Cost-effectiveness of Early Surgery Versus Endoscopy-first Approach for Painful Chronic Pancreatitis in the ESCAPE Trial

Marinus A. Kempeneers, MD, PhD, Yama Issa, MD, PhD,*†*
Marco J. Bruno, MD, PhD,‡ Hjalmar C. van Santvoort, MD, PhD,§¶
Marc G. Besselink, MD, PhD, Marja A. Boermeester, MD, PhD,*✉*
and Marcel G. Dijkgraaf, PhD,‖ for the Dutch Pancreatitis Study Group

Objective: Economic evaluation of early surgery compared to the endoscopy-first approach in CP.

Background: In patients with painful CP and a dilated main pancreatic duct, early surgery, as compared with an endoscopy-first approach, leads to more pain reduction with fewer interventions. However, it is unknown if early surgery is more cost-effective than the endoscopy-first approach.

Methods: The multicenter Dutch ESCAPE trial randomized patients with CP and a dilated main pancreatic duct between early surgery (surgery within 6 weeks) or the endoscopy-first approach in 30 centers (April 2011–September 2016). Healthcare utilization was prospectively recorded up to 18 months after randomization. Unit costs of resources were determined, and cost-effectiveness and cost–utility analyses were performed from societal and healthcare perspectives. Primary outcomes were the costs per unit decrease on the Izbicki pain score and per gained quality-adjusted life-year.

Results: In total, 88 patients were included in the analysis, with 44 patients randomized to each group. Total costs were lower in the early surgery group but did not reach statistical significance (mean difference €−4,815 (95% bias-corrected and accelerated confidence interval €−13,113 to €3411; $P = 0.25$). Early surgery had a probability percentage of 88.4% of being more cost-effective than the endoscopy-first approach at a willingness-to-pay threshold of €0 per day per unit decrease on the Izbicki pain score. The probability percentage per additional gained quality-adjusted life-year was 75.7% at a willingness-to-pay threshold of €50,000.

Conclusion: In patients with painful CP and a dilated main pancreatic duct, early surgery was more cost-effective than the endoscopy-first approach.

Keywords: chronic pancreatitis, cost-effectiveness, cost-utility, endoscopy, pancreatic duct, Surgery, willingness-to-pay

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Chronic pancreatitis (CP) is a progressive inflammatory disease with pain as most important clinical problem. CP may cause various local complications and endocrine and exocrine pancreatic insufficiency. A prominent part of patients with CP have an obstructed and hence dilated main pancreatic duct which is considered as one of the most important causes of pain in CP. In current practice, patients with an enlarged pancreatic duct are treated according to an endoscopy-first approach: medical management is tried first; when it fails, endoscopic intervention is the next step. Surgical intervention is kept as a last resort when other treatments have failed after several attempts and pain becomes unmanageable.[1-3] Several observational studies suggested that early surgery could temper disease progression, leading to more pain relief and less pancreatic insufficiency. Recently, the multicenter randomized ESCAPE trial showed that early surgery provides better pain reduction with fewer interventions than the endoscopy-first approach.[4] Despite these better results, costs of surgical procedures are likely to be higher than endoscopic procedures.[5] With increased numbers of endoscopic procedures in CP costs may rise. If surgical costs are higher than an endoscopic approach although being more effective, this could impede further implementation of early surgery in obstructive painful CP.

Data on cost-effectiveness of treatment in CP is very limited. One study published a cost-effectiveness analysis comparing surgical with endoscopic drainage in patients with obstructive CP.[5] This analysis was based on the long-term outcomes of a randomized trial of patients with refractory CP pain after long-term opioid dependence.[6,7] The cost-effectiveness analysis showed that at long-term, surgical drainage is highly cost-effective compared to endoscopic drainage.

It is, however, unknown if the early surgical treatment strategy is also more cost-effective, as compared to the endoscopy-first approach in which some patients still needed surgery after several endoscopic procedures. Therefore, the aim of this study was to undertake an economic evaluation of these 2 treatment strategies using data from the multicenter ESCAPE trial, in which early surgery was compared to the endoscopy-first approach in CP.

From the *Department of Surgery, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; †Department of Surgery, Gelre Hospital, Apeldoorn, the Netherlands; ‡Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands;; §Department of Surgery, St Antonius Hospital, Nieuwegein, the Netherlands; ¶Department of Surgery, University Medical Center Utrecht, Utrecht, the Netherlands; and ‖Department of Epidemiology and Data Science, Amsterdam Public Health, Amsterdam UMC, University of Amsterdam, the Netherlands.

