ORIGINAL ARTICLE

The “Big short” of minimally invasive pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. A cost-effectiveness analysis based on randomized trials

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Abstract

Background: The cost-effectiveness of a laparoscopic (LPD) and robotic pancreaticoduodenectomy (RPD), compared with the open approach (OPD), is still under debate.

Methods: A Markov decision model was developed to compare OPD, LPD, and RPD. The healthcare costs and quality-adjusted life years (QALYs) were estimated by calculating the incremental cost-effectiveness ratio (ICER) per QALY gained. A willingness-to-pay (WTP) of $130,049 was assumed as the threshold. A probabilistic sensitivity analysis (PSA) was performed to reflect the uncertainty of various parameters.

Results: In the base case scenario, LPD and RPD were associated with increased costs of US $30,047 and US $30,822, respectively, leading to an ICER of US $-3,911,669 and US $-1,164,992 per QALY. When comparing LPD with OPD, three main factors influence the model: OPD costs (68.8 %), LPD costs (27.9 %), and the complication rate after LPD (2.3 %). In comparing RPD with OPD, two main factors affect the model: RPD costs (75.2 %) and OPD costs (23.3 %). PSA analysis confirmed that OPD was the most cost-effective choice in most cases (62.6 %), while RPD and LPD were the most cost-effective procedures in 26.2 % and 11.9 %, respectively.

Conclusion: The RDP and LPD were not cost-effective. OPD remained the best approach.

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Introduction

Pancreaticoduodenectomy (PD) is the gold standard treatment for head pancreatic ductal adenocarcinoma (PDAC). In the era of minimally invasive surgery (MIPD), PD is one of the few surgical interventions for which the open approach (OPD) remains the gold standard of care.[1] Laparoscopic PD (LPD) was proposed in the ’90s of the past century as the natural evolution of OPD.[2] However, the first randomized controlled trials (RCTs), recently published, have not met the expectations.[3–6] At least three meta-analyses of RCTs[7–9] demonstrated that LPD has marginal advantages, probably not significant from the clinical point of view. Moreover, LPD seems to be a challenging surgical procedure, implying a fatiguing learning curve estimable in more than 100 procedures.[10] The robotic approach (RPD) has been proposed as an alternative to overcome the problems of LDP.[11,12] Two recent RCTs[13,14] comparing OPD with RPD have been published but with conflicting results. RPD partially betrayed the expectations because the patients’ advantages remained uncertain and impalpable from the clinical point of view. Moreover, some doubts about safety remained due to conflicting results,[13,14] and data about long-term survival were unavailable. Finally, recent data[13,15] suggested non-negligible incremental costs for RPD and LPD.

Thus, we must change the perspective to answer the question about the routine use of MIPD in treating patients with head PDAC. Currently, it is reasonable and logical to affirm that the minimally invasive approach did not reduce the significant morbidity and mortality rate compared to OPD. Thus, other clear advantages should be the only reason to adopt RPD and LPD in clinical practice, but in the best scenario, the only benefit could be a shorter LOS (one or two days). In this setting, a cost-effectiveness analysis seems appropriate to evaluate the acceptability of MIPD. To our knowledge, this is the first study about the cost-effectiveness of MIPD that has been conducted to assess sustainability in different countries.

Material and methods

The study was carried out without involving human participants. The analysis followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline.[16] A Markov decision-analytic model was created using clinical data from RCTs about MIPD and resectable PDAC treatment. When RCT was unavailable, the data from high-quality nonrandomized studies were used. The last search was carried out on August 22, 2024. The systematic review was conducted using Pubmed, Scopus, the ISI-Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL), updating the last systematic search. The search string was the following: (“robotic surgical procedures"[MeSH Terms] OR “robotic"[Text Word] OR “laparoscopy"[MeSH Terms] OR “laparoscopy"[Text Word]) AND (“Pancreaticoduodenectomy"[MeSH Terms] OR “Pancreaticoduodenectomy"[Text Word] OR “Whipple"[Text Word] OR “Whipple procedure"[Text Word] OR “pancreatectomy"[Text Word] OR “pancreatic surgery"[Text Word] OR “pancreatic resection"[-Text Word]). The research was conducted by translating the string into an appropriate form using the SR accelerator.[17] Studies were selected for evaluation based on their level of evidence. Probabilities were directly derived from the literature or calculated following the Declining Exponential Approximation of Life Expectancy (DEALE) method.[18] Briefly, the DEALE method is a validated approach used to approximate life expectancy and transition probabilities in decision-analytic models, particularly when survival data are available as aggregated percentages. Specifically, when the survival probability at a given time point (*e.g.*, 5-year survival) is known, the corresponding annual mortality rate (λ) can be estimated using the formula: $\lambda = -\ln(S)/t$ where S is the survival proportion at time t. Once the hazard rate is known, the transition probability per cycle (*e.g.*, per year) can be calculated using the formula: $p = 1 - e\hat{}(-\lambda \cdot \Delta t)$, where Δt is the length of the Markov cycle (in this case, 1 year). This approach is beneficial when reconstructing Markov transition matrices from published Kaplan–Meier curves or summary survival data.

