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ORIGINAL ARTICLE

Laparoscopic versus Robotic Peripheral Pancreatectomy: A Systematic Review and Meta-analysis

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Summary

Purpose: *The current systematic review and meta-analysis aimed to compare Laparoscopic Distal Pancreatectomy (LPD) with Robotic Distal Pancreatectomy (RDP) in terms of length of hospital stay (LOS), perioperative, postoperative and economic parameters.*

Methods: *A systematic review of the literature was undertaken and data from studies fulfilling the predetermined inclusion criteria were extracted. Meta-analyses were performed to combine the results of various studies in the forms of Weighted Mean Difference (WMD), Odds Ratio (OR) and Risk Difference (RD), as appropriate.*

Results: *A significantly lower LOS (WMD:0.75, 95%CI:0.17-1.33) and longer operative duration (WMD:-28.29, 95%CI:-49.98--6.6) for the RDP group was found. The rate of open conversion was higher in the LDP group (OR:2.38, 95%CI:1.75-3.22), while the rate of spleen preservation was lower (OR:0.49, 95%CI:0.31-0.79). No significant difference was noted in the intraoperative blood loss (WMD:34, 95%CI:-10.28-78.29), postoperative blood transfusion (OR:0.99, 95%CI:0.66-1.49) and overall morbidity analyses (OR:1.08, 95%CI:0.88-1.32). A significantly higher yield of lymph nodes was achieved in the RDP group (WMD:-2.09, 95%CI:-4.17--0.01), while no differences were found when positive resection margins (RD:0.02, 95%CI:-0.02-0.07) and specimen length (WMD:0.08, 95%CI:0.42-0.58) were considered. Finally, RDP was associated with significantly higher operative (WMD:-2733.42, 95%CI:-4189.77--1277.08) and total (WMD:-3799.68, 95%CI: -4438.39--3160.98) costs.*

Conclusion: *RDP seems to be a viable option for both benign and malignant pancreatic disorders, although there are concerns regarding economic parameters. Large randomized controlled trials will shed more light on the subject.*

Key words: *Distal Pancreatectomy; Laparoscopic Surgery; Pancreatic Cancer; Robotic Surgery*

Introduction

Distal pancreatic resection is utilized for the surgical management of inflammatory or neoplastic pancreatic disorders located in the body and tail of the pancreas [1].

Laparoscopic distal pancreatectomy (LDP) is a relatively new procedure in the general surgeon's armamentarium. In fact, it was only in 1996 when Cuschieri et al and Gagner et al reported the first two case series of patients with pancreatic pathology (chronic pancreatitis and insulinomas, respectively) treated with a LDP [2,3]. The experience of surgeons with the laparoscopic technique has been increasing since, allowing for the achievement of similar results when comparing LDP with open pancreatectomy, for both benign and neoplastic disorders [4,5]. Not only does laparoscopy allows for similar outcomes but it also results in smaller surgical incisions and faster recovery for the patients [6].

The rise of robotic applications in surgery resulted in the development of the robotic distal pancreatectomy (RDP) approach. Performed for the

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first time by Melvin et al in 2003 for a neuroendocrine tumor [7], RDP is the most contemporary technique available for the surgical management of pancreatic diseases [8]. When the robotic approach to the pancreas was introduced, it was believed that it would help minimize the ergonomic issues faced by surgeons using laparoscopic tools, thus, resulting in better outcomes [9]. Even though the perceived ergonomic advantages of the robot indeed transpired into everyday surgical practice, the long-awaited oncological and surgical benefits for the patients were not observed and the critics of RDP argue that robotic procedures are lengthier and more costly [9,10].

Although surgical and technological advancements have made distal pancreatectomy a much safer procedure than it was before [11,12], both LDP and RDP are still associated with several complications [13]. Particularly, postoperative pancreatic fistula (POPF), spleen sacrifice, intraoperative and postoperative blood loss and surgical infections increase the overall morbidity and mortality of the patients [13].

Evidently, even though minimally invasive procedures such as LDP and RDP are both comparable to or even better than the open approach for pancreatic lesions, it is still debatable which one, if any, results in more favorable outcomes for the patients. The aim of the current systematic review and meta-analysis is to compare the LDP and RDP approaches in terms of various parameters spanning the spectrum of perioperative and postoperative care and cost-effectiveness.

Methods

Literature search

In order to retrieve the eligible studies, a systematic literature search in the electronic databases (Medline, Web of Science and Scopus) was performed. The last literature screening date was 10 September 2018.

The following Boolean search algorithm was implemented: (Distal pancreatectomy OR left pancreatectomy OR peripheral pancreatic resection) AND (laparoscopic OR laparoscopy OR robotic OR robot).

Eligibility criteria

As eligible studies were considered all retrospective and prospective human studies, comparing LDP and RDP, in terms of malignant or benign primary diseases, whose outcomes of interest were provided in English and were retrievable.

Exclusion criteria for this meta-analysis included: 1) non-human studies, 2) studies not reported in English, 3) with no outcome of interest, 4) with no comparison group, 5) irretrievable outcome data and 6) manuscripts in the form of editorials, letters, conference abstracts and expert opinions.

Study selection and data collection

After removing the duplicate entries, the titles and abstracts of the remaining studies were screened. The next step included a full text review of the articles in order to assess consistency with the eligibility criteria. Electronic database screening, study selection, data extraction and quality assessment was performed blindly and in duplicate by two independent researchers (DA and PK). In case of a discrepancy, mutual revision and discussion was applied. If the disagreement was not resolved, the opinion of a third investigator was considered (TK).

Endpoints and definitions

The primary endpoint of the present study was the pooled mean difference of the length of hospital stay (LOS) in patients who were submitted to either, laparo-

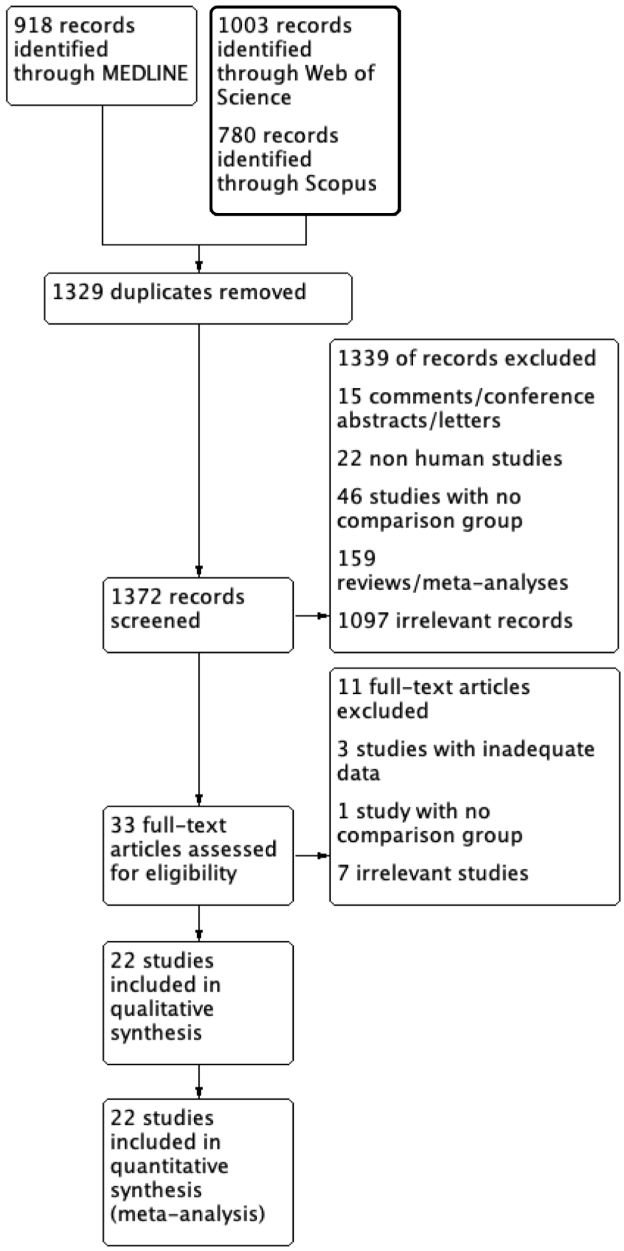

Figure 1. Flow diagram for study selection according to PRISMA guidelines.