✉m.a.boermeester@amsterdamumc.nl.

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METHODS

ESCAPE Trial

This economic evaluation was based on data from the multicenter randomized clinical ESCAPE trial of which the rationale, design and clinical outcomes have been described previously.[4]

The trial was approved by the medical ethics committee of the Amsterdam UMC, location Academic Medical Center and by all participating centers. In brief, patients with definite CP according the M-ANNHEIM criteria[8] were included from the 30 participating centers if they had a dilated main pancreatic duct (≥5 mm) and only recently started opioids for severe pain; weak opioids (codeine, tramadol, and hydrocodone) for ≤6 months or strong opioids (morphine, oxycodone, fentanyl, pethidine, buprenorphine) for ≤2 months (see Supplemental Digital Content Table A1, http://link-s.lww.com/SLA/D475 for the complete eligibility criteria). Randomization was stratified for pancreatic head enlargement and patients were allocated to early surgery (surgery within 6 weeks after randomization) or the endoscopy-first approach, in which patients underwent medical treatment, endoscopy including lithotripsy if needed, and surgery if needed. Failure criteria per treatment step are described in the methods section of the original ESCAPE publication.[4] Medical treatment consisted of pain medication according the World Health Organization pain ladder, co-medication for neuropathic pain and pain specialist and dietitian consultation.[1,9] All interventions in both treatment groups were discussed and performed by multidisciplinary teams in 7 predefined CP expert centers. The predefined primary outcome was pain, measured by the Izbicki pain score every 2 weeks integrated over an 18-month follow-up period.

Cost-effectiveness Analysis

The economic evaluation of early surgery against the endoscopy-first approach was evaluated from a healthcare perspective as well as from a societal perspective and therefore medical costs, patient/family costs and costs of productivity loss for employers were included. The time horizon was 18 months following randomization and given this time horizon, no discounting of effects and costs took place. The primary economic outcome in the cost-effectiveness analysis was the costs per unit of measurement of the Izbicki pain score. The cost-effectiveness analysis directly relates to the mean area under the curve" (AUC) Izbicki pain score during follow-up, which was the primary clinical outcome in the ESCAPE trial.[4] The primary economic outcome in the cost-utility analysis was the costs per additionally gained quality-adjusted life-year (QALY). This study was reported in accordance with the CHEERS guidelines.[10]

Cost Components and Data Resources

The medical costs included costs of all diagnostic and therapeutic procedures, all admissions at the Intensive Care Unit, Medium Care Unit, general ward and consultations during admission. Also, outpatient clinic visits, general practitioner visits, institutionalized care admissions (nursing home, rehabilitation center), home care and pain medication during follow-up were included. Patient/family costs included nonreimbursable expenses of the patient for private household assistance and travelling to and from the hospital because of hospital admission and outpatient clinic visits. Other costs included costs for productivity loss due to sick leave from work.

Data on volumes of used healthcare resources were mainly derived from the patients' medical records and gathered with case report forms. Data on general practitioner visits and institutionalized care admissions (nursing home, rehabilitation center) were collected retrospectively from patients' medical records. Additional information was collected by questionnaires comprising items concerning costs for patients which were sent to the patients at randomization and at 6, 12 and 18 months after randomization. Volumes for outpatient clinic visits were calculated according a standard prototype for each patient due to missing data about these visits. According optimal standard care, a patient with CP should have a control outpatient clinic visit every 6 months. Besides, after every surgical and endoscopic procedure, a regular outpatient clinic visit is performed. Therefore, the prototype was as follow: 2 follow-up visits per year and 1 additional visit after every surgical and endoscopic treatment. Volumes to calculate travel expenses were gathered by measuring the mean distance from 10 random patient's houses to the treating CP expert center based on address information; as CP treatment requires specialized expertise (which is limited to a small number of hospitals in the Netherlands) the average distance to a hospital for visits to the outpatient clinic provided by the 2014 Dutch manual for costing in healthcare research was considered unsuitable.[11] Travel expenses because of visits to the general practitioner were not included because of the very low costs.

Data on labor capacity were collected using the Health and Labor Questionnaire that was included in the 6 monthly questionnaires.[12] Costs associated with loss of productivity due to illness or recovery in patients below the age of 65 were estimated based on patient reported absences from paid labor. Productivity costs were calculated by following the friction cost method, which assumes that each employee is replaceable in the workforce.[13] The mean weekly working hours per worker at randomization and during follow-up were calculated for the total group. When patients reported to have a job, but did not fill in weekly working hours, the mean weekly hours stratified by sex and by age category (≤50 and > 50 years) were used.