Model overview

The model was limited to the patients with PDAC, excluding those with branch duct intraductal papillary mucinous neoplasm (IPMN), neuroendocrine neoplasms (Pan-NENs), or other less aggressive peri-ampullary tumors. The Markov model simulated the five-year life expectancy of patients with anatomically resectable PDAC of the pancreatic head. Three different approaches were used: OPD, LPD, and RPD. The primary endpoint was to compare the cost-effectiveness of the three strategies. The secondary endpoint was to verify the economic sustainability of MIPD across different countries. The Markov model hypothesized for the patients three transitional states of health (Fig. 1): 1) “alive and disease-free,” which means that the patient is alive after surgery and without recurrent disease; 2) “alive with recurrence” which means that the patients have a local or distant recurrence; 3) Dead, indicating that the patient died due to postoperative mortality (due to surgery),

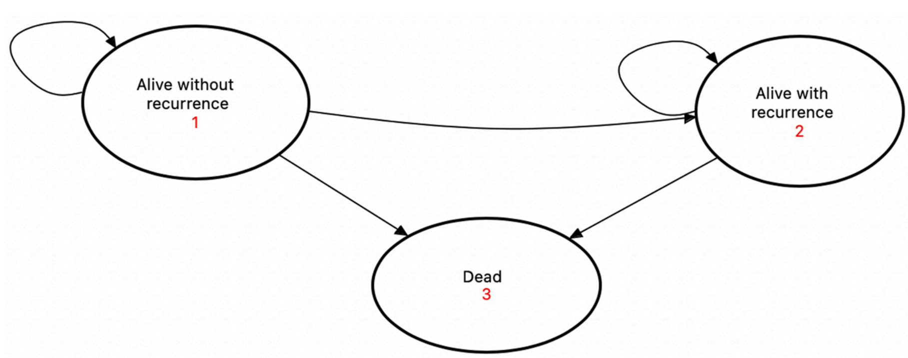

Figure 1 Markov model structure

Legend: The figure reported the transition state of the model. There were three transition states: 1) “alive and disease-free,” which means that the patient is alive after surgery and without recurrent disease; 2) “alive with recurrence,” which means that the patients have a local or distant recurrence; 3) dead, which indicated that patient was death for postoperative mortality, background mortality or disease.

background mortality (related to age and sex), or disease-related death (related to the recurrence of the disease).

The following assumptions were made: i) the rate of laparotomic exploration without resection was assumed to be 0 because the aim of the study was not to assess the accuracy of preoperative staging; ii) the intention-to-treat principle was used; iii) the cost of adjuvant therapy was not considered because the aim of the study was not the evaluation of the cost-effectiveness of different types of chemotherapy; iv) the FOLFIRINOX adjuvant chemotherapy was assumed, because the aim was not the evaluation of the efficacy of different chemotherapy regimens.

Probability, health costs, and utilities definitions

Data input was reported in Table 1 as mean and 95 CI or SD. The willingness to pay (WTP) was established based on the World Health Organization (WHO) recommendation.[19–21] The willingness to pay" (WTP) was the maximum estimated cost

Table 1 Probabilities, utilities, and cost using for the Markov model

Variables	Base-case value	Plausible 95CI or SD	Distribution	References
Model parameters				
GPD	43,394	1636–78,675	γ	22,23
WTP	130,049	78,675–236,025	γ	22,23
Age (years)	70	20–84	γ	24
Markov Horizont	5	–	Fixed	Assumption
Discount rate for costs	0.030	–	Fixed	25
Discount rate for utility	0.015	–	Fixed	25
Probabilities				
Major compilation after OPD (CDC>2)	0.26	0.13 to 0.39	γ	26–31
Major compilation after LPD (CDC>2)	0.29	0.09 to 0.50	γ	26–29
Major compilation after RPD (CDC>2)	0.32	0.22 to 0.59	γ	30,31
Omission adjuvant therapy (CDC>2)	0.44	0.21 to 0.56	γ	33
Omission adjuvant therapy (CDC<3)	0.26	0.10 to 0.38	γ	33
In-hospital mortality after PD	0.02	0 to 0.04	γ	34
Risk of recurrence				
Risk of recurrence with AT (1st year)	0.61	0.01	γ	35
Risk of recurrence without AT (1st year)	1.21	0.01	γ	36
Risk of recurrence with AT (2nd year)	0.58	0.01	γ	35
Risk of recurrence without AT (2nd year)	0.83	0.01	γ	36
Risk of recurrence with AT (3rd year)	0.28	0.01	γ	35
Risk of recurrence without AT (3rd year)	0.41	0.01	γ	36
Risk of recurrence with AT (4th year)	0.16	0.01	γ	35
Risk of recurrence without AT (4th year)	0.17	0.01	γ	36
Risk of recurrence with AT (5th year)	0.02	0.01	γ	35
Risk of recurrence without AT (5th year)	0.10	0.01	γ	36
Long term survival				
Risk of background mortality	0.17	0.23	γ	37
Risk of death with AT (1st year)	0.09	0.01	γ	35
Risk of death without AT (1st year)	0.34	0.01	γ	36
Risk of death with AT (2nd year)	0.32	0.01	γ	35
Risk of death without AT (2nd year)	0.60	0.01	γ	36
Risk of death with AT (3rd year)	0.28	0.01	γ	35
Risk of death without AT (3rd year)	0.71	0.01	γ	36
Risk of death with AT (4th year)	0.25	0.01	γ	35
Risk of death without AT (4th year)	0.43	0.01	γ	36

Table 1 (*continued*)