Table 1. Included studies

<table>
<tr><th>First author – YOP (Country)</th><th>Study Type (Single|Multiple Centers)</th><th>Group</th><th>Sample</th><th>Age</th><th>Sex (Male|Female)</th><th>BMI (kg/m2)</th><th>Number of Surgeons (MIS Experience)</th><th>Follow-up Period</th></tr>
<tr><td>Fisher et al. – 2018 (USA)</td><td>Retrospective (Single)</td><td>LDP</td><td>146</td><td>58 (10.37)</td><td>66|80</td><td>n/a</td><td>n/a (n/a)</td><td>n/a</td></tr>
<tr><td></td><td></td><td>RDP</td><td>53</td><td>59 (10.37)</td><td>20|33</td><td></td><td></td><td></td></tr>
<tr><td>Raoof et al. – 2018 (USA)</td><td>Retrospective (Multiple)</td><td>LDP</td><td>605</td><td>138 (<65)</td><td>322|283</td><td>n/a</td><td>n/a (n/a)</td><td>Median: 25 months</td></tr>
<tr><td></td><td></td><td>RADP</td><td>99</td><td>23 (<65)</td><td>45|54</td><td></td><td></td><td></td></tr>
<tr><td>Souche et al. -2018 (France)</td><td>Prospective (Single)</td><td>LDP</td><td>23</td><td>66 (9.75)</td><td>9|14</td><td>25(3.5)</td><td>n/a (Yes)</td><td>n/a</td></tr>
<tr><td></td><td></td><td>RDP</td><td>15</td><td>57 (9.5)</td><td>3|12</td><td>23(3)</td><td></td><td></td></tr>
<tr><td>Goh et al. – 2017 (Singapore)</td><td>Retrospective (Single)</td><td>LDP</td><td>31</td><td>56 (13.25)</td><td>18|13</td><td>23.9(4.3)</td><td>8 (n/a)</td><td>90 days</td></tr>
<tr><td></td><td></td><td>RADP</td><td>8</td><td>57 (11.75)</td><td>2|6</td><td>27.6(2.3)</td><td>3 (n/a)</td><td></td></tr>
<tr><td>Ielpo et al. – 2017 (Spain)</td><td>Retrospective (Single)</td><td>LDP</td><td>26</td><td>61.3 (9.5)</td><td>17|9</td><td>24.5(3.37)</td><td>Multiple (Yes)</td><td>n/a</td></tr>
<tr><td></td><td></td><td>RDP</td><td>28</td><td>59.7 (9.5)</td><td>16|12</td><td>24.1(3.25)</td><td></td><td></td></tr>
<tr><td>Liu et al. – 2017 (China)</td><td>Retrospective (Single)</td><td>LDP</td><td>102</td><td>49.6 (15.2)</td><td>47|55</td><td>n/a</td><td>3 (Yes)</td><td>n/a</td></tr>
<tr><td></td><td></td><td>RDP</td><td>102</td><td>48.1 (15.5)</td><td>34|68</td><td></td><td></td><td></td></tr>
<tr><td>Xourafas et al. – 2017 (USA)</td><td>Retrospective (Multiple)</td><td>LDP</td><td>694</td><td>62 (17.5)</td><td>275|419</td><td>28.4(10.5)</td><td>n/a (n/a)</td><td>n/a</td></tr>
<tr><td></td><td></td><td>RDP</td><td>200</td><td>62 (16.5)</td><td>83|117</td><td>28.8(10)</td><td></td><td></td></tr>
<tr><td>Zhang et al. – 2017 (China)</td><td>Retrospective (Single)</td><td>LDP</td><td>31</td><td>48.7 (12.3)</td><td>12|19</td><td>23.3(2.7)</td><td>n/a (n/a)</td><td>Median: 23 months</td></tr>
<tr><td></td><td></td><td>RDP</td><td>43</td><td>47.9 (10.5)</td><td>20|23</td><td>23.9(3.2)</td><td></td><td>Median: 16 months</td></tr>
<tr><td>Eckhardt et al. – 2016 (Germany)</td><td>Retrospective (Single)</td><td>LDP</td><td>29</td><td>59 (17)</td><td>12|17</td><td>26.99(4.35)</td><td>1 (n/a)</td><td>Median: 30.5 months</td></tr>
<tr><td></td><td></td><td>RADP</td><td>12</td><td>48.5 (11.75)</td><td>4|8</td><td>23(3.62)</td><td></td><td>Median: 6 months</td></tr>
<tr><td>Morelli et al. – 2016 (Italy)</td><td>Retrospective (Single)</td><td>LDP</td><td>15</td><td>49.3 (17.1)</td><td>2|13</td><td>26.5(1.9)</td><td>2 (Yes)</td><td>>1 year</td></tr>
<tr><td></td><td></td><td>RADP</td><td>15</td><td>58.2 (13.7)</td><td>6|9</td><td>26.4(3.1)</td><td></td><td></td></tr>
<tr><td>Adam et al. – 2015 (USA)</td><td>Retrospective (Multiple)</td><td>LDP</td><td>474</td><td>64 (13)</td><td>248|226</td><td>n/a</td><td>n/a (n/a)</td><td>n/a</td></tr>
<tr><td></td><td></td><td>RDP</td><td>61</td><td>65 (14)</td><td>28|33</td><td></td><td></td><td></td></tr>
<tr><td>Butturini et al. – 2015 (Italy)</td><td>Prospective (Single)</td><td>LDP</td><td>21</td><td>55 (12.7)</td><td>6|15</td><td>24.19</td><td>Multiple (n/a)</td><td>Median: 15 months</td></tr>
<tr><td></td><td></td><td>RDP</td><td>22</td><td>54 (12.7)</td><td>5|17</td><td>25.33</td><td></td><td>Median: 10.5 months</td></tr>
<tr><td>Chen et al. – 2015 (China)</td><td>Prospective (Single)</td><td>LDP</td><td>50</td><td>56.5 (15)</td><td>18|32</td><td>24.6(3)</td><td>2 (Yes)</td><td>Median: 27 months</td></tr>
<tr><td></td><td></td><td>RADP</td><td>69</td><td>56.2 (13.3)</td><td>23|46</td><td>24.6(2.8)</td><td></td><td></td></tr>
<tr><td>Lai et al. -2015 (China)</td><td>Retrospective (Single)</td><td>LDP</td><td>18</td><td>63.2 (17.9)</td><td>4|14</td><td>25.7(2.7)</td><td>n/a (n/a)</td><td>Mean: 113.5 months</td></tr>
<tr><td></td><td></td><td>RDP</td><td>17</td><td>61.2 (10.4)</td><td>10|7</td><td>24.1(2.3)</td><td></td><td>Mean: 27.4 months</td></tr>
<tr><td>Lee et al. – 2015 (USA)</td><td>Retrospective (Single)</td><td>LDP</td><td>131</td><td>58 (15)</td><td>57|74</td><td>28.2</td><td>4 (Yes)</td><td>Median: 13 months</td></tr>
<tr><td></td><td></td><td>RDP</td><td>37</td><td>58 (11.1)</td><td>10|27</td><td>28.7</td><td></td><td></td></tr>
</table>

Continued on the next page

First author – YOP (Country)	*Study Type (Single|Multiple Centers)*	*Group*	*Sample*	*Age*	*Sex (Male|Female)*	*BMI (kg/m2)*	*Number of Surgeons (MIS Experience)*	*Follow-up Period*
Balzano et al. – 2014 (Italy)	Retrospective (Multiple)	LDP	140	n/a	n|a	n/a	n/a (n/a)	n/a
		RADP	31					
Duran et al. – 2014 (Spain)	Retrospective (Single)	LDP	18	58.3 (10)	9|9	n/a	Multiple (Yes)	n/a
		RDP	16	61 (11.6)	9|7			
Ito et al. – 2014 (Japan)	Retrospective (Single)	LDP	10	52.4	n|a	n/a	n/a (n/a)	n/a
		RDP	4	52.7	1|3			
Benizri et al. – 2013 (France)	Retrospective (Single)	LDP	23	52.3 (14.7)	10|13	26.5(4.7)	2 (Yes)	n/a
		RADP	11	50.1 (21.1)	3|8	25.6(5.8)		
Daouadi et al. – 2013 (USA)	Retrospective (Single)	LDP	94	59 (16)	10|20	29(7.1)	7 (Yes)	n/a
		RADP	30	59 (13)	33|61	27.9(5.1)		
Kang et al. – 2010 (S. Korea)	Retrospective (Single)	LDP	25	56.5 (13.9)	11|14	23.4 (2.6)	n/a (n/a)	n/a
		RADP	20	44.5 (15.9)	8|12	24.2 (2.9)		
Waters et al. – 2010 (USA)	Prospective (Single)	LDP	18	59	9|9	n/a	n/a (n/a)	n/a
		RDP	17	64	6|11			

Abbreviations:YOP – Year of Publication, LDP/RDP/RADP – Laparoscopic/Robotic/Robot-Assisted Distal Pancreatectomy, BMI – Body Mass Index, MIS – Minimally Invasive Surgery, n/a – not available

scopic (LDP), or robotic distal pancreatectomy (RDP) for benign, or malignant diseases.

The secondary outcomes included comparisons between the two techniques in terms of perioperative outcomes, such as operative duration, intraoperative blood loss and transfusion frequency, open conversion and spleen preservation rates. Furthermore, the postoperative complications rates (e.g. postoperative pancreatic fistula, severe complications, fluid collections, postoperative hemorrhage, surgical site infection, reoperation, readmission, mortality and overall complications) of LDP and RDP were also compared.

More specifically, postoperative pancreatic fistula (POPF) was categorized on the basis of the ISGPF classification [14]. As severe complication was considered any postoperative adverse event graded ≥III according to Clavien-Dindo classification [15].