Unit Costs

The base year for costs was 2015. Yearly consumer price indices were used to standardize unit costs estimated in different calendar years. For each cost component the preferable method to count volumes and estimate unit costs was in accordance with the 2014 Dutch manual for costing in healthcare research.[11] Unit costs from this guideline were applied to outpatient clinic visits, institutionalized care (nursing home, rehabilitation center), formal and informal home care, and production loss.

Unit costs of medical care were applied from hospital ledger data. A mix of bottom–up (personnel, material) and top–down (overhead) local unit costing was performed in 2 CP expert centers, Amsterdam UMC and Erasmus MC Rotterdam, for the most frequently performed major interventions (surgical, endoscopic or radiological) and diagnostic imaging procedures. The resulting unit costs were averaged across hospitals for use in the cost analysis. The unit costs of multiple treatments range considerably, depending on technique, place of treatment etc. In these cases, the mean of the costs was taken as the best estimate. See Table 1 for the costs of the used major units. Unit drug costs were derived from consumer reimbursement prices provided by the National Health Insurance Board (www.medicijnkos-ten.nl, accessed October 2017) and accounted for dosing and way of administration (intravenous, oral, rectal). Only pain medication for CP during follow-up were included. Use of other medication during hospital stay was included in the unit costs per inpatient day.

TABLE 1. Costs of Major Used Units

	Unit	Costs Per Unit in 2015 (€)	Source
Diagnostic procedures			
Abdominal CT	Procedure	188.51	Hospital ledger 2015
Abdominal MRI	Procedure	434.36	Hospital ledger 2015
Abdominal ultrasound	Procedure	142.38	Hospital ledger 2015
Endoscopic ultrasound	Procedure	709.38	Hospital ledger 2015
Therapeutic procedures			
Single ESWL	Procedure	800.00	Hospital ledger 2015
ESWL (3x) / ERCP (1x)	Procedure	3036.54	Hospital ledger 2015
ERCP	Procedure	636.54	Hospital ledger 2015
Lateral pancreatojejunostomy	Procedure	4318.48	Hospital ledger 2015
Frey procedure	Procedure	4318.48	Hospital ledger 2015
Hospital stay			
Intensive care unit	Day	2022.55	Hospital ledger 2015
Medium care unit	Day	1386.12	Hospital ledger 2015
General ward	Day	746.57	Hospital ledger 2015
Outpatient clinic visit			
Academic outpatient clinic visit	Visit	163.00	Hospital ledger 2015

CT indicates computed tomography; ERCP, endoscopic retrograde cholangio-pancreatography; ESWL, extracorporeal shock-wave lithotripsy; MRI, magnetic resonance imaging.

Quality-adjusted Life-years

Pain may exert a considerably debilitating influence on the quality of one's (daily) life. In addition to various pain measures, quality of life was assessed by a 6-monthly EQ-5D-3L questionnaire. The EQ-5D contains a description of the health state in 5 dimensions: "mobility", "self-care", "usual activities", "pain/complaints", and "anxiety/depression". Patients indicated for each dimension whether they experience no, some, or serious health problems. An individual health status profile results, for example, no problems with mobility and with self-care, some problems with usual activities and with anxiety/depression, and serious problems with pain/discomfort.[14] Each health status profile is converted into a single utility score using a previously determined scoring algorithm based on a time trade-off elicitation technique during interviews with noninstitutionalized adults from the general Dutch population.[15] Missing EQ-5D questionnaires were multiple imputed. Taking the product sum of the utility scores with the lengths of the periods in-between the actual measurement and the previous one during follow-up provides the QALY estimate for each patient for the first year postrandomization. These estimates were used in the cost-utility analysis.

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. The Izbicki pain score during 18 months of follow-up was analyzed using a "linear trapezoidal AUC" analysis. It was presented as mean AUC per follow-up moment to present a score that is comparable with the mean Izbicki score during follow-up. QALY's were presented as corrected additionally gained QALY. Correction of QALY's for the baseline EQ-5D score was calculated for each patient individually by calculating the delta between the QALY and the baseline EQ-5D score, which was multiplied by 1.5 because of the 18 months of follow-up. Both differences in the mean AUC for the Izbicki pain score during follow-up as differences in QALY's during follow-up between early surgery and the endoscopy-first approach were assessed with a Student *t* test including bias-corrected accelerated bootstrapping, stratified for treatment group and pancreatic head enlargement and drawing 5000 samples of the same size as the original sample separately for each group and with replacement (95% bias-corrected and accelerated bootstrap confidence interval [BCA 95% CI]).

