

A meta-analysis of robotic-assisted pancreatectomy versus laparoscopic and open pancreatectomy

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ABSTRACT

الأهداف: يستخدم استئصال البنكرياس بالروبوت بشكل متكرر. لكن الدراسات التي تنطرق إلى استئصال البنكرياس بالروبوت تعد قليلة لحجم العينة الصغير ومؤسسة صحية واحد.

الطريقة: قمنا بإجراء بحث الاللكترونية باستخدام محرك بحث المكتبة الأمريكية والإمبيس لمقارنة الدراسات التي تستخدم الروبوت لاستئصال البنكرياس أما عن طريق المنظار أو طريق الفتحة لمرضى البنكرياس خلال الفترة من يونيو ٢٠٠٠م حتى يونيو 2012م. تم جمع المتغيرات باستخدام اختلاف المتوسط SD نسبة OR وجمعت المتغيرات الثنائية باستخدام طريقة RP. كانت نسبة الثقة في كل الاختبارات الإحصائية ٩٥٪. وجدنا ٤ دراسات مناسبة للدراسة والتي تقارن استئصال البنكرياس بالروبوت و المنظار و ٤ دراسات تقارن الروبوت بطريقة الفتحة.

النتائج: كان هنالك ٦ دراسات تطابق معايير الدراسة وأظهرت نتائج الدراسة أن استئصال البنكرياس بالروبوت يقلل من خسارة الدم ومدة التنويم في المستشفى بشكل أكثر من استئصال البنكرياس بطريقة الفتحة. وبالنسبة لناسور البنكرياس لم تظهر أي اختلافات إحصائية بين الروبوت والمنظار والفتحة، كما لم تظهر اختلافات إحصائية في معدل التحويل أثناء العملية بين الوبوت والمنظار. كما أن استئصال البنكرياس بالروبوت يرفع من معدل البتر ومعدل المحافظة على الطحال.

خاتمة: ارتبط استئصال البنكرياس بالروبوت مع ارتفاع معدلات البتر ومعدل المحافظة على الطحال بالمقارنة مع المنظار وطريقة الفتحة. إضافة إلى ذلك، استئصال البنكرياس بالروبوت يقلل من معدل خسارة الدم ومدة الإقامة في المستشفى أكثر من الطريقة المفتوحة. أن طريقة استئصال البنكرياس بالروبوت مناسبة للمرضى المصابين بأمراض البنكرياس.

Objectives: To perform a meta-analysis of eligible studies from multiple medical centers to assess the safety, feasibility, and efficacy of robotic-assisted pancreatectomy (RP).

Methods: We searched the electronic databases PubMed and EMBASE for studies comparing RP with laparoscopic pancreatectomy (LP) and open

pancreatectomy (OP) for patients with pancreatic disease from June 2009 to June 2012. Continuous variables were pooled using the standardized mean difference (SMD) and odds ratio (OR), and dichotomous variables were pooled using the risk difference (RD) method. For all analyses, the 95% confidence interval (CI) was calculated. Three studies comparing RP and LP, and 4 studies comparing RP and OP were suitable for meta-analysis.

Results: Six published studies met the inclusion criteria. Our results showed that RP can reduce estimated blood loss and duration of hospitalization more than OP. For pancreatic fistula, there were no statistical differences between RP, OP, and LP, and no significant differences in intraoperative conversion rates between RP and LP. Robotic-assisted pancreatectomy may be able to increase microscopic negative margins of resection (R0) and spleen preserving rates.

Conclusion: Robotic-assisted pancreatectomy was associated with increased R0 resection rates and spleen preserving rates than LP and OP. Moreover, RP can reduce estimated blood loss and duration of hospitalization more than OP. A robotic approach to pancreatectomy may be suited to patients with pancreatic disease.