Analysis in terms of oncological outcomes (e.g. positive resection margins, extracted lymph nodes and specimen length) was also implemented. Finally, LDP and RDP were also compared concerning the operative and overall costs. Data regarding the above mentioned endpoint were converted to Euro based on the current currency rate.

Quality scoring and publication bias

The quality and methodological evaluation of the eligible studies included the assessment on the basis of Newcastle-Ottawa Scale (NOS) [16]. Rating based on this tool was performed in terms of selection and comparability of the study groups and the confirmation of exposure. Each trial was appointed a score ranging from 0 to 9. Cohen's K statistic was also calculated.

In order to determine the possible presence of publication bias, the funnel plot of the primary endpoint was visually inspected. Furthermore, Egger's test was also calculated on the basis of the primary outcome.

Statistics

Data analysis and statistical computations were performed using the IBM SPSS version 23 and RevMan version 5.3. The endpoints of the present meta-analysis were presented in the form of Weighted Mean Difference (WMD) and Odds Ratio (OR) or Risk Difference (RD), for continuous and dichotomous variables, respectively. The results of the analyses were opposed with the corresponding 95% Confidence Intervals (95% CI).

In case that an eligible trial did not provide the mean or the Standard Deviation (SD) of a continuous variable, then they were calculated from the respective median and range, according to the formula described by Hozo et al [17].

For dichotomous variables, the statistical method applied was the Mantel-Haenszel (MH) and for continuous variables the Inverse Variance (IV). Both Fixed Effects (FE) and Random Effects (RE) models were estimated. The model that was finally reported was based on the Cochran Q test. More specifically, if the heterogeneity levels were significant (Q test $P<0.1$), then the RE model was applied. Heterogeneity levels were also quantified through the calculation of I^2. Statistical significance was considered at the level of $P<0.05$.

Table 2. Patient characteristics

First Author	*Group*	*Diagnosis*									*ASA Grade*				*Previous Operation*
		PDAC	*SCT*	*MCT*	*IPMT*	*NET*	*SPT*	*Pancreatitis| Pseudocyst*	*IPAS*	*Benign Stricture*	*I*	*II*	*III*	*IV*	
Fisher et al.	LDP					Data not available									
	RDP														
Raoof et al.	LDP					Data not availabe									
	RADP														
Souche et al.	LDP	n/a	1	3	7	8	0	n/a	1	n/a	5	18	0	0	5
	RDP		1	2	2	8	1		0		8	7	0	0	2
Goh et al.	LDP	4	7	3	2	15	5	1	n/a	n/a	31	0	0	0	10
	RADP										7	1	0	0	1
Ielpo et al.	LDP	13	2	2	3	7	0	1	0	0	3	20	3	0	n/a
	RDP	15	1	1	4	6	0	2	0	0	2	23	3	0	
Liu et al.	LDP	25	16	20	7	15	15	4	4	4	8	91	3	0	n/a
	RDP	26	16	17	6	16	16	5	5	5	10	90	2	0	
Xourafas et al.	LDP					Data not available					13	235	421	25	n/a
	RDP										2	63	126	9	
Zhang et al.	LDP	0	0	0	0	31	0	0	0	0	22	9	0	0	n/a
	RDP	0	0	0	0	43	0	0	0	0	32	11	0	0	
Eckhardt et al.	LDP	1	7	5	11	0	4	0	0		Data not available				n/a
	RADP	0	3	3	5	0	0	0	0						
Morelli et al.	LDP					Data not available						2.3(0.46)			5
	RADP											2.4(0.51)			5
Adam et al.	LDP	234	n/a	n/a	n/a	197	n/a	n/a	n/a	n/a	Data not available				n/a
	RDP	33				24									
Butturini et al.	LDP	2	2	7		9	1	n/a	0	n/a	5	16	0	0	13
	RDP	3	0	6		8	3		1		3	18	1	0	15
Chen et al.	LDP	9	n/a	16	5	3	8	n/a	n/a	n/a	5	43	1	0	n/a
	RADP	15		26	6	3	10				7	59	3	0	
Lai et al.	LDP	2	6	4	0	2	1	3	n/a	n/a	4	14	0	0	n/a
	RDP	3	6	2	1	4	0	0			6	11	0	0	
Lee et al.	LDP	19	n/a	16	18	41	7	n/a	n/a	n/a		3			n/a
	RDP	4		6	4	8	2					2.5			
Balzano et al.	LDP	29	22	34	13	49	n/a	1	n/a	n/a	Data not available				n/a
	RADP														
Duran et al.	LDP	8	n/a	n/a	0	5	n/a	2	n/a	n/a	4	11	3	0	n/a
	RDP	9			2	4		0			0	16	0	0	
Ito et al.	LDP	0	1	1	0	2	3	0	0	0					
	RDP					Data not availabe					Data not availabe				n/a
Benizri et al.	LDP	3	3	4	3	7	2	1	0	0	20	3	0		10
	RADP	0	2	2	1	2	3	0	0	0	10	1	0		6
Daouadi et al.	LDP	14		30	11	21	6	n/a	n/a	n/a	42		51		48
	RADP	13		4	5	9	0				11		19		22
Kang et al.	LDP	n/a	3	2	10	3	4	1	1	1	Data not available				n/a
	RADP		4	5	2	3	4	1	1	0		2.9			n/a
Waters et al.	LDP	2	2	3	2	5	n/a	n/a	n/a	n/a		2.8			
	RDP	0	1	3	6	5									

LDP/RDP/RADP – Laparoscopic/Robotic/Robot-Assisted Distal Pancreatectomy, n/a – not available, PDAC - Pancreatic Ductal Adenocarcinoma, SCT – Serous Cystadenoma, MCT – Mucinous Cystadenoma, IPMT – Intraductal Papillary Mucinous Neoplasms, NET – Neuroendocrine Tumors, SPT – Solid Pseudopapillary Tumors,IPAS – Intrapancreatic Accessory Spleen , ASA – American Society of Anesthesiologists

Study protocol

This systematic review and meta-analysis was conducted on the basis of the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA guidelines [18].

Results

Study selection

Electronic database search resulted in the retrieval of 2701 records (Figure 1). More specifically, 918 entries were identified through Medline, 1003 through Web of Science and 780 through Scopus. After the removal of 1329 duplicate records, 1372 titles and abstracts were screened. During this phase of literature screening 1339 studies (15 comments, conference abstracts, or letters, 22 non- human studies, 46 studies with no comparison group, 159 reviews or meta-analyses and 1097 irrelevant records) were excluded. Full text assessment of the remaining 33 articles identified 3 studies that did not provide adequate outcome data, 1 study without a comparison group and 7 irrelevant records. More specifically, from this group, 2 studies [19,20] that compared single site laparoscopic or robotic distal pancreatectomy were excluded. Finally 22 studies were included in the qualitative and quantitative analysis [21].

Study characteristics

The characteristics of the included studies are summarized in Table 1 (Supplementary Material). Publication year ranged from 2010 to 2018. In total, 18 [21-38] and 4 [39-42] studies had a retrospective and a prospective study design, respectively. Nine studies [23-25,27,29,31,35,36,40] reported the application of a robotic assisted operative technique. Only 4 studies [22,23,36,37] were conducted in more than one institutions. Furthermore, gender, age and BMI allocation between the study subgroups is also displayed in Table 1. Multiple (≥3) operating surgeons were reported in 7 studies [21,25,26,29,33,34,39]. Experience in minimally invasive techniques was documented in 9 studies [21,24-26,33-35,40,41]. Mean postoperative follow up period spanned from 3 months [29] up to 113 months [32].

Considering the underlying pathology, the neuroendocrine tumors (NET), was the most frequent diagnosis, followed by the adenocarcinoma (PDAC) of the pancreas (Table 2 Supplementary Material). Other diagnoses included the mucinous cystadenoma (MCT), serous cystadenoma (SCT), intraductal papillary mucinous neoplasms (IPMT) and solid pseudopapillary tumors (SPT). Benign patholo-

Table 3. Tumor characteristics

First Author	*Group*	*Tumor Size*	*Tumor Site*		*Tumor*				*Nodes*		*Grade*			*Neoadjuvant*		*Adjuvant*		
			Body	*Tail*	*1*	*2*	*3*	*4*	*0*	*1*	*Low*	*Intermediate*	*High*	*Chemotherapy*	*Chemoradiation*	*Chemotherapy*	*Chemoradiation*	*Radiation*
Fisher et al.	LDP	n/a	n/a			n/a			n/a			n/a			n/a			
	RDP																	
Raoof et al.	LDP	3.7(1.7)	182	423	66	106	406	12	279	301	62	300	189	16	10	221	124	11
	RDP	3.5(1.5)	29	70	12	22	64	0	45	45	15	49	25	7	2	40	18	1
Souche et al.	LDP	3.5(1.5)	n/a			n/a			n/a			n/a		n/a			n/a	
	RDP	2.8(1.3)																
Goh et al.	LDP	2.5(1.5)	n/a			n/a			n/a			n/a		n/a			n/a	
	RADP	3(1.4)																
Ielpo et al.	LDP	3.83(2)	n/a			n/a			n/a			n/a		9			n/a	
	RDP	3.54(1.95)												8				
Liu et al.	LDP	4.56(3.2)	n/a			n/a			n/a			n/a		n/a	2		n/a	
	RDP	4.2(1.44)																