Costs were calculated for individual patients by multiplying actual (healthcare) resource use and unit costs. Mean costs per patient over the period of the trial were calculated. Differences in groups were assessed and to account for sampling variability, 95% CIs were calculated using bias-corrected accelerated bootstrapping, stratified by treatment group and drawing 5,000 samples of the same size as the original sample separately for each group and with replacement (BCa 95% CI).[16] To compare total costs despite missing data on individual components (homecare use and absence from work), means per patient were imputed.

Incremental cost-effectiveness and cost-utility ratios were calculated for the extra costs per unit decrease of the Izbicki pain score and the extra costs per additionally gained QALY. Cost-effectiveness planes were used to show the bootstrap results. In addition, cost-effectiveness acceptability curves were drawn for reasonable values of willingness-to-pay (WTP) per unit decrease of the pain score (up to €1000) and per QALY gained (up to €100,000) from a societal perspective (total costs) as well as from a healthcare perspective (medical costs).

In the original report of the ESCAPE trial, an additional corrected primary outcome was calculated posthoc by adjustment for age and pancreatic head enlargement.[4] Therefore, exploratory subgroup analyses were performed for patients above or under the median age of the total group (≥52 years vs <52 years) and patients with and without pancreatic head enlargement (≥4cm vs <4cm). Results of the subgroup analyses were presented in the Supplemental Digital Content as net cost benefit (NBC) and net health benefit (NBE) from both societal and healthcare perspectives. NBC was calculated as WTP level multiplied by the difference in mean effectiveness (ΔE) minus difference in mean costs (ΔC) (NBC = WTP × ΔE − ΔC). NBE was calculated as difference in ΔE minus difference in mean costs (ΔC) divided by WTP level (NBE = ΔE − ΔC/WTP).[17,18] Because of the exploratory nature of the subgroup analyses, only point estimates were used without CIs. Positive net benefits indicate healthcare efficiency.

RESULTS

Between April 2011 and September 2016, a total of 88 patients were randomly assigned to early surgery or to the endoscopy-first approach. Baseline characteristics were

TABLE 2. Baseline Characteristics

	Early Surgery (N = 44)	Endoscopy-first Approach (N = 44)	*P* Value
Age − years − mean ± SD	49 ± 10	56 ± 9	0.002
Male sex − no. (%)	33 (75)	34 (77)	0.80
Enlarged pancreatic head (≥4cm) − no. (%)	21 (48)	23 (52)	0.67
Alcoholic etiology − no. (%)	34 (77)	27 (61)	0.11
Body-mass index − mean ± SD	22 ± 3	22± 5*	0.51
Duration of chronic pancreatitis − months − median (IQR)	12 (3 to 60)*	12 (5 to 36)*	0.94
Smoker − no. (%)			0.15
Current	41 (93)	36 (86)*	
Past	3 (7)	6(14)	
Never	0 (0)	0 (0)	
Alcohol consumption − no. (%)			0.87
Current	9 (21)	6 (14)*	
Past	32 (73)	33 (79)	
Never	3 (7)	3 (7)	

IQR indicates interquartile range; SD, standard deviation.
*missing in 2 patients.

comparable except for the mean age (early surgery 49 ± 10 years vs endoscopy-first approach 56 ± 9 years, $P = 0.002$; Table 2). Of the 44 patients assigned to early surgery, 41 underwent surgery, with a median time from randomization to surgery of 40 days (interquartile range, 32–65). In the endoscopy-first approach, 44 underwent medical treatment, and 39 endoscopic treatment with a median of 3 procedures. 22 of 39 patients had large intraductal stones (diameter ≥7 mm), for which they underwent extracorporeal shock-wave lithotripsy. Eventually, 13 endoscopy-first patients (29.5%) underwent surgery after a median of 299 days (interquartile range, 230–454).[4]

Data on productivity loss was missing or nonapplicable in 68 patients since 31 patients were incapacitated at inclusion, 17 were retired and 20 had no job for other reasons. Only 13 patients in the early surgery group and 7 patients in the endoscopy-first approach group were still working. As part of the out-of-pocket costs, a mean travel distance for 10 random patients per treatment arm was calculated. This resulted in 123.8 km (return trip) per hospital visit.

