacking in the English literature. In this study, LDP gave patients a significantly better QoL than ODP in some functional domains as well as in physical functioning and role functioning. These results were not surprising. In fact, the PF and the RF domains explore the ability of patients at work and confirm the hypothesis that a laparoscopic approach permits a quick return to normal activities. Moreover, symptomatic domains as well as sleeping disturbance also seemed to be favourably influenced by the laparoscopic approach. These results were confirmed by a multivariate analysis designed to avoid interference from various factors capable of modifying some symptomatic or functional domains. At the time of interview, the rate of overall incisional hernia was low (3 %), and no difference was found between LDP and ODP.

Few studies[9–12] have compared the costs of the laparoscopic and the open approaches in distal pancreatectomies; however, the results are conflicting. Eiom et al.[9] first reported the costs of LDP in comparison with ODP, showing that the overall costs of the laparoscopic approach were significantly lower than those of ODP. Limongelli et al.[10] reported that the

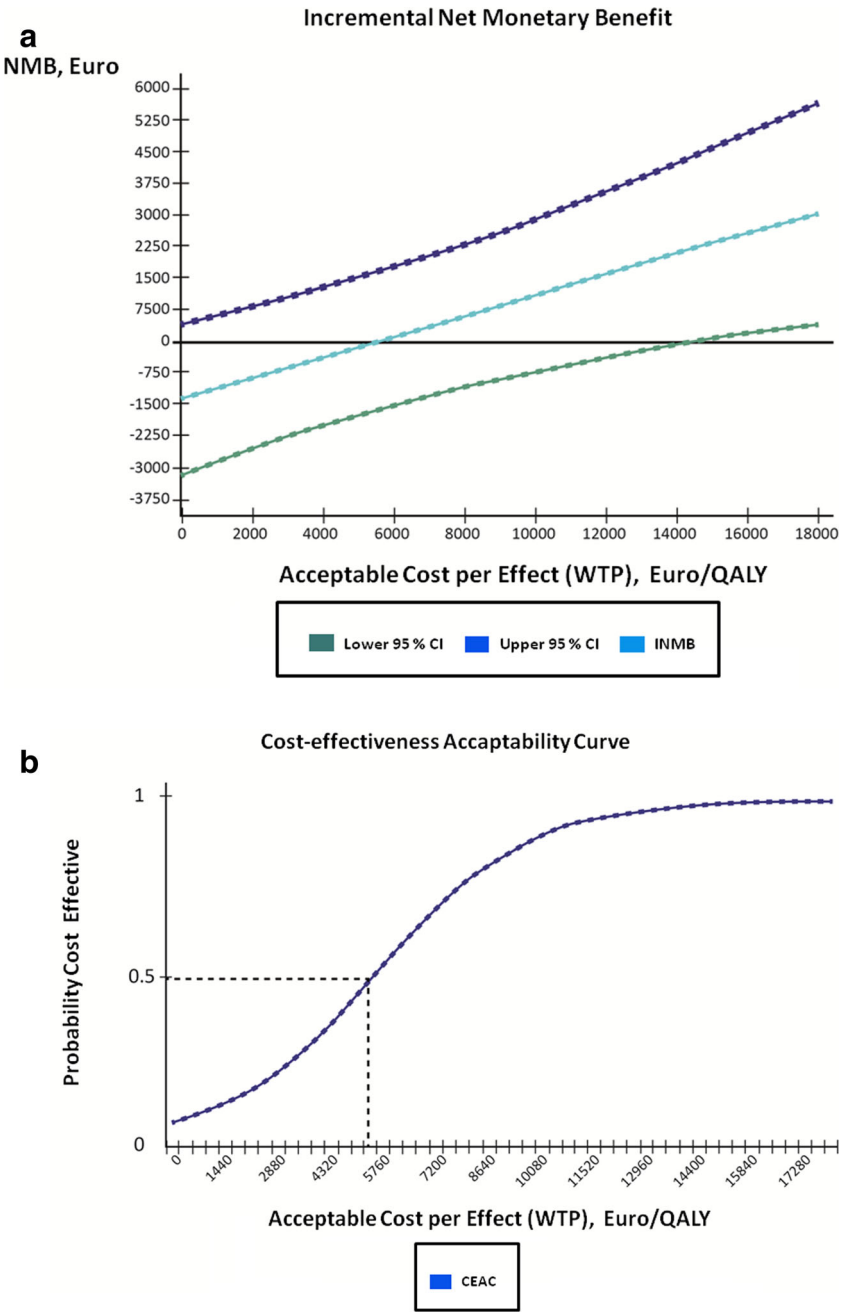

Fig. 3 **a** Incremental net monetary benefit (INMB) with 95 % confidence interval. CI 95 %: lower and upper confidence interval. **b** The cost-effectiveness acceptability curve (CEAC). *WTP* willingness to pay