Continued on the next page

First Author	Group	Tumor Size	Tumor Site		Tumor				Nodes		Grade			Neoadjuvant		Adjuvant		
			Body	Tail	1	2	3	4	0	1	Low	Intermediate	High	Chemotherapy	Chemoradiation	Chemotherapy	Chemoradiation	Radiation
Xourafas et al.	LDP	n/a	n/a			T>3 n=136			n/a	92		n/a		8	2		n/a	
	RDP					T>3 n=46				29				17	7			
Zhang et al.	LDP	1.6(0.74)	6	25		n/a			n/a		24	5	2	n/a			n/a	
	RDP	1.6(0.88)	13	30							35	7	1					
Eckhardt et al.	LDP	2.05(2.7)	11	18		n/a			n/a			n/a		n/a			n/a	
	RADP	2.1(0.85)	4	8														
Morelli et al.	LDP	n/a	n/a			n/a			n/a			n/a		n/a			n/a	
	RADP	3.6(2)	115	359		n/a			n/a			n/a		n/a			n/a	
Adam et al.	LDP	3.8(2.2)	17	44														
	RDP	3.5(1.5)	n/a			n/a			n/a			n/a		n/a			n/a	
Butturini et al.	LDP	2.55(2.125)																
	RDP																	
Chen et al.	LDP	3.5(1.7)	34	16	n/a	3	7	n/a	n/a			n/a		n/a		9	n/a	n/a
	RADP	3.5(1.6)	47	22		5	10									14		
Lai et al.	LDP	n/a	n/a			n/a			n/a			n/a		n/a			n/a	
	RDP																	
Lee et al.	LDP	n/a	n/a			n/a			n/a			n/a		n/a			n/a	
	RDP																	
Balzano et al.	LDP	3(1.8)	n/a			n/a			n/a			n/a		n/a			n/a	
	RADP																	
Duran et al.	LDP	4.13(2.34)	n/a			n/a			n/a			n/a		8			n/a	
	RDP	2.78(1.63)												9				
Ito et al.	LDP	n/a	n/a			n/a			n/a			n/a		n/a			n/a	
	RDP																	
Benizri et al.	LDP	2.7(1.3)	n/a			n/a			n/a			n/a		n/a			n/a	
	RADP	3.6(2.5)																
Daouadi et al.	LDP	2.9(1.9)	n/a			n/a			n/a			n/a		n/a			n/a	
	RADP	2.6(1.4)																
Kang et al.	LDP	3.0 (1.4)	n/a			n/a			n/a			n/a		n/a			n/a	
	RADP	3.5 (1.3)																
Waters et al.	LDP	4(3)	n/a			n/a			n/a			n/a		n/a			n/a	
	RDP	2(1)																

Table 4. Operative characteristics

First Author	*Group*	*Stump*	*Transection*	*Drain*	*Trocars*
Fisher et al.	LDP		n/a		
	RDP				
Raoof et al.	LDP		n/a		
	RADP				
Souche et al.	LDP	stapler & glue	harmonic	yes	n/a
	RDP	stapler & glue	electrohook and bipolar	yes	
Goh et al.	LDP		n/a		
	RADP				
Ielpo et al.	LDP	stapler	energy devices	n/a	5
	RDP	stapler	energy devices		5
Liu et al.	LDP	stapler	energy devices	n/a	4
	RDP	stapler	n/a		5
Xourafas et al.	LDP	n/a	n/a	82	n/a
	RDP			16	
Zhang et al.	LDP	stapler	n/a	yes	4
	RDP	stapler		yes	5
Eckhardt et al.	LDP	stapler or Tachosil	harmonic, electrohook and vascular clips	yes	4
	RADP	stapler or Tachosil	harmonic, electrohook and vascular clips	yes	5
Morelli et al.	LDP	stapler & oversewn	electrocautery	yes	4 or 5
	RADP	stapler & oversewn	monopolar scissors	yes	5
Adam et al.	LDP		n/a		
	RDP				
Butturini et al.	LDP	stapler	energy devices	yes	4
	RDP	stapler	energy devices	yes	5
Chen et al.	LDP	n/a	n/a	yes	n/a
	RADP			yes	
Lai et al.	LDP	stapler & oversewn	energy devices	n/a	6
	RDP	stapler & oversewn	monopolar scissors		5
Lee et al.	LDP	stapler	energy devices	surgeon's preference	4 or 5
	RDP	stapler	energy devices		4 or 5
Balzano et al.	LDP	stapler & oversewn or ultrasonic devises or patch	n/a	n/a	n/a
	RADP				
Duran et al.	LDP		n/a		
	RDP				
Ito et al.	LDP	stapler	esulon g	n/a	5
	RDP	n/a	esulon g		n/a
Benizri et al.	LDP	stapler	energy devices	n/a	5(0.5)
	RADP	stapler	energy devices		6(0.5)
Daouadi et al.	LDP	stapler & oversewn	n/a	n/a	n/a
	RADP	stapler & oversewn			
Kang et al.	LDP		n/a		
	RADP				
Waters et al.	LDP	stapler or oversewn	n/a	n/a	4 or 5
	RDP	stapler or oversewn			5

gies such as pancreatitis, pseudocysts, accessory spleens and benign strictures were also recorded. Moreover, Table 2, displays the ASA grading of the included patients. In total, 142 patients had been submitted to previous abdominal operations.

Mean tumor size reported in the two subgroups ranged from 1.6 cm [38] up to 4.56 cm [34] (Table 3 Supplementary Material). Moreover, 458 and 1015 tumors were located in the pancreatic body and tail, respectively. The stage and the histological grade of the malignant pathologies are also provided in Table 3. Details regarding the status of the neoadjuvant or adjuvant treatment of the patients were reported in only 2 studies [36,40]. Finally, details concerning the operative technique, such as the closure of the pancreatic stump, the transection method, the use of drain and the number of trocars are summarized in Table 4 (Supplementary Material).

Quality of studies

Table 5 (Supplementary Material), summarizes the methodological and quality evaluation of the included studies on the basis of the NOS scale. Although the overall score ranged from 2 to 7 stars, the quality level of the majority of the studies was considered to be in an adequate level. Interrater agreement was estimated to be in a more than adequate level (Cohen's k statistic: 95.5%, p<0.0001).

	LDP			RDP				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Adam et al.	6	4	474	8	10	61	3.6%	-2.00 [-4.54, 0.54]
Benizri et al.	9	10.5	23	10	4.25	11	1.2%	-1.00 [-5.97, 3.97]
Butturini et al.	7	7.5	21	7	6	22	1.7%	0.00 [-4.07, 4.07]
Chen et al.	14.7	8.4	50	11.6	6.6	69	3.1%	3.10 [0.30, 5.90]
Daouadi et al.	7.1	4	94	6.1	1.7	30	8.6%	1.00 [-0.01, 2.01]
Duran et al.	19.16	15	18	8.87	1.45	16	0.7%	10.29 [3.32, 17.26]
Eckhardt et al.	13	6.75	29	10.5	3	12	2.8%	2.50 [-0.49, 5.49]
Fisher et al.	4	2.2	146	5	1.48	53	10.6%	-1.00 [-1.53, -0.47]
Goh et al.	6	2.25	31	6	2.5	8	5.1%	0.00 [-1.90, 1.90]
Ielpo et al.	13.1	8.25	26	8.9	3.25	28	2.3%	4.20 [0.81, 7.59]
Ito et al.	24	11	10	14	3	4	0.6%	10.00 [2.58, 17.42]
Kang et al.	7.3	3	25	7.1	2.2	20	6.4%	0.20 [-1.32, 1.72]
Lai et al.	14.2	14	18	11.4	6.9	17	0.6%	2.80 [-4.45, 10.05]
Lee et al.	5	0.3	131	5	0.75	37	11.4%	0.00 [-0.25, 0.25]
Liu et al.	8.58	3.6	102	7.67	2.19	102	9.4%	0.91 [0.09, 1.73]
Morelli et al.	8.8	3.8	15	6.5	1.9	15	4.5%	2.30 [0.15, 4.45]
Raoof et al.	6	2.2	605	5	2.2	99	10.8%	1.00 [0.53, 1.47]
Souche et al.	9	3	23	8	2.25	15	5.9%	1.00 [-0.67, 2.67]
Waters et al.	6	7.7	18	4	1	17	2.1%	2.00 [-1.59, 5.59]
Xourafas et al.	5	18.3	694	5	6	200	6.2%	0.00 [-1.60, 1.60]
Zhang et al.	14.4	7.2	31	12.8	6.8	43	2.5%	1.60 [-1.65, 4.85]
Total (95% CI)			2584			879	100.0%	0.75 [0.17, 1.33]

Heterogeneity: Tau² = 0.75; Chi² = 74.83, df = 20 (P < 0.00001); I² = 73%
Test for overall effect: Z = 2.55 (P = 0.01)

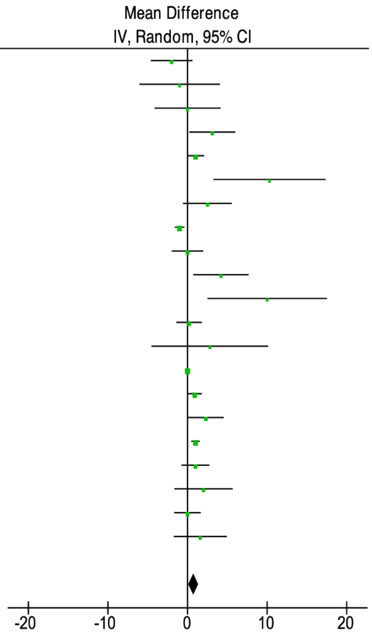

Figure 2. Forest plots for length of hospital stay (LOS) between the groups.