Costs

Mean volumes and costs of healthcare utilization per patient and the mean differences in costs are shown in the Supplemental Digital Content Table A2, http://links.lww.com/SLA/D475 and specified in Supplemental Digital Content Table A3, http://link-s.lww.com/SLA/D475. The mean total costs without productivity loss were €17,551 for early surgery and €22,402 for the endoscopy-first approach, leading to a cost difference of −€4851 (BCa 95% CI −€13,113 to €3411, $P = 0.25$) in favor of early surgery. Due to the small number of working patients and unbalanced distribution among study groups, productivity loss was not included in the total costs bootstrap analyses, but only presented in Supplemental Digital Content Table A2, http://links.lww.com/SLA/D475. In these working patients, costs due to productivity loss were €32,396 for the endos-copy-first approach and €19,387 for the early surgery group.

The subtotal of healthcare costs (medical costs) was lower in the early surgery approach, as compared to the endoscopy-first approach (€16,058, BCa 95% CI: €13,999–€18,413 versus €19,647, BCa 95% CI: €14,604–€26,263; cost difference −€3,589, $P = 0.26$). The costs of both diagnostic and therapeutic procedures were comparable among both study groups. Costs of outpatient clinic visits were higher for the endoscopy-first approach due to the significantly more intervention-related outpatient clinic visits (−€285, BCa 95% CI −€383 to −€187, $P < 0.001$). None of the patients was referred to a rehabilitation center or nursing home during follow-up and therefore, institutional care costs were €0.00.

Clinical Outcome and Quality-adjusted Life-years

The mean AUC for the Izbicki pain score during follow-up was 37 (BCa 95% CI: 30–44) for the early surgery group and 49 (BCa 95% CI: 42–56) for the endoscopy-first approach. The bootstrapped difference in mean AUC for the Izbicki pain score was 12 points in favour of early surgery (BCa 95% CI: 1–22, $P = 0.03$). Based on the generic Dutch general population preferences, additional gained QALYs were comparable among groups: 0.267 QALYs (BCa 95% CI: 0.128–0.402) in the early surgery group vs 0.272 QALYs (BCa 95% CI: 0.120–0.410) in the endoscopy-first approach group; mean difference of 0.005 QALYs (95% CI: −0.206 to 0.192) in favour of the endoscopy-first approach was not statistically significant ($P = 0.96$).

Incremental Cost-effectiveness from the Societal and Healthcare Perspective

The differences in costs between early surgery and the endos-copy-first approach were €4851, while a decrease of 12 points on the Izbicki pain score (0–100) were gained. This resulted in a ICER of €4043 saved per 10 points decrease of Izbicki pain score for choosing early surgery instead of the endoscopy-first approach. Bootstrap results (n = 5000) for the incremental cost-effectiveness ratio are displayed in Figure 1A, showing that in most of the bootstraps early surgery was less expensive and leads to an Izbicki pain score decrease, compared to the endoscopy-first approach (most bootstraps in lower right quadrant). From a societal perspective, the probability percentage of early surgical intervention being cost-effective ranged from 88.4% at a WTP value of €0% to 98.8% at a WTP of €1000 (Fig. 1B). From a healthcare perspective, the probability percentage of early surgical intervention being cost-effective ranged from 87.6% at a WTP of €0% to 98.8% at a WTP of €1000.

Incremental Cost-utility from the Societal and Healthcare Perspective

As presented above, the early surgery approach was €4851 less expensive in the unit costs, while 0.005 less QALYs were gained than the endoscopy-first approach. When presenting these results reversed, the endoscopy-first approach gained thus 0.005 more QALY's against €4851 more unit costs compared to the early