Variables	Base-case value	Plausible 95CI or SD	Distribution	References
Risk of death with AT (5th year)	0.19	0.01	γ	35
Risk of death without AT (5th year)	0.16	0.01	γ	36
Costs (US$)				
OPD	19,715	14,433	γ	30
LPD	30,047	7282	γ	38
RPD	30,822	20,529	γ	30
Utility			γ	
Healthy	1			Assumption
Before progression	0.800	0.620 to 0.810	γ	39
After progression	0.730	0.620 to 0.800	γ	39
Dead	0			Assumption

Legend: GDP = Gross Domestic Product pro-capita for European countries; WTP= Willingness to pay; SD= Standard deviation; OPD= Open Pancreatico-duodenectomy; LPD = Laparoscopic pancreaticoduodenectomy; RPD = Robotic pancreaticoduodenectomy; CDC= Clavien Dindo Classification; AT = Adjuvant Therapy; KM=Kaplan-meier.

sustainable per capita from the health care system to guarantee one quality-adjusted life-year (QALY).[20] WTP for the base case scenario was calculated considering the Euro area's gross domestic product (GDP),[21] and WTP was set to be equal to 3xGDP per capita, namely 43,394 (1636—78,675, 95 CI).[22] However, we consider "optimal" a therapeutic option if it requires an incremental cost equal to GDP. GDPs of different world areas were utilized for threshold analysis.[23] The age with the plausible range was obtained from the SEER database, namely 70 years (20—84, 95 CI).[24] The number of Markov cycles (follow-up in years) was set to be 5. The discount rate was 3 % for the costs and 1.5 % for the utilities.[25] The significant morbidity (defined as Clavien Dindo >2)[26] probabilities after PD were based on the meta-data of 6 RCTs about MIPD vs. OPD. Major morbidity rates were 26 % (13 %—39 %, 95 CI) for OPD,[3–5,12,13] 29 % (9 %—50 %, 95 CI) for LPD,[3–6] and 32 % (22 %—59 %, 95 CI) for RPD.[12,13] The omission of adjuvant therapy was 44 % (21 %—56 %, 95 CI) for patients with significant morbidity, while 26 % (10 %—38 %, 95 CI) for those without.[27,28] The 90-day mortality probabilities after PD were based on the benchmark for PD.[29] In-hospital mortality rate was assumed to be 2 % (0 %—4 %, 95 CI) for all procedures. Survival data for patients who underwent adjuvant therapy were obtained from the Kaplan—Meier curve of the PRODIGE study.[30] This study reflects the clinical profile of patients eligible for minimally invasive pancreaticoduodenectomy, excluding those with vascular involvement, poor performance status, or significant comorbidities who are generally not candidates for MIPD.

Survival data for patients who did not receive adjuvant treatment were obtained from the Kaplan—Meier curve of the CONKO-001 study.[31] Background mortality was based on the lifetable of the European Union area.[32]All costs were reported in US $. Costs related to OPD and RPD were extracted from Klotz et al.,[13] while data for LPD was obtained from a retrospective study of Gaber et al. [15] The costs of OPD, LPD, and RPD were assumed to be $19,715 ± 14,433 (SD), $30,047 ± 7282 (SD), and $30,882 ± 20,529 (SD). Utilities were 0.800 (0.620—0.810, 95 CI) and 0.730 (0.620—0.800, 95 CI) for patients who underwent PD without recurrence[33] and with recurrence.

Simulation methodology and statistical analysis

For each strategy, we calculated mean costs and QALYs, with their respective standard deviations (SD). From these values, we derived the incremental cost and incremental QALY, which were combined to obtain the incremental cost-effectiveness ratio (ICER), defined as the additional cost needed to gain one extra QALY, according to the formula: $ICER = (Cost_1 - Cost_0)/(QALY_1 - QALY_0)$ where $Cost_1$ and $QALY_1$ refer to the new strategy, and $Cost_0$ and $QALY_0$ to the comparator. To improve readability, we also reported the net monetary benefit (NMB). NMB translates QALYs into monetary units, making comparisons easier, according to the formula: $NMB = (QALYs \times WTP) - Costs$. A higher NMB indicates a more cost-effective strategy. The incremental NMB (iNMB) represents the difference between two strategies: when iNMB = 0, the procedures are equivalent; when iNMB <0, the baseline strategy is preferable; when iNMB >0, the alternative strategy is preferable. For the base case scenario, the fixed (base case) values of all variables were used, performing a deterministic sensitivity analysis (DSA). One-way analysis was conducted to assess the impact of covariates on incremental NMB (iNMB) variability, identifying the most influential parameters through tornado diagrams. Additionally, a probabilistic sensitivity analysis (PSA) with 100,000 Monte Carlo simulations was conducted, where all parameters were randomly varied within their respective probability distributions. In other words, we also took into account the plausible 95 % CI or SD, hypothesizing that patients simulated could have different characteristics, probabilities, recurrence, and survival. This approach allowed us to estimate the likelihood that each strategy would be cost-effective, making the results externalizable. Finally, ICERs were also assessed across different world regions using gross domestic product (GDP) thresholds to evaluate economic sustainability.[23,39] In fact, the same procedure could be cost-effective in an area with a high GDP, while at the same time being not cost-effective in another region with a low GDP.

Results

Markov simulation showed a five-year overall survival rate of 43.7 %, 43.6 %, and 43.2 % for OPD, LPD, and RPD, respectively. The disease-free survival rate was 11.9 %, 11.9 %, and 11.7 % for OPD, LPD, and RPD, respectively. Supplementary Fig. 1 shows the transitional states according to the 5-year follow-up.