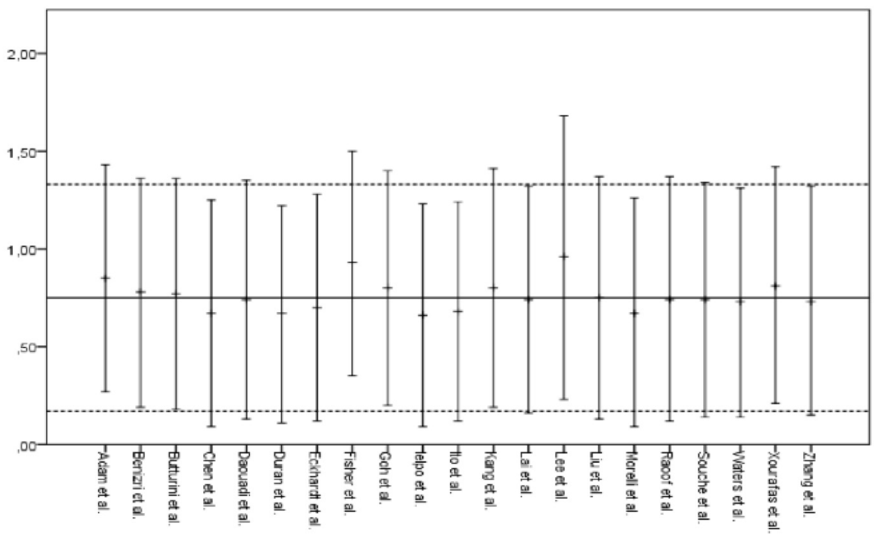

Figure 3. Sensitivity analysis. As a result of the lack homogeneity between the studies, further analyses were performed.

Endpoints

Overall, 21 studies provided extractable data from a total of 3463 patients concerning the primary endpoint (Figure 2). Meta-analysis of these data, showed a statistically significant (p=0.01) lower LOS (WMD: 0.75, 95%CI: 0.17-1.33) in the group where robotic distal pancreatectomies were performed. Heterogeneity levels were significantly high (Q test P<0.00001, I^2=73%). As a result of the lack of homogeneity between the studies, further analyses were performed. Figure 3 (Supplementary Material), summarizes the results of the sensitivity analysis. Meta-regression regarding the year of publication (p=0.56), sample size (p=0.13), age (p=0.869), BMI (p=0.482), follow up (p=0.06) and tumor size (p=0.83) did not provide any statistically significant results. Furthermore, subgroup analysis was performed, in order to identify possibly heterogeneity introducing factors (Table 6 Supplementary Material). Heterogeneity was reduced without altering the outcome of the primary endpoints when studies applying a prospective design (WMD: 1.43, 95%CI: 0.19-2.73, Q test P=0.53, I^2=0%), or a robotic assisted technique (WMD: 1, 95%CI: 0.58-1.43, Q test P=0.4, I^2=4%), or stapling and over-sewing the pancreatic stump (WMD: 1.30, 95%CI: 0.42-2.19, Q test P=0.69, I^2=0%) were introduced.

Table 5. Newcastle-Ottawa scoring

Study	*Selection*				*Comparability*	*Exposure/Outcome*			*Total*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	
Fisher et al.	*	*	*	*		*	*	*	7/9
Raoof et al.	*	*	*	*		*	*	*	7/9
Souche et al.	*	*							2/9
Goh et al.	*	*	*			*		*	5/9
Ielpo et al.	*	*	*			*			4/9
Liu et al.	*	*			**	*	*		6/9
Xourafas et al.	*	*	*			*	*		5/9
Zhang et al.	*	*	*	*		*		*	6/9
Eckhardt et al.	*	*	*			*		*	5/9
Morelli et al.	*	*			**	*	*		6/9
Adam et al.	*	*	*		**	*	*		7/9
Butturini et al.	*	*	*			*		*	5/9
Chen et al.	*	*	*		**	*	*		7/9
Lai et al.	*	*	*			*	*		5/9
Lee et al.	*	*	*			*	*		5/9
Balzano et al.	*	*							2/9
Duran et al.	*	*	*			*			4/9
Ito et al.		*				*	*		3/9
Benizri et al.	*	*	*			*			4/9
Daouadi et al.	*	*	*			*			4/9
Kang et al.	*	*	*			*			4/9
Waters et al.	*	*	*			*			4/9

Table 6. Subgroup analysis results

Subgroup		*WMD (95%CI)*	*Q test P*	I^2
Prospective Study		1.46(0.19, 2.73)	0.53	0%
Multi Center		0.07(-1.40, 1.55)	0.04	68%
Robotic Assisted		1(0.58, 1.43)	0.4	4%
≥3 Surgeon		0.99(-0.27, 2.25)	0.004	71%
Experience in MDP		1.40(0.45, 2.35)	0.0001	77%
Pancreatic Stump	Stapler	0.99(-0.17, 2.15)	0.007	66%
	Stapler & Oversewn	1.30(0.42, 2.19)	0.69	0%

Regarding the other perioperative outcomes (Figure 4), although the operative duration was significantly higher in RDP (WMD: -28.29, 95%CI: -49.98--6.6, Q test P<0.00001, I^2=87%), there was no significant difference in terms of intraoperative blood loss (WMD: 34, 95%CI: -10.28-78.29, Q test P<0.00001, I^2=87%). In addition to this, the implementation of a robotic operative approach, resulted to significantly lower rates of open conversion (OR: 2.38, 95%CI: 1.75-3.22, Q test P<0.0001, I^2=22%) and respectively, higher rates of spleen preservation (OR: 0.49, 95%CI: 0.31-0.79, Q test P=0.0005, I^2=61%) (Figure 5). The percentages of perioperative blood transfusion did not differ between LDP and RDP (Figure 5, OR: 0.99, 95%CI: 0.66-1.49, Q test P=0.7, I^2=0%).

RDP and LDP were equivalent in terms of overall postoperative morbidity (Figure 6, OR: 1.08, 95%CI: 0.88-1.32, Q test P=0.83, I^2=0%). More specifically, no statistical difference was identified in the rates of POPF grade A (OR: 1.12, 95%CI: 0.79-1.59, Q test P=1, I^2=0%), POPF grade B (OR: 1.04, 95%CI: 0.71-1.53, Q test P=0.54, I^2=0%), POPF grade C (OR: 0.89, 95%CI: 0.38-2.09, Q test P=0.76, I^2=0%), CD ≥III adverse events (OR: 0.92, 95%CI: 0.62-1.38, Q test P=0.18, I^2=27%), fluid collections (OR: 1.37, 95%CI: 0.68-2.75, Q test P=0.49, I^2=0%), postoperative hemorrhage (OR: 0.98, 95%CI: 0.58-1.68, Q test P=0.85, I^2=0%), SSI (OR: 0.77, 95%CI: 0.43-1.38, Q test P=0.55, I^2=0%), reoperation (OR: 1.34, 95%CI: 0.71-2.52, Q test P=0.74, I^2=0%), readmission (OR: 0.73, 95%CI: 0.44-1.20, Q test P=0.49, I^2=0%) and mortality (OR: 2.87, 95%CI: 0.67-12.38, Q test P=0.71, I^2=0%) (Figure 7, Supplementary Material).

Positive resection margin risk did not differ between the two study subgroups (Figure 8A Supplementary Material, RD: 0.02, 95%CI: -0.02-0.07, Q test P=0.04, I^2=48%). Despite this, a higher lymph node yield was achieved through the robotic approach (Figure 8B Supplementary Material, WMD: -2.09, 95%CI: -4.17--0.01, Q test P<0.00001, I^2=86%).