operative costs for LDP were significantly higher than those for ODP (2889 vs. 1989 Euros); the entire cost of the associated hospital stay was higher in the ODP group (8955 vs. 6714 Euros); the total cost was comparable in the LDP and the ODP groups (9603 vs.. 10,944 Euros). Fox et al.[11] reported a significant reduction in hospital stay and total costs in the laparoscopic approach without differences in operative costs. Abu Hilal et al.[12] reported higher operative costs, a shorter hospital stay and lower total costs when comparing the LDP and the ODP groups. In our experience, the analysis of crude costs showed that operative costs were higher when LDP was compared with ODP (6869 vs. 4076 Euros; $P<0.001$). This difference depended on the disposable surgical instruments (such as trocars, graspers, harmonic scalpels and linear staplers) routinely used in our laparoscopic series (2172 vs. 177 Euros; $P<0.001$) while, when the surgery was performed by a skilled laparoscopic surgeon,[10] the operative time and relative costs (4697 vs. 4529 Euros; $P=0.521$) were similar.

Finally, in the English literature, a real cost-effectiveness analysis for LDP is lacking. In fact, this analysis is required for any new treatment proposed in clinical practice, not only for the total cost of the procedures but also for the effectiveness of the treatment. Our results showed that LDP may have some advantages in a mid-term follow-up regarding QoL with

respect to ODP, perhaps in terms of in-hospital costs at the time of surgery. The cost-effectiveness analysis confirmed the hypothesis that LDP was a more expensive procedure (mean cost difference 1379 Euros; $P<0.001$) than ODP but, at the same time, it was more effective (mean QALY difference 0.2; $P=0.005$). In fact, the majority of the replications obtained with the bootstrap method were found in the northeast quadrant of the cost utility plot (uncertain quadrant). To explore the acceptability of LDP cost, we calculated both the ICER and the WTP resulting in 5622 Euros and 5400 Euros for additional QALY gain, respectively, considering that the Italian GDP per capita is 24,048 Euros. Thus, in the Italian health care system, LDP may be considered an acceptable surgical procedure for benign and low-grade malignant disease.

In addition, a sensitivity analysis was carried out using a hypothetical scenario in which it was decided to utilise all reusable instruments except for the linear stapler (but calculating the use of the least expensive three-row stapler available) and the harmonic scalpel in the laparoscopic approach. This choice was made because the division and the closure of the pancreatic remnant in the laparoscopic approach could be more difficult without these devices, increasing the hypothetical operative time and relative costs. This simulation showed that a notable reduction of the costs (almost 40 %) could be obtained by utilising some reusable instruments, such as trocars, graspers and clips appliers.

This study had some limitations: the retrospective design, the small sample size and absence of propensity score matching, only partially balanced by the comparison of demographics, clinical, surgical and pathological characteristics of the two study groups.

In conclusion, our study yielded some new information regarding LDP. In fact, LDP can be considered not only safe and feasible by Italian and European health care services but also acceptable in terms of cost-effectiveness because, even though it is more expensive than ODP, it allows obtaining a better QoL. Thus, the higher cost of LDP is acceptable; it can be additionally reduced by the careful use of disposable laparoscopic instruments. However, these results should be confirmed by prospective studies involving large cohorts of patients.