DSA and sensitivity analysis

The simulation performed on the base case scenario (Table 2) showed that OPD dominated MIPD arms from a cost-effectiveness point of view. The LPD and RPD have an incremental cost of $10,320 and $11,107, while the QALY produced in five years of follow-up were similar: 3.181, 3.178, and 3.171. The resulting ICERs were negative and equal to - $ 3,911,669 and 1,164,992 per QALY for LPD and RPD, respectively. The highest NMB was observed for OPD: $393,914. On the contrary, LPD produced only$383,238, with a negative iNMB of $10,676. RPD produced $381,567, with a negative iNMB of $12,347. Sensitivity analysis showed the factors influencing the head-to-head comparisons. Comparing LPD with OPD, three main factors could change the iNMB: OPD costs (68.8 % variability), LPD costs (27.9 % variability), and complication rate after LPD (2.3 % variability). The remaining factors, all together, were responsible for about 1 % of the variability. Increasing the OPD costs, the iNMB was reduced, and when the fee for OPD was superior to $30,391, LPD became the best choice. Decreasing the costs of LPD, the differences between the procedures were reduced without inverting the iNMB. Decreasing the complication rate of LPD, the disadvantage of LPD was reduced without inverting the iNMB (Fig. 2). Comparing RPD with OPD, two main factors could change the iNMB: RPD costs (75.2 % variability) and OPD costs (23.3 % variability). The remaining factors, all together, were responsible for about 1.4 % of the variability. Decreasing the RPD costs, the iNMB was reduced, and when the fee for RPD was superior to $18,475, RPD became the best choice. Increasing the costs of OPD, the differences between the procedures were reduced without inverting the iNMB (Fig. 3).

PSA

The simulation of an RCT with three parallel arms confirmed that OPD was the dominant choice from a cost-effective point of view. The LPD and RPD have an incremental cost of $10342 ± 17,533 and $11,163 ± 17,335, while the QALY produced in five years of follow-up were similar: 3.019 ± 0.401, 3.017 ± 0.401, and 3.011 ± 0.399, for OPD, LPD and RPD, respectively. The resulting ICERs were negative and equal to 4,643,171 and 1,404,948 per QALY for LPD and RPD, respectively. The highest NMB was confirmed for OPD: $372,919 ± 54,078. On the contrary, LPD produced only 362,287 ± 52,581, with a negative iNMB of $17,632 ± 1497. RPD produced $360,722 ± 55,743, with a negative iNMB of $12,197 ± 1665. The analysis of 100,000 patients per arm showed OPD was the most cost-effective choice in 62.6 % of cases, while RPD and LPD were the most cost-effective procedures only in 26.2 % and 11.9 %, respectively. The cost-utility plan showed that head-to-head comparisons.

Table 2 DSA microsimulation and PSA analysis (100,000 samples for each arm)

Strategy	Mean Cost (±SD)	Incremental cost (±SD)	QALY(±SD)	Incremental QALY (±SD)	ICER	NMB (±SD) ^
DSA						
OPD	19,715	10,320	3.181	−0.003	−3,911,669 per QALY	393,914
LPD	30,047	11,107	3.178	−0.010	−1,164,992 per QALY	383,238
RPD	30,822		3.171			381,567
PSA						
OPD	19,683 ± 14,495		3.019 ± 0.401			372,919 ± 54,078
LPD	30,024 ± 7232	10342 ± 17,533	3.017 ± 0.401	−0.002 ± 0.001	−4,643,171 per QALY	362,287 ± 52,581
RPD	30,846 ± 20,572	11,163 ± 17,335	3.011 ± 0.399	−0.008 ± 0.002	−1,404,948 per QALY	360,722 ± 55,743

Legend: DSA = Deterministic sample analysis; PSA = Probabilistic sample analysis. In PSA, the results refer to 100,000 samples for each arm. Any sample can assume different characteristics based on the variance of parameters reported in Table 1. In other words, 100,000 patients with different characteristics were examined. SD = Standard deviation; QALY = Quality-adjusted life years expectancy; ICER = incremental cost-effectiveness ratio; NMB = Net monetary Benefit; ^ NMB was obtained by transforming QALY and related cost in $ unit and following this formula: NMB = (QALY*WTP) — costs. The higher the NMB, the more cost-effectiveness the strategy.