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Since the introduction of laparoscopic pancreatectomy (LP) in 1994, the laparoscopic approach has become one of the most popular pancreatic resection approaches and even out numbers traditional open surgery in some centers.¹ Collectively, several reports suggest that LP has resulted in better post-operative outcomes, such as reduced blood loss and length of hospital stays, than open pancreatectomy (OP) in patients with pancreatic diseases.^{2,3} Despite the success, inherent limitations of LP confused surgeons including the usage of non-articulated instruments, working in confined spaces, and lacking the perception of depth.⁴ Currently, the advent of the da Vinci robotic surgical system has allowed surgeons to overcome several inherent limitations of laparoscopic surgery.⁵ Compared with LP, robotic, minimally invasive surgery has some advantages, including augmented dexterity, tremor filtration, and 3-D imaging.⁶ These advantages allow more accurate and precise surgical procedures. To date, for gynecologic, cardiothoracic, urologic surgery, and cholecystectomy, numerous studies reported that robot-assisted surgery has advantages than laparoscopic and open surgery.⁷⁻⁹ Several studies also reported the clinical application of robotic-assisted pancreatectomy (RP) for pancreatic diseases.¹⁰⁻¹² However, most studies reporting RP have been limited by small sample size and single-institution design. Therefore, we performed a meta-analysis of eligible studies to assess the safety, feasibility, and efficacy of the da Vinci robotic surgical system for pancreatectomy. Most of previous retrospective analyses mainly pay attention to comparing LP and OP. It seems that LP can get a better clinical outcome than OP.³ However, few systematic review studies are concerned with comparing the advantages and disadvantages between RP with OP and LP. It is unknown whether costly RP is superior to LP and traditional OP. In this article, we focused on comparing the estimated blood loss, duration of hospitalization, pancreatic fistula, spleen preserving, and intraoperative conversion rates between RP and both OP and LP. Through our study, we want to know the pros and cons of 3 different pancreatic surgical procedures, and provide reference for surgeons.

Methods. We searched the electronic databases PubMed and EMBASE for studies published from June 2009 to June 2012 comparing RP with LP and OP for patients with pancreatic disease. We utilized the search terms “humans”, “robotic”, “pancreatic” and “pancreas”, and we used both free text and MeSH searches for keywords. We also manually searched the abstracts presented at major international conferences.

In addition, the reference lists in selected articles were searched manually. There was no location and language restriction, except that abstracts not written in English were excluded.

Data search, extraction, and criteria of inclusion and exclusion referred to previous articles.^{3,13} The search was carried out by 2 reviewers independently. Eligible studies were examined to extract the following information: the last name of the first author, the year of publication, the type of study, characteristics of the study population, the indications of operation, the number of patients who underwent surgery with each technique, the rate of conversion from da Vinci robotic surgical system to open techniques, and the rate of conversion from laparoscopic to open technique. The characteristics of the included studies are shown in Table 1. In addition, we recorded perioperative and postoperative outcomes, including operating time, estimated blood loss, duration of hospitalization, postoperative complications, and total hospitalization costs.

To enter our analysis, studies had 1) to compare characteristics and perioperative outcomes of patients undergoing RP, OP, or LP and 2) to involve a previously unreported patient group (if patient material was reported more than once by the same institution, only the most recent and informative article was included). It is best to select randomized controlled trial (RCT) articles, and case-matched studies also can be included. However, strengths of the case-matched articles, comparability of cases and controls, and adequacy of follow-up should be considered. Unmatched studies were excluded from this study, as their results are more likely to be biased.

The following studies were not considered for meta-analysis: 1) studies in which the outcomes of interest were not reported or were impossible to calculate for RP, OP and LP; 2) studies not designed to compare RP with LP and OP; and 3) studies only focusing on robotic or laparoscopic procedures or skills.

Statistical analysis. Continuous variables were pooled using the standardized mean difference (SMD) and odds ratio (OR) methods, and dichotomous variables were pooled using the risk difference (RD) method. In studies reporting only the median, range, and size of the trial, the means and standard deviations (SD) were calculated.¹⁴ If necessary, the mean and SD were pooled using the method provided by Killeen.¹⁵

Statistical heterogeneity between studies was evaluated using the χ^2 test and the I² statistic.¹⁶ Heterogeneities <25, 25-50, and >50 % were defined as low, moderate, and high, respectively.¹⁷ A random effects model was used for studies with high statistical

heterogeneity and a fixed effects model was used for studies with low or moderate statistical heterogeneity.¹⁸ Potential causes of heterogeneity were explored by carrying out sensitivity and sub-group analyses. Sensitivity analysis was performed by replacing a value of effect with another, or by removing individual studies from the data set. We also analyzed the effect on the overall results to identify sources of significant heterogeneity. Publication bias among the included studies was assessed graphically by funnel plots.

For all analyses, the 95% confidence interval (CI) was calculated. The CI throughout the study was set at 95 %. A *p* value of <0.05 was considered statistically significant. All statistical analyses were performed by Stata 12.0 (Stata, College Station, Texas, USA).

Results. A flowchart outlining our outcome definitions following Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines is presented in Figure 1.¹⁹ Three studies comparing RP and LP published between 2010 and 2012²⁰⁻²² met the inclusion criteria and were suitable for meta-analysis (group 1). The pathological indications for surgery on patients in study were benign or malignant lesions. Interestingly, all of the 3 studies focused on comparing RP with LP for distal pancreatectomy. Two of these studies were conducted in the United States, and one in Korea. The reports primarily described retrospective studies of comparable patients. In these studies, 67 patients underwent RP and 137 patients underwent LP. Four studies comparing RP and OP published between

Table 1 - Main characteristics and results of the eligible studies.