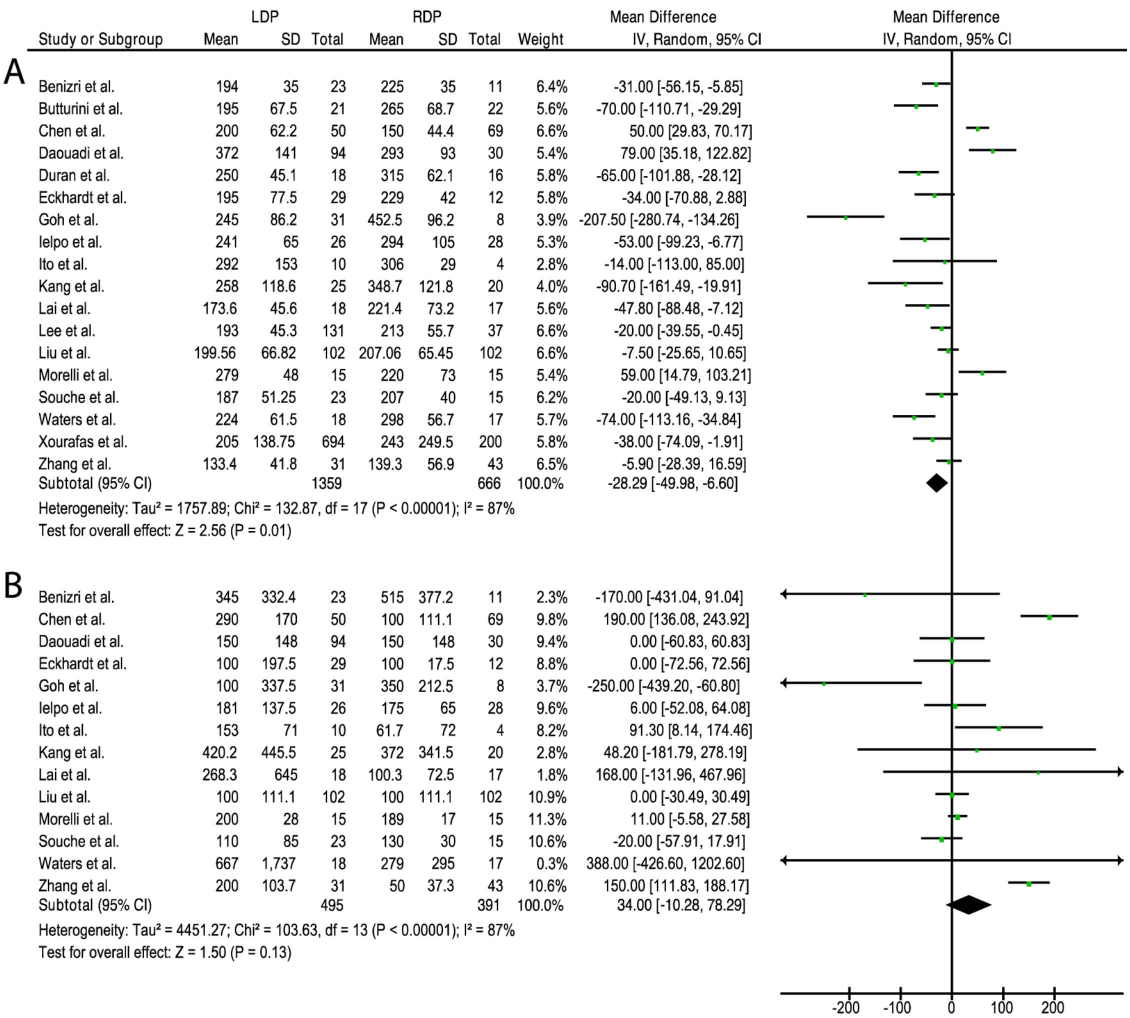

Figure 4. Perioperative outcomes. Forest plots of perioperative outcomes for **(A)** operative duration and **(B)** intraoperative blood loss.

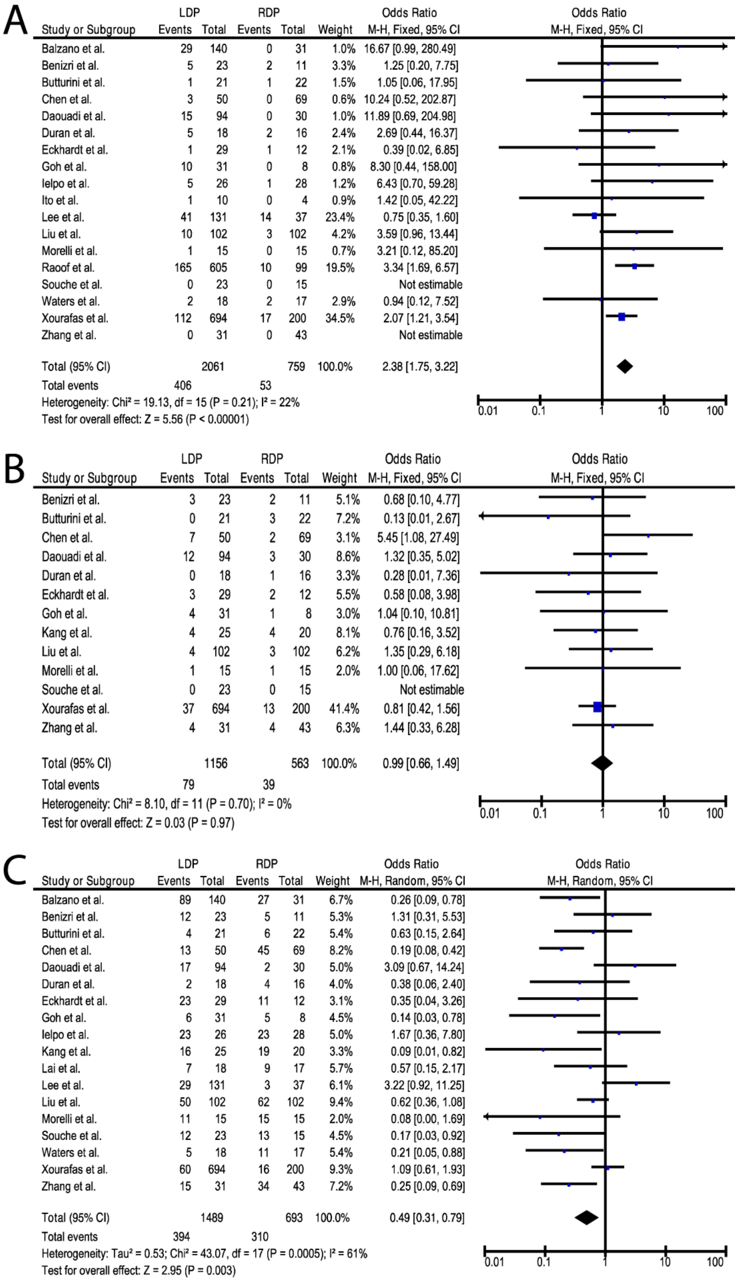

Figure 5. Open conversion, blood transfusion and spleen preservation. Forest plots of open conversion **(A)**, blood transfusion **(B)** and spleen preservation **(C)**.