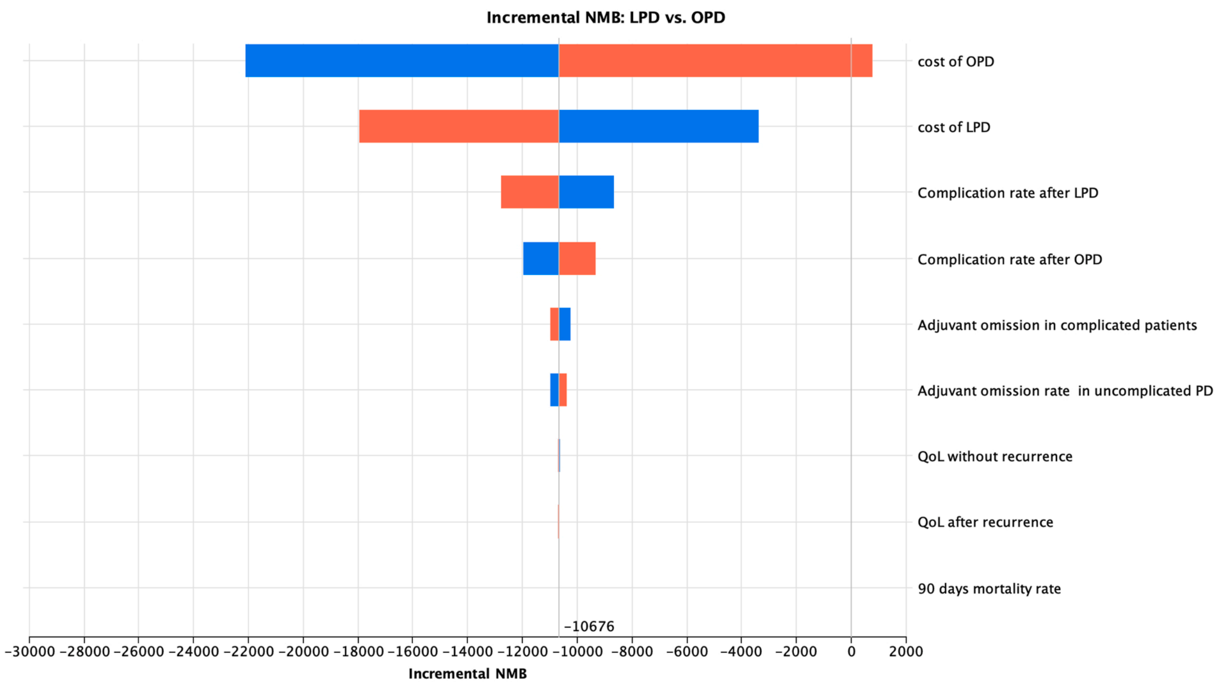

Figure 2 Tornado diagram for OPD versus LPD

Legend: ICER = Incremental Cost-Effective Ratio expressed in $ per QALY; NMB=Net monetary benefit; PD= Pancreaticoduodenectomy; LPD = Laparoscopic pancreaticoduodenectomy; OPD=Open pancreaticoduodenectomy; red bar indicates the effect of covariate increase; blue bar indicates the effect of covariate decrease; the gray line indicates the mean results.

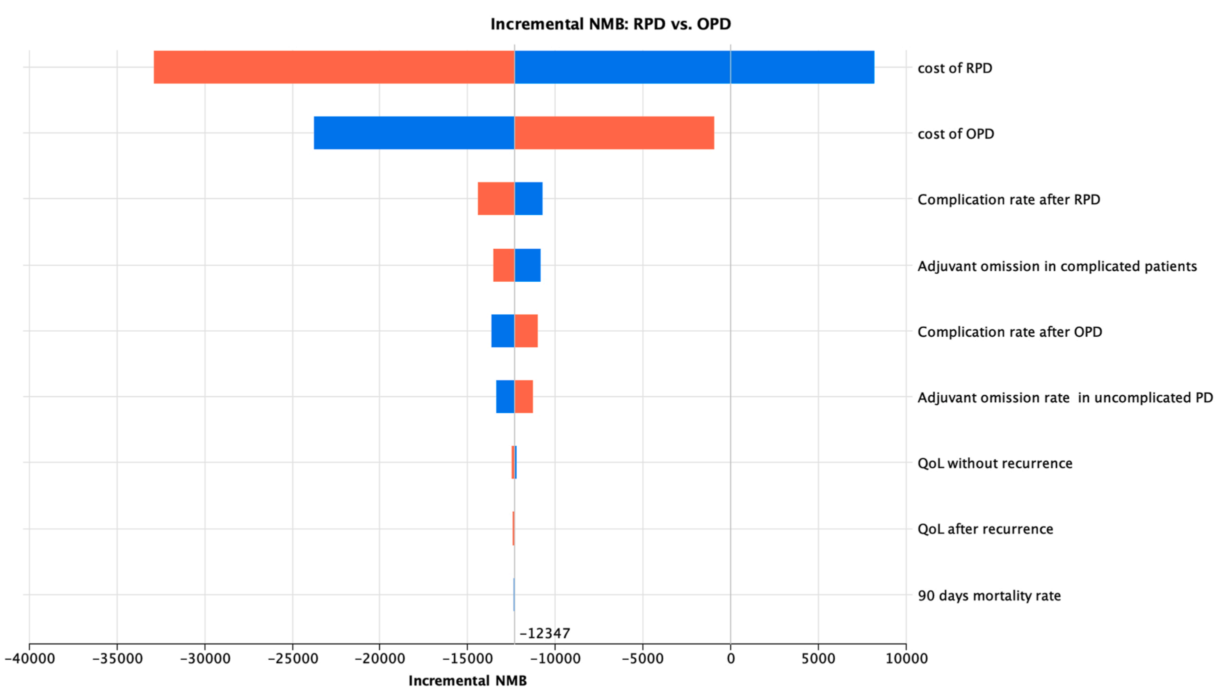

Figure 3 Tornado diagram for OPD versus RPD

Legend: ICER = Incremental Cost-Effective Ratio expressed in $ per QALY; NMB=Net monetary benefit; PD= Pancreaticoduodenectomy; RPD = Robotic pancreaticoduodenectomy; OPD=Open pancreaticoduodenectomy; red bar indicates the effect of covariate increase; blue bar indicates the effect of covariate decrease; the gray line indicates the mean results.