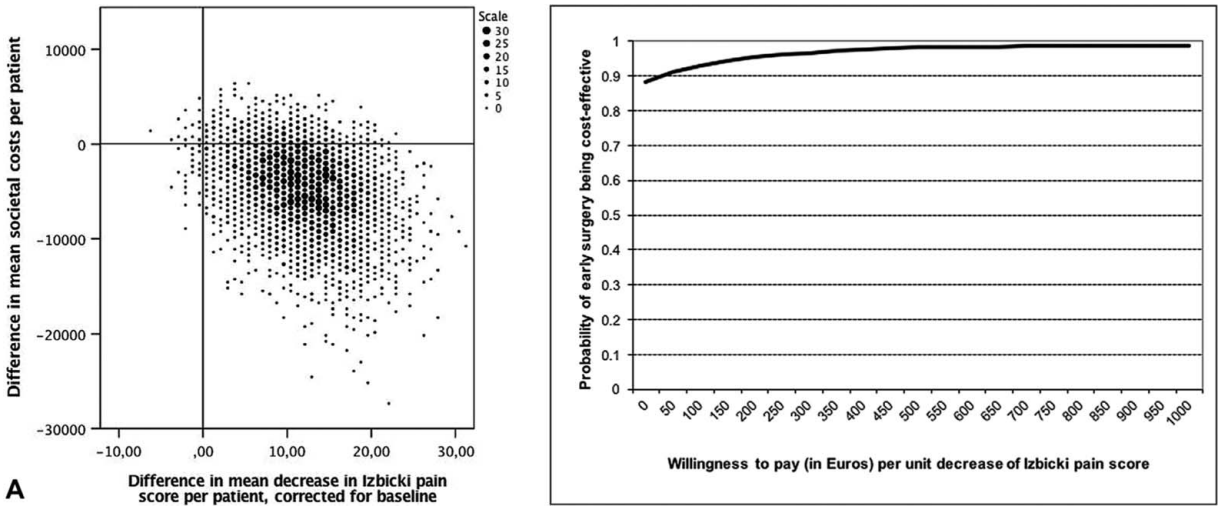

FIGURE 1. Cost-effectiveness plane and acceptability curve. A. Differences in societal costs (without productivity loss) of early surgery versus endoscopy-first approach on the Y-axis and the differences in Izbicki pain score decrease of early surgery versus endoscopy-first approach on the X-axis.

surgery approach and therefore, the ICUR was €970,200 more costs per gained QALY when choosing the endoscopy-first approach instead of early surgery. Bootstrap results (n = 5000) for the incremental cost-utility ratio are displayed in Figure 2A. Early surgery was less expensive with more QALYs gained in 42.1% of bootstraps (Fig. 2A; lower right quadrant), and less expensive with fewer QALYs gained in 46.3% of bootstraps (Fig. 2A; lower left quadrant). In only 5.5% of the bootstraps, early surgery was more expensive and resulted in more QALYs gained (Fig. 2A; upper right quadrant). Furthermore, early surgery was more expensive with fewer QALYs gained in 6% (Fig. 2A; upper left quadrant). The corresponding cost-effectiveness acceptability curve for WTP values up to €100,000 per additional QALY gained in Figure 2B shows that the probability percentage of early surgical intervention being cost-effective ranged from 88.4% at a WTP of €0 to 65.4% at a WTP of €100,000. Given a baseline health utility level in this patient population ranging from about 0.40 to 0.55 the disease burden will likely be mid-range, indicating a maximum WTP in the Netherlands of €50,000 as most plausible.

At a WTP of €50,000 the probability percentage of early surgical intervention being cost-effective equalled 75.7%. From a healthcare perspective, the probability of early surgical intervention being cost-effective ranged from 87.6% at a WTP of €0 via 70.9% at a WTP of €50,000 to 61% at a WTP of €100,000.

In summary, at the most plausible WTP-level of €50,000 given the burden of disease in this patient group, the probability of early surgical intervention being cost-effective ranged from 75.7% to 70.9%, depending the perspective chosen (societal or healthcare).

Subgroup Analyses

Subgroup analyses were performed for 4 groups based on age (≥52 years vs < 52 years) and pancreatic head enlargement