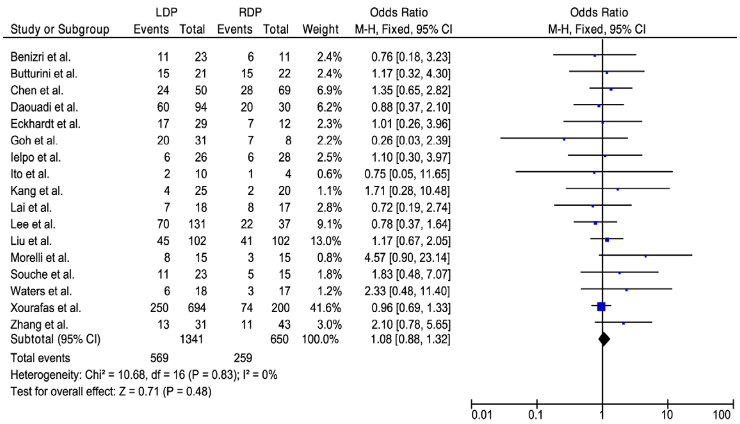

Figure 6. Overall morbidity. Forest plots on the comparison of overall morbidity

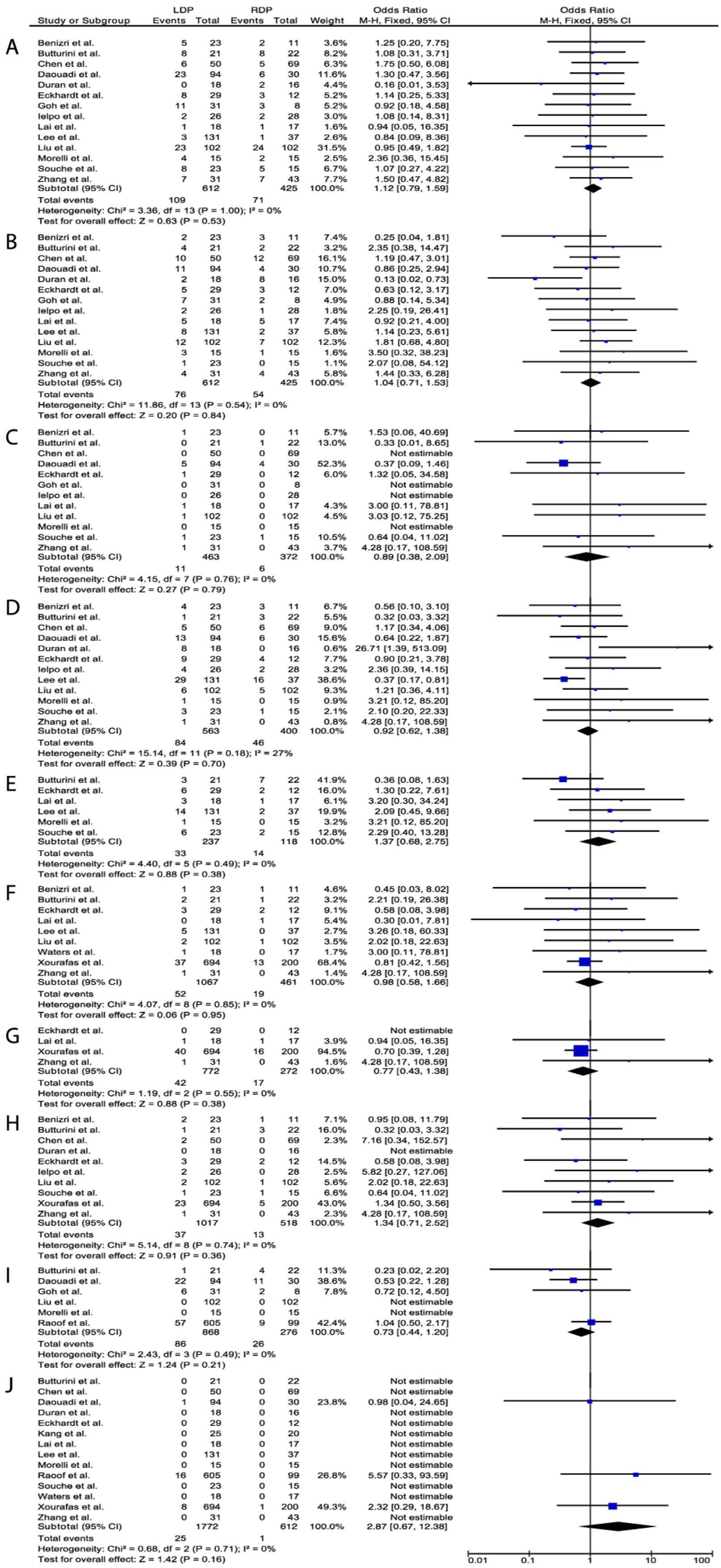

Figure 7. Postoperative complications. Forest plots on the comparisons of postoperative complications showing the results for **A** postoperative pancreatic fistula (POPF),ISGF classification A, **B** POPF ISGPF classification B, **C** POPF ISGPF classification C, **D** Clavien-Dindo≥3, Complication, **E** Fluid collection, **F** Postoperative hemorrhage, **G** Surgical site infection (SSI), **H** Reoperation, **I** Readmission, and **J** mortality.

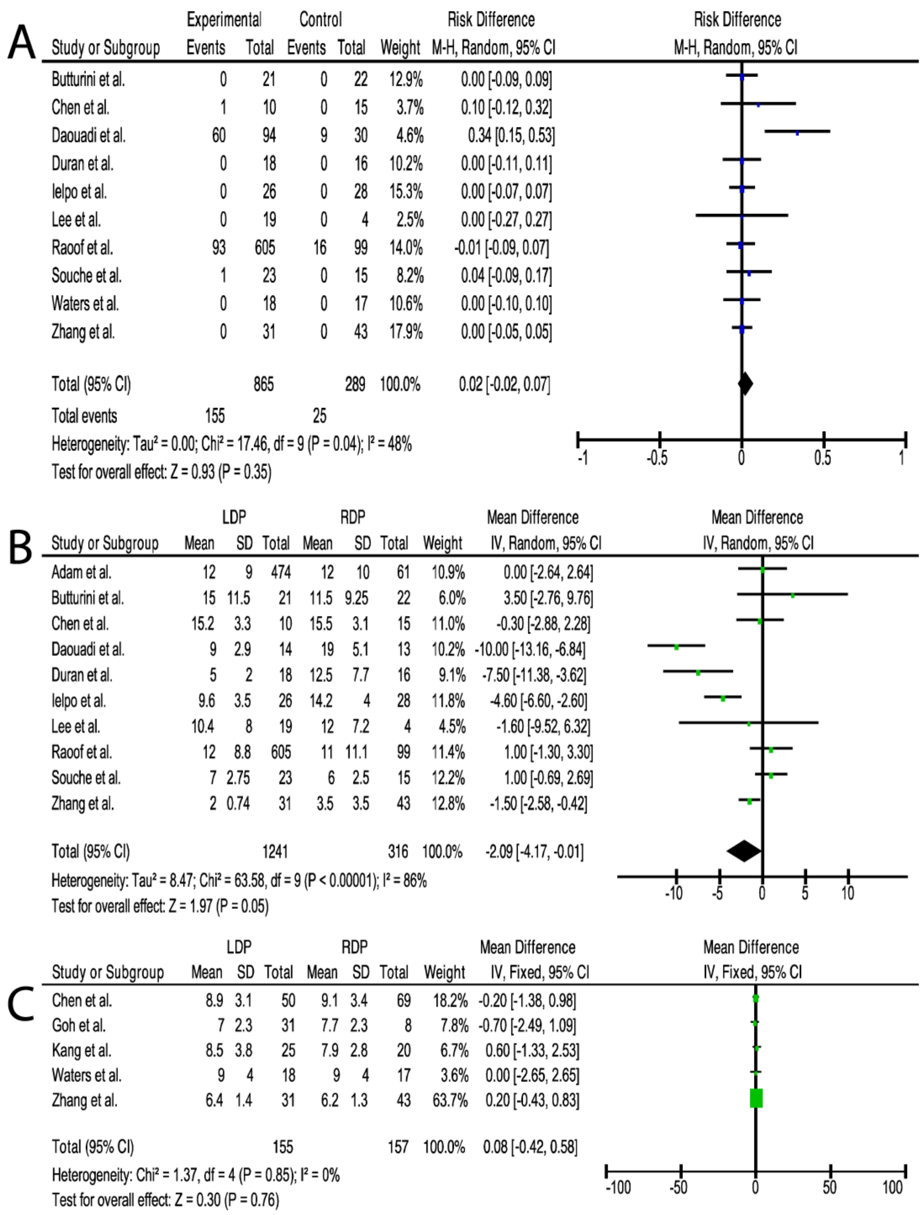

Figure 8. Oncologic outcomes. Forest plots on the comparisons of oncologic outcomes showing the results for **A** Positive resection margins, **B** Extracted lymph nodes and **C** Specimens length.

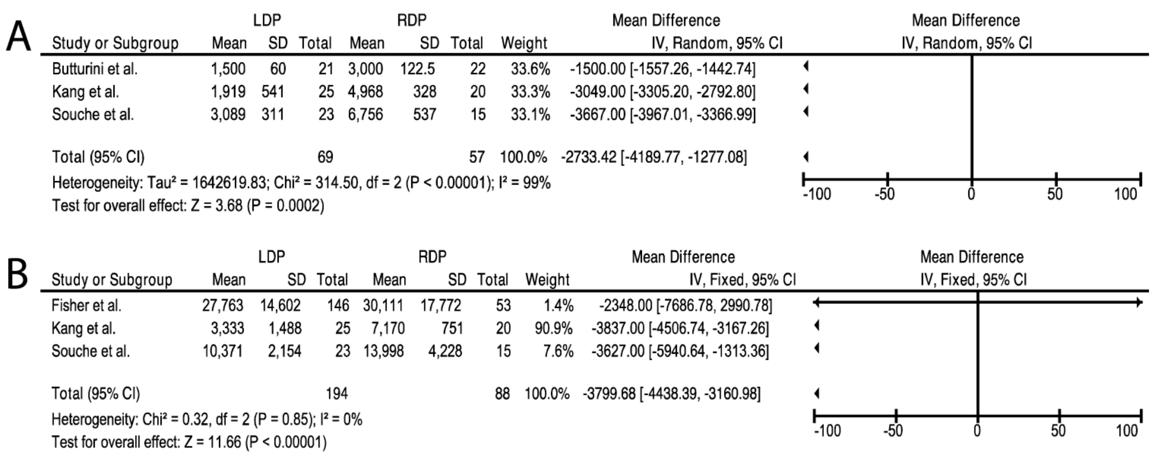

Figure 9. Cost analysis. Forest plots on cost analysis showing the results for the comparisons of **A** Operative cost, **B** Total hospitalization cost.