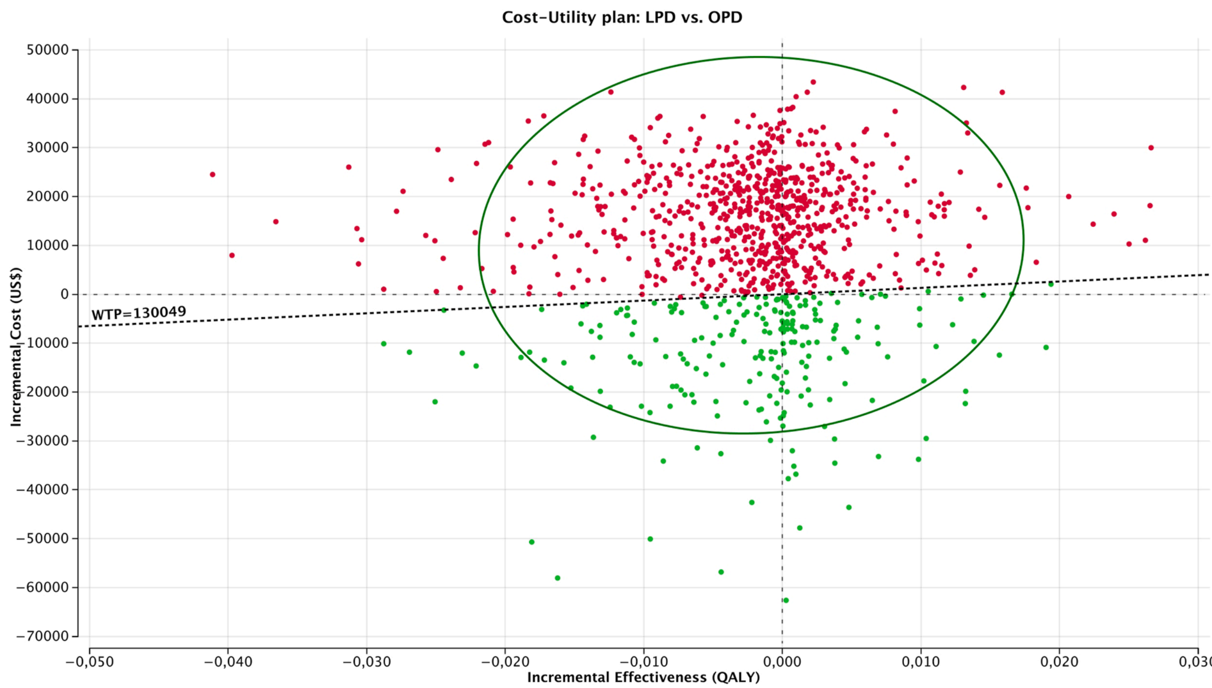

Figure 4 Cost-utility plan after PSA for OPD versus LPD
The costs were reported in $; the utility in QALY. The referent arm was an open pancreaticoduodenectomy (OPD). The new strategy is LPD. Four quadrants can be observed: i) north-east or uncertainty quadrant in which the new strategy was acceptable only when inferior to the willingness to pay (WTP) calculated as three times the gross domestic product per capita of Euro area; north-west and southwest quadrants, in which the new strategy was rejected because less efficacy; the southeast quadrant, in which the new strategy was accepted because less expensive and more effective. The Incremental Cost-Effective Ratio is expressed in $ per QALY and is represented by green points (one for each replication). The ellipse shows the 95%CI of replications.

Considering the OPD versus LPD comparison (Fig. 4) only 8.5 % of cases fell in the acceptance quadrant (southeast), where the LPD was superior in efficacy and less expensive. Most procedures (46.7 %) were in the first reject quadrant (northwest), where the LPD was less effective and more costly. The 13.5 % were in the second reject quadrant (southwest) because LPD was less expensive and less effective. Finally, 30.6 % of LDPs fell in the uncertainty (northeast) quadrant, resulting in a more effective and more costly approach, but only 0.2 % of procedures were economically sustainable (below the WTP line).

Considering the OPD versus RPD comparison, most comparisons (46.7 %) were in the first reject quadrant (northwest), where the RPD was less effective and more costly. Another 27.5 % were in the second reject quadrant (southwest) where RPD was less expensive and less effective. The 10 % of RDPs fell in the uncertainty (northeast) quadrant, resulting in a more effective and more costly approach, but only 0.1 % of procedures were economically sustainable (below the WTP line). Finally, only 4.7 % of the comparisons were in the acceptance quadrant (southeast), where the RPD was superior in efficacy and less expensive (Fig. 5).

WTPs threshold analysis

The WTPs threshold analysis considered only the ICER for the uncertain quadrant. Regarding LPD, only 30.6 % of replication was included, and the mean ICER was $25,941,915. Regarding RPD, only 10 % of replication was included, and the mean ICER was $48,373,132. As shown in Supplementary Table 1, according to the GDPs of different areas, less than 10 % of LPD or RPD performed for PDAC are sustainable from a cost-effectiveness point of view in all areas of the world.