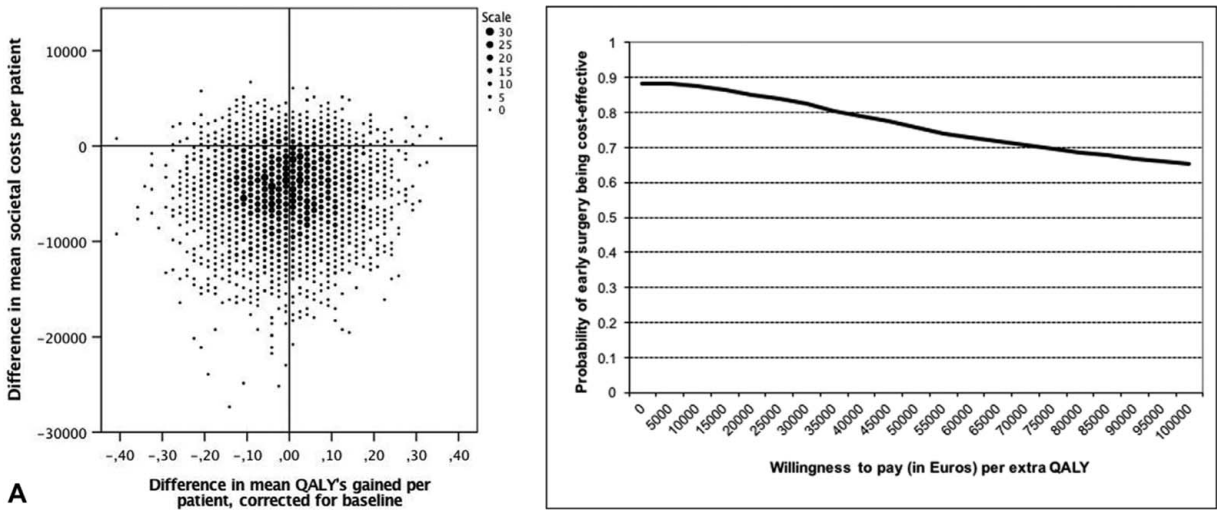

FIGURE 2. Cost-utility plane and acceptability curve. A. Differences in societal costs (without productivity loss) of early surgery versus endoscopy-first approach on the Y-axis and the differences in mean QALY's gained of early surgery versus endoscopy-first approach on the X-axis.

(≥4cm vs < 4 cm). NBC and NBE ratios were calculated for WTP levels of €20,000, €50,000, and €80,000.

From a healthcare as well as a societal perspective, early surgery was cost-effective for all WTP levels in the groups of young patients without pancreatic head enlargement, young patients with pancreatic head enlargement, and older patients without pancreatic head enlargement (Supplemental Digital Content Tables A4 & A5, http://link-s.lww.com/SLA/D475). Early surgery compared to the endoscopyfirst approach was not cost-effective in the group of older patients with pancreatic head enlargement at all WTP levels (see Supplemental Digital Content Table A5, http://links.lww.com/SLA/D475).

DISCUSSION

In about 3 of every 4 patients with painful CP, early surgery will be a cost-effective alternative for an endoscopy-first strategy, from a societal as well as healthcare perspective and at an acceptable level of WTP per QALY of €50,000 in this patient population.

The probability of early surgery being the most cost-effective strategy will even be higher if pain decrease instead of QALY gains are targeted. The potential cost savings had a substantial impact on the incremental cost-utility and cost-effectiveness ratios.

The clinical results of the ESCAPE trial showed that early surgery, when compared to an endoscopy-first approach, resulted in lower pain scores with fewer interventions in a period of 18 months.[4] Despite these lower pain scores during follow-up for the early surgery group, quality of life, as measured by the SF-36 Health Survey questionnaire, was not significantly different between both groups.[4] This controversy between lower pain scores and comparable quality of life was also seen in the present study, in which the difference between groups in gained QALYs was negligible. Potentially, the differences in pain scores between both groups were too small to distinguish a meaningful difference in gaining QALYs. This is one of the reasons that there is still discussion if the endoscopy-first approach could still be an option in a subgroup of patients with CP. It, however, remains questionable if it is clinically beneficial if the multiple steps associated with the endoscopy-first approach are worth doing since their failure rate is high.[4] It may be intuitive that endoscopy first then surgery is less cost effective than surgery alone. However in the endoscopy-first approach, surgery becomes obsolete when relief of symptoms is achieved. In this current study, 70.5% of patients in the endoscopy-first approach group did not underwent surgery during study follow-up. Hence, the early surgery compared to the endoscopy-first approach was cost-effective for decreasing the Izbicki pain score. When taking the clinical and economic outcomes together, there is substantial confidence that early surgery is not only an effective, but also an efficient treatment strategy in patients with CP.