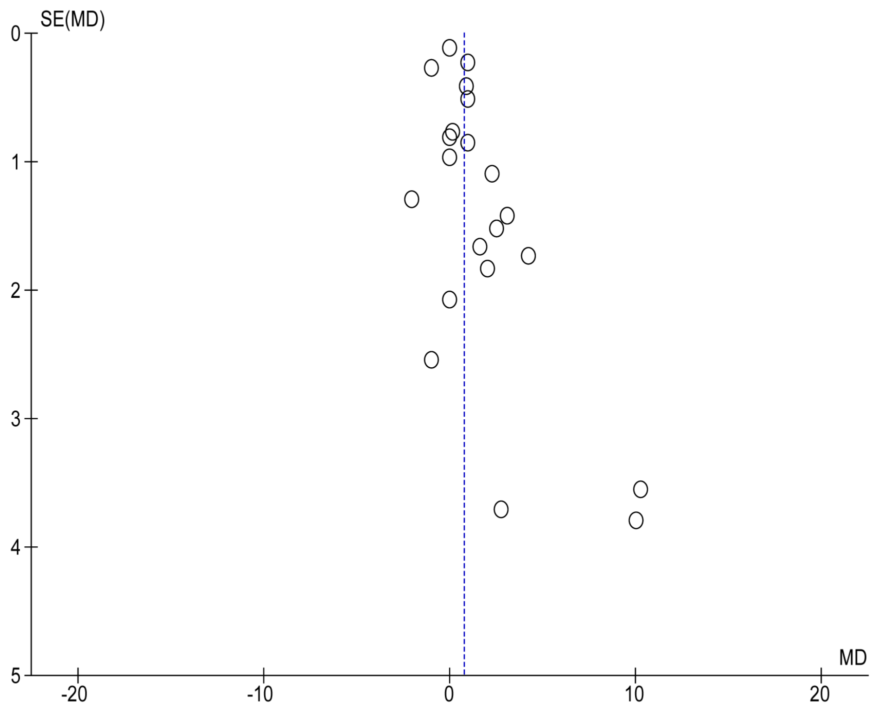

Figure 10. Funnel plot for the primary endpoint assessing the publication bias for the primary endpoint of the study (LOS).

RDP and LDP resulted to an equivalent specimen length (Figure 8C Supplementary Material, WMD: 0.08, 95%CI: -0.42-0.58, Q test P=0.85, I^2=0%).

Finally, as far as the cost outcomes were concerned, statistically significant results were estimated in both analyses. More specifically, RDP was associated with higher operative (Figure 9A Supplementary Material, WMD: -2733.42, 95%CI: -4189.77--1277.08, Q test P<0.00001, I^2=99%) and total costs (Figure 9B Supplementary Material, WMD: -3799.68, 95%CI: -4438.39--3160.98, Q test P=0.85, I^2=0%), when compared to LDP.

Risk of bias across studies

The funnel plot of the primary endpoint is displayed in Figure 10 (Supplementary Material). Visual inspection of the graphical representation reveals an asymmetrical distribution of the eligible studies in the two sides of the combined effect size line. Furthermore, Egger's test was statistically significant, thus confirming the presence of publication bias (p=0.029).

Discussion

This systematic review and meta-analysis evaluated the safety and feasibility of RDP utilization in the treatment of benign and malignant disorders of the pancreas. The results show that RDP leads to decreased LOS, decreased rate of open conversion and increased spleen preservation rates, although it seems to be costlier than LDP. Finally, RDP appears to be comparable, if not better, to LDP when oncological parameters, such as positive resection margins and number of lymph nodes harvested, are taken into consideration.

Operative duration is a major factor in robotic surgery, because the procedures tend to be more time consuming than the laparoscopic ones [43,44]. Individual studies that were published in the past comparing LDP with RDP in regards to this subject were not conclusive. Some authors [21] have reported statistically significant longer operation times for the RDP groups but others [38] did not observe such a difference. The two latest meta-analyses investigating the subject, concluded that LDP and RDP are equally long [13,45].

On the contrary, the results of the present meta-analysis suggest that a difference in the duration of these procedures does exist, with the operative duration being longer in the RDP group. This dissonance between the results of this and past meta-analyses may be explained by the larger number of studies included in the current article offering a more comprehensive picture of the subject.

Spleen preserving distal pancreatectomy is the operation of choice in benign diseases of the pancreatic body and tail [46-48], as it possesses the benefits of lower risk of developing cancer in the future and prevents overwhelming post-splenectomy infection [49]. Spleen preservation is feasible both with LDP [50,51] and RDP [52].

Two major spleen preserving surgical techniques have been described in the literature, the Warshaw method [53] and the Kimura [48] method. Warshaw's method consists of the ligation of the splenic vessels and the preservation of the left gastroepiploic artery and short gastric vessels while Kimura's method maintains splenic vascularization by preserving the splenic vessels.

The results of the current meta-analysis support the previously published evidence that RDP results in higher rates of spleen preservation when compared to the LDP.

Open conversion of MIS increases the length of the procedure and is associated with multiple complications. A variety of factors influence the surgeons' decision to convert an operation, amongst them bleeding, adhesions and insufficient visualization of important structures [54,55]. Several predictive factors for open conversion of minimally invasive distal pancreatectomy have been proposed and surgeons should keep them in mind when assessing patients for their eligibility for minimally invasive surgery (MIS). These include chronic pancreatitis, large malignant neoplasms, higher BMI, low serum albumin and smoking [56].

The rate of open conversion in this current study was greater in the LDP group. This difference might be attributed to the better field visualization and increased range of motion provided by the robot [56,57].

Intraoperative blood loss is associated with an increased risk of complications [58], while blood transfusion during surgery for malignancies is connected to an elevated relapse risk [59]. Both parameters were found to be equal in the LDP and RDP groups.

POPF remains one of the most significant complications after pancreatic surgery [60], as it can lead to the development of an abscess, a pseudoaneurysm and even sepsis [61,62]. It is a relatively common complication of peripheral pancreatectomy as it is reported in up to 60% of the cases [63].

The pathogenetic mechanism of fistula formation is closely linked to intraoperative damage to the major or accessory pancreatic ducts and anastomotic leakage [63]. A recent meta-analysis on the risk factors for the formation of POPF after distal pancreatectomy concluded that patients with low pancreatic tissue density, high BMI, considerable intraoperative blood loss and blood transfusion, as well as those that underwent longer operations are more susceptible to POPF development [64]. Interestingly, several authors report young age [65,66] and splenectomy [12,67] as risk factors.

Multiple intraoperative and perioperative interventions, such as various stump closure methods, somatostatin analogs administration and earlier intraperitoneal drain removal, have been proposed to reduce the rates of POPF. None has been established as the gold-standard due to the lack of statistically significant evidence [68].

The implementation of MIS has been also studied as a potential way to reduce the rates of POPF, but no significant difference has been reported when comparing open pancreatectomy versus LDP versus RDP, even though RDP results in higher rates of spleen preservation [13,69,70].

In line with results from the existing literature, the current study reports no difference in POPF occurrence when comparing LDP and RDP.

Overall morbidity as well as individual postoperative variables, such as severe complications (Clavien-Dindo ≥ 3) fluid collections, postoperative hemorrhage, SSI, reoperation, readmission and mortality, were found to be equal in the LDP and RDP groups.

In this study, no difference was noted between LDP and RDP groups regarding positive resection margins, while greater yield of lymph nodes was found in the RDP group.

It is widely known in the surgical oncology community that R0 resection in pancreatic cancer, defined as complete resection of the tumor with negative resection margins as determined by histopathology, is associated with better median survival time and 5-year survival rate [71-73]. Lymph node pathologic examination is an integral part of disease staging for pancreatic cancer [74]. As a consequence, the number of lymph nodes that the surgeon can harvest during surgery is an important tool to assess the effectiveness of the surgical method implemented.

As LDP has been previously found to be equally effective with open distal pancreatectomy in regards to R0 resection and lymph node yield [75], we can conclude that RDP can be effectively and safely implemented in pancreatic cancer care by experienced surgeons.

One of the most important advantages of MIS is shorter time needed for recovery [65]. Thus, evaluation of the LOS is an important parameter when analyzing such procedures. In the current study, LOS was significantly shorter in the RDP group. This could be an argument in favor of the robot when considering the overall cost effectiveness [13].

Robotic MIS has always been considered more costly than its laparoscopic counterpart [76], but data addressing cost-effectiveness specifically for RDP are not widely available. The majority of the studies on the subject report significantly higher operative cost for the robotic group when comparing RDP with LDP [13,31,42,77]. On the other hand, some authors argue that when total hospitalization costs are taken into consideration RDP seems to be as cost-effective as LDP [42,77].

This meta-analysis found that RDP is not only associated with higher operative costs but also with higher total hospitalization costs.

The present meta-analysis had some limitations that should be taken into consideration. Importantly, most of the studies included were nonrandomized and the majority were retrospective in their design, thus potentially introducing some selection bias. Furthermore, we only included studies written in English and as a result, we may have excluded possibly relevant studies written in other languages. Finally, heterogeneity was high in most of the analyses performed.

To conclude, this meta-analysis demonstrates the potential of RDP to become a widespread, viable option for both benign and malignant pancreatic disorders. Further investigation through multicentric Randomized Controlled Trials is needed to conclusively assess the safety and feasibility of RDP.

Conflict of interests

The authors declare no conflict of interests.

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