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References

1. Ammori BJ, Ayiomamitis GD. Laparoscopic pancreaticoduodenectomy and distal pancreatectomy: a UK experience and a systematic review of the literature. Surg Endosc. 2011;25(7):2084-99.
2. Nakamura M, Nakashima H. Laparoscopic distal pancreatectomy and pancreatoduodenectomy: is it worthwhile? A meta-analysis of laparoscopic pancreatectomy. J Hepatobiliary Pancreat Sci. 2013;20(4):421-8
3. Jin T, Altaf K, Xiong JJ, Huang W, Javed MA, Mai G, Liu XB, Hu WM, Xia Q. A systematic review and meta-analysis of studies comparing laparoscopic and open distal pancreatectomy.HPB (Oxford). 2012;14(11):711-24.
4. Pericleous S, Middleton N, McKay SC, Bowers KA, Hutchins RR. Systematic review and meta-analysis of case-matched studies comparing open and laparoscopic distal pancreatectomy: is it a safe procedure? Pancreas. 2012;41(7):993-1000.
5. Sui CJ, Li B, Yang JM, Wang SJ, Zhou YM. Laparoscopic versus open distal pancreatectomy: a meta-analysis. Asian J Surg. 2012;35(1):1-8.
6. Xie K, Zhu YP, Xu XW, Chen K, Yan JF, Mou YP. Laparoscopic distal pancreatectomy is as safe and feasible as open procedure: a meta-analysis. World J Gastroenterol. 2012 28;18(16):1959-67.
7. 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(6):1048-59.
8. Jusoh AC, Ammori BJ. Laparoscopic versus open distal pancreatectomy: a systematic review of comparative studies. Surg Endosc. 2012;26(4):904-13.
9. Eom BW, Jang JY, Lee SE, Han HS, Yoon YS, Kim SW. Clinical outcomes compared between laparoscopic and open distal pancreatectomy. Surg Endosc. 2008;22(5):1334-8.
10. Limongelli P, Belli A, Russo G, Cioffi L, D'Agostino A, Fantini C, Belli G. Laparoscopic and open surgical treatment of left-sided pancreatic lesions: clinical outcomes and cost-effectiveness analysis. Surg Endosc. 2012;26(7):1830-6.
11. Fox AM, Pitzul K, Bhojani F, Kaplan M, Moulton CA, Wei AC, McGilvray I, Cleary S, Okrainec A. Comparison of outcomes and costs between laparoscopic distal pancreatectomy and open resection at a single center. Surg Endosc. 2012;26(5):1220-30
12. Abu Hilal M, Hamdan M, Di Fabio F, Pearce NW, Johnson CD. Laparoscopic versus open distal pancreatectomy: a clinical and cost-effectiveness study. Surg Endosc. 2012;26(6):1670-4.
13. Pecorelli N, Balzano G, Capretti G, Zerbi A, Di Carlo V, Braga M. Effect of surgeon volume on outcome following pancreaticoduodenectomy in a high-volume hospital. J Gastrointest Surg. 2012 16(3):518-23.
14. Overby DW, Apelgren KN, Richardson W, Fanelli R. SAGES guidelines for the clinical application of laparoscopic biliary tract surgery. Surg Endosc. 2010;24(10):2368-86.
15. Ricci C, Casadei R, Buscemi S, Taffurelli G, D'Ambra M, Pacilio CA, Minni F. Laparoscopic distal pancreatectomy: what factors are related to the learning curve? Surg Today. 2014 [Epub ahead of print])
16. Casadei R, Ricci C, D'Ambra M, Marrano N, Alagna V, Rega D, Monari F, Minni F. Laparoscopic versus open distal pancreatectomy in pancreatic tumours: a case-control study. Updates Surg. 2010 Dec;62(3-4):171-4.
17. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250:187-96.
18. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8-13.
19. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ,

Büchler MW. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20-25.

20. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC. 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: 365Y376.
21. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16:139Y144.
22. Guide to the Methods of Technology Appraisal. London: British National Institute of Health and Clinical Excellence, 2008.
23. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyzes. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276:1339-41.
24. Italian Gross Domestic Product. Available at: http://www.istat.it/en/archive/GDP accessed March 2014.;
25. Shillcutt SD, Walker DG, Goodman CA, Mills AJ. Cost effectiveness in low- and middle-income countries: a review of the debates surrounding decision rules. Pharmacoeconomics. 2009;27:903-17.
26. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. Br J Psychiatry. 2005;187:106 8.;
27. Nixon RM, Wonderling D, Grieve RD. Non-parametric methods for cost-effectiveness analysis: the central limit theorem and the bootstrap compared. Health Econ. 2010 Mar;19(3):316-33.
28. Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, Tomazic A, Bruns CJ, Busch OR, Farkas S, Belyaev O, Neoptolemos JP, Halloran C, Keck T, Niedergethmann M, Gellert K, Witzigmann H, Kollmar O, Langer P, Steger U, Neudecker J, Berrevoet F, Ganzera S, Heiss MM, Luntz SP, Bruckner T, Kieser M, Büchler MW. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet. 2011;377(9776): 1514-22.