A comparison of surgery with endoscopy regarding economic effects in CP has been previously described in 2 studies. First, a Japanese retrospective study of 68 patients has been published in 2011.[19] In this study, patients were classified into a surgical and an endoscopic treatment group, with endoscopy subdivided in short-term stenting (< 1 year) and long-term stenting (> 1 year). Medical costs were similar between the short-term endoscopy group and the surgery group ($15,400/year versus $10,800/year, $P = 0.11$). The long-term endos-copy group had higher medical costs compared to the surgery group ($20,300/year versus $10,800/year, $P = 0.003$). No patient reported outcomes were measured and no cost-effectivity analysis was per-formed.[19] Second, in the study of Larameeet al,[5] cost-effectiveness analysis was performed based on the long-term results of the CEPAN trial in patients with late phase CP, refractory pain and long-term opioid dependency.[6,7] From a UK National Health Service perspective, the total costs were £22,443 for the endoscopy group and £15,410 for the surgery group, resulting in a cost difference of £7033 (95% CI 869–14,638;
$P = 0.03$) in favor of surgery. A threshold of £20,000 per gained QALY was considered cost-effective by the National Institute forHealth and Care Excellence. The probability percentage of cost-effectiveness for surgery at this threshold was 100%, after which the authors concluded that surgery is highly cost-effective compared with endos-copy. In contrast, present study included patients in the early phase of treatment with short-term opioid use. Thereby, this study did not compare surgery with endoscopy, but the early surgical treatment strategy with the endoscopy-first strategy, which also comprised surgical treatment if endoscopy failed to be effective. The results of these studies together suggest that surgery is a cost-effective treatment in all phases of treatment in patients with painful CP and ductal obstruction.

Exploratory subgroup analyses were performed since, in the ESCAPE trial, an additional corrected primary outcome was calculated posthoc by adjustment for age and pancreatic head enlargement. Adjustment for age was performed because of a statistical difference at baseline between the early surgery group and the endoscopy-first group. Adjustment for pancreatic head enlargement took place since it was a stratification factor in the randomization.

From a societal as well as healthcare perspective, early surgery was cost-effective in young patients with or without pancreatic head enlargement, and in older patients without pancreatic head enlargement. Surprisingly, the endoscopy-first approach was more cost-effective than early surgery in older patients with pancreatic head enlargement. Potentially, early surgical treatment in patients with an enlarged pancreatic head (Frey procedure in the ESCAPE trial) has a more complicated course in older patients. However, the number of patients in this subgroup were small and skewed (5 patients in early surgery versus 18 patients in the endoscopy-first group) which may have led to a distorted view of reality. Future research including larger numbers of patients is needed regarding surgical and endoscopic treatment in older patients with large pancreatic heads.

A strength of this study was the extensiveness of the cost-effectivity analyses. It would not be acceptable to conclude that early surgery is cost-effective based solely on point-estimated data if sampling uncertainty is not adequately accounted for. The sample size of the ESCAPE trial was limited and the strength of the evidence in favor of or against an early surgery strategy instead of an endoscopy-first approach will potentially be of relevance for updates of treatment guidelines and providers' willingness to implement the economically preferable approach. We concluded that early surgery will be a cost-effective alternative for an endoscopy-first strategy in about 7 of every 8 to 10 patients. If we observed that early surgery would be cost-effective in only 6 of every 11 patients, it would potentially be concluded that there is limited evidence in favor of or against either strategy.

Another strength of our study was that most data on cost components were gathered for each patient individually. This was however not possible for the outpatient clinic visits, which addresses the first limitation of this study. Volumes for outpatient clinic visits were calculated according a standard

prototype for each patient due to missing data about these visits. Although this represents optimal standard care, it represented probably not the actual clinical situation during follow-up and therefore the healthcare costs could be over- or underestimated to some extent. A second limitation was that productivity loss was not included in the total costs bootstrap analyses. This was due to the small number of working patients and an unbalanced distribution, since most included patients were incapacitated or retired at the start and during the study. The costs associated with productivity loss are a potential large amount of money which could have affected the cost-effectivity analysis from a societal perspective. In the patients with data on productivity loss, the costs for productivity loss were higher in the endoscopy-first approach and therefore, from a societal perspective, early surgery as being cost-effective could be underestimated.

The current study performed a cost-effectivity analysis of early surgery versus endoscopy-first approach in patients with painful CP and an obstructed pancreatic duct from a Dutch healthcare perspective. Some caution is recommended in extrapolating the results to other settings, since cost-effectivity analyses may not always translate well to other healthcare systems. However, the treatment strategies in patients with painful CP and an obstructed pancreatic duct are quite universal around the globe and interventions in this study are executed according international clinical guide-lines.[1-3] Although costs can vary widely among countries, the trends in cost differences between early surgery and the endoscopic-first strategy is expected to be similar in most (Western) countries.

The economic results of the ESCAPE trial, showing that early surgery is a cost-effective approach, provides further support in the discussion that early surgery should replace the endoscopy-first approach in patients with painful obstructive CP. However, follow-up studies and replication studies are still needed to further analyze the long-term effects and financial consequences.

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