Discussion

This study demonstrated that MIPD was not cost-effective for treating patients with resectable PDAC and should not be used routinely. In the last twenty years, surgeons have been exposed to commercial pressure to use minimally invasive approaches, particularly robotic,[34–36] for major abdominal procedures. Even if the minimally invasive approach has become the gold standard of care for some procedures, the routine use of MIPD for PDAC care remains uncertain. Some consensus conferences[1,37] have remarked on the safety of MIPD, but the data obtained

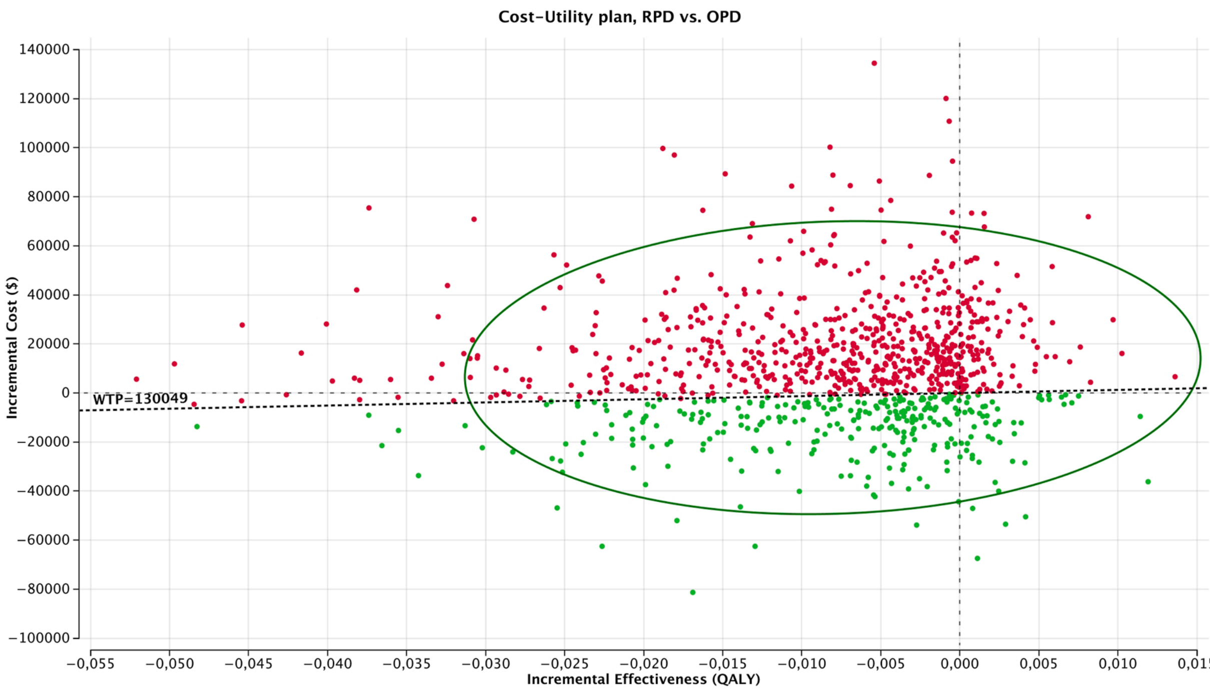

Figure 5 Cost-utility plan after PSA for OPD versus RPD

The costs were reported in $; the utility in QALY. The referent arm was an open pancreaticoduodenectomy (OPD). The new strategy is RPD. Four quadrants can be observed: i) north-east or uncertainty quadrant in which the new strategy was acceptable only when inferior to the willingness to pay (WTP) calculated as three times the gross domestic product per capita of Euro area; north-west and southwest quadrants, in which the new strategy was rejected because less efficacy; the southeast quadrant, in which the new strategy was accepted because less expensive and more effective. The Incremental Cost-Effective Ratio is expressed in $ per QALY and is represented by green points (one for each replication). The ellipse shows the 95%CI of replications.

from recent RCTs[3–8,13,14] demonstrate only short-term and debatable advantages, accompanied by increased costs. In this scenario, two key points should be remembered: i) PD in PDAC aims to prolong the survival of patients; ii) PDAC is a terrible disease, and even when resected, the disease-free and overall survival remains unsatisfactory. Having said this, the only rational approach for analyzing the question about MIPD was to use a cost-effective model. It should be noted that the model aimed to evaluate the impact of different surgical approaches in patients who are candidates for PD. The costs of chemotherapy were not considered because the complete trajectory of treatment for PDAC patients remains the same, regardless of an open or minimally invasive approach: namely, surgery plus chemotherapy.

The World Health Organization's (WHO's) Choosing Interventions that are Cost-Effective (CHOICE) program supports priority-setting processes, ensuring that health stewards know how to spend resources to achieve the highest health gain as one consideration in strategic planning.[38] The WHO has clearly defined the acceptability threshold for a new therapeutic intervention. A new surgical procedure should be accepted only when the costs to produce one QALY per person are inferior to three times the GDP per capita.[20] Unfortunately, neither LPD nor RPD is acceptable from this point of view, and this is easy to understand. None of the available studies have demonstrated that the MIPD approach improves overall or disease-free survival in PDAC. Indeed, there is no rational reason to think that. The current Markov model confirmed this prediction. All cohorts of patients who underwent PD experienced a high rate of PDAC recurrence and disease-related deaths during five years of follow-up. It should also be acknowledged that the survival observed in our model, derived from the PRODIGE cohort[30], is higher than that reported in unselected population-based studies, reflecting the inclusion of fit patients for MIPD treated in high-volume centers. Like death, the recurrence rate could reduce QALY, reducing the quality of life (QoL). Pezzilli et al.[39] demonstrated that QoL after PD depended mainly on the recurrence of the disease. This finding also confirms that, since RPD does not modify the natural history of PDAC, the potential short-term economic advantages of a minimally invasive approach are often nullified by the disease's aggressiveness, making RPD rarely cost-effective, even when it appears less expensive. Moreover, both LPD and MIPD have shown a slightly higher rate of postoperative major morbidity than OPD, at least before the surgical proficiency achievement.[40] This fact could reduce the rate of patients who received adjuvant chemotherapy, reducing disease-free and overall survival, at least for those patients treated during the learning curve. This slightly reduced performance of MIPD, highlighted in some RCTs,[5,13] could explain the small changes in life quality-adjusted expectancy in favor of OPD, as observed in the model. In summary, no additional QALYs were obtained using MIPD instead of OPD in the more optimistic scenario. For this reason, any further costs for MIPD could result in unsustainable outcomes, from an economic perspective, in any area of the world, because the ICER produced when positive was many hundreds or thousands of dollars higher than the WTP.

Examining NMBs, it is easy to understand the risk associated with the “surgical bubble” of MIPD. NMB transforms the benefits into monetary units because each individual produces wealth. Moreover, NMB highlights the value of life because it assumes that an individual in a fully healthy state is worth three times his GDP. Thus, for each MIPD procedure, we deprive the Healthcare System of approximately $10,000 without adding anything to the cure of PDAC. For example, the monthly cost per patient of FOLFIRINOX or Gem Nab administration was $10,507 and $12,812, respectively.[41]

Finally, the threshold analysis clarified a fascinating and pivotal point: the probability that the MIPD was in a sustainable therapeutic choice varies by region: in Europe and North America, the acceptability threshold was in the order of tens of thousands of dollars, while in developing areas, the threshold was in the order of a few thousand dollars. However, considering only the world’s wealthiest countries, less than 10 % of MIPD procedures performed for PDAC are sustainable from a cost-effectiveness perspective.

This study presents strengths and limitations. Mathematical models do not replace randomized controlled trials. However, they can provide helpful results in filling knowledge gaps when it is unrealistic to expect such studies to be carried out. The difficulties in planning an RCT, including only PDAC and with five years of follow-up with QoL evaluation, are well known.

Another limitation was the data based on non-RCTs, such as those on LPD costs or QoL, which we acknowledged as a limitation ourselves. This limitation may reduce the model’s quality at the origin. However, we developed a prudent model using high-quality data for postoperative and long-term outcomes. Thus, the target events influencing the model, such as the recurrence or death rates, were highly plausible. Moreover, despite applying an annual discount rate that allows for the adjustment of procedure prices, the final costs may not accurately reflect those of a real-life scenario. Indeed, the costs could also be influenced by other factors, such as the development of new technologies, the presence of competing pharmaceutical companies, or regional healthcare policy.

Another limitation of our model is that long-term outcomes of RPD and LPD are not yet available from RCTS. Therefore, any potential late benefits of minimally invasive surgery could not be captured in our analysis. However, given that the prognosis of PDAC is mainly determined by tumor biology and response to systemic therapy, it is unlikely that MIPD alone could radically change the survival.

Moreover, some patient-reported outcomes, such as return to regular activity or incisional hernia, were not included in our model. Although these endpoints could favor MIPD in the short term, the resources invested to achieve such transient or non-relevant benefits are often nullified by the extreme aggressiveness of PDAC or the need to perform adjuvant chemotherapy. At the same time, in other disease processes with more favorable prognoses or without the need for adjuvant chemotherapy, such as Intraductal papillary mucinous neoplasms or neuroendocrine tumors, minimally invasive approaches might prove more cost-effective, as short-term advantages could translate into meaningful long-term benefits. However, these indications for PD are relatively uncommon and account for only a minority of cases each year, limiting their overall impact on health system resources. Also, the effect of the learning curve should be taken into account. Even if all included RCTs reported that surgeons declared the completion of the learning curve in RPD, it is well known that mastery may require 200—250 procedures. However, this limitation is also a strength of the study: the fact that the learning curve for MIPD may require several procedures or decades represents an intrinsic limitation of the technique, which limits its applicability in routine clinical practice.

Finally, it is essential to emphasize that the cost-effectiveness of these three competing strategies is particularly relevant in situations where both treatments are equally applicable. However, in real life, some patients, such as those with vascular involvement or who underwent neoadjuvant therapy, may be less suitable for MIPD. On the contrary, MIPD could be easy and less expensive to perform in patients with less aggressive peri-ampullary disease. Indeed, it should be noted that if MIPD seems not to be sustainable from an economic point of view for the PDAC, this observation could not be true for other less aggressive diseases with better prognosis, such as IPMN, Pan-NEN, or periampullary disease non-PDAC. Moreover, if MIPD costs, especially those of the robotic approach, are significantly reduced, they could become cost-effective.

In conclusion, the present study suggested that both RPD and LPD have marginal or null advantages compared with OPD. Despite the optimistic conclusion of some studies, LPD and RPD do not have the role of game changers in performing PD. On the contrary, excessive use of these procedures could reduce the resources available in the health care system to treat patients with PDAC.

Henceforth, the MIPD should only be used in clinical practice in selected cases.

Disclosure

Ricci Claudio, Alberici Laura, D’Ambra Vincenzo, Ingaldi Carlo, Marco Fichera, Casadei Riccardo disclose any conflicts of interest.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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