Author	Year	Country	Study size (n)			Gender (F)		Age (y) (mean±SD)		Location*
			Total	RP	LP/OP	RP	LP/OP	RP	LP/OP	
Kang et al ²⁴	2010	Korea	45	20	25	12	14	44.5±16	56.5±14	Distal
Zhou et al ²⁵	2011	China	16	8	8	4	3	64.4±9	59.4±9	Neck
Waters et al ²²	2010	America	57	17	18/22	11	9/12	64±NS	59/59±NS	Distal
Boggi et al ²³	2012	Italy	8	3	5	3	2	41.6±12	47.4±15	Neck/body
Kang et al ²⁰	2011	Korea	15	5	10	0	6	50±12	38.7±13	Neck/body
Daouadi et al ²¹	2012	America	124	30	94	20	61	59±13	59±16	Distal

*lesion location, RP - robotic-assisted pancreatectomy, LP - laparoscopic pancreatectomy, OP - open pancreatectomy, NS - no state, Distal - distal pancreas, Neck - pancreatic neck, body - pancreatic body.

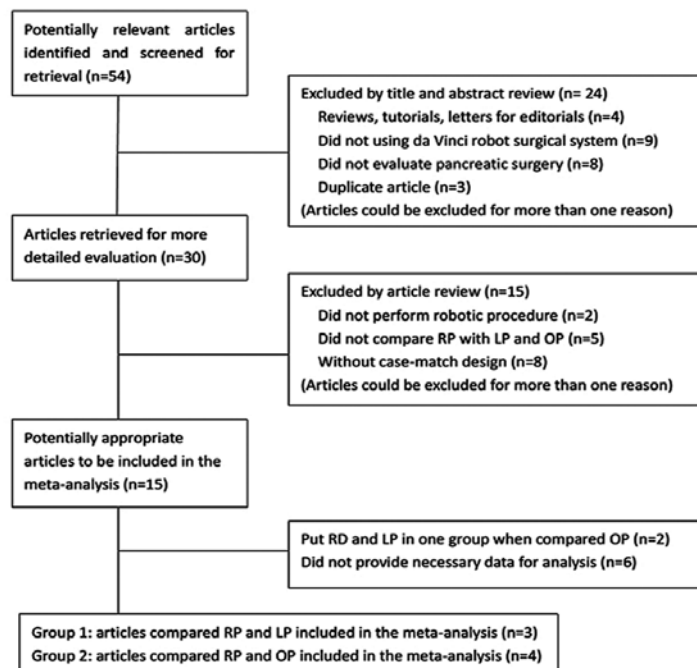


Figure 1 - A flow diagram detailing the search process (one article was included both in Group 1 and Group 2). RP - robotic-assisted pancreatectomy, LP - laparoscopic pancreatectomy, OP - open pancreatectomy

2010 and 2012²²⁻²⁵ met the inclusion criteria and were suitable for meta-analysis (group 2). One of these studies was conducted in the United States, one in Italy, and one in Korea, one in China. In these studies, 33 patients underwent RP and 45 patients underwent OP. The 2 reviewers had 100% agreement in their review of the data extraction.

Operating time. In group 1, all of the studies provided information on operating time. For patients undergoing RP, the mean operating time was 310.9 min and for LP was 331.8 min. There was no significant statistical difference for operating times between RP and LP (SMD 0.44; 95% CI -0.73 to 1.61; $p=0.462$) (Figure 2A). Because of the evidence of heterogeneity among studies ($p=0.000$, $I^2=91.9\%$), a random effects model was used. In group 2, all of the articles reported information on operating time. For patients undergoing RP, the mean operating time was 432 min and for OP was 286.4 min. There was a significant statistical difference for operating times between RP

and OP (SMD 1.79; 95% CI 0.71 to 2.86; $p=0.001$) (Figure 2A). Because of the evidence of heterogeneity among studies ($p=0.038$, $I^2=64.8\%$), a random effects model was used.

Estimated blood loss. In group 1, all of the studies provided information on estimated blood loss. For patients undergoing RP, the mean blood loss was 249 ml and, for LP was 267.2 ml. There was no significant statistical difference for blood loss between RP and LP (SMD -0.09; 95% CI -0.39 to 0.21; $p=0.542$) (Figure 2B). Because there was no evidence of heterogeneity among studies ($p=0.741$, $I^2=0.00\%$), a fixed effects model was used. In group 2, 3 articles reported information on blood loss. For patients undergoing RP, the mean blood loss was 244.9 ml and, for OP was 631.1 ml. There was a significant statistical difference for blood loss between RP and OP (SMD -0.87; 95% CI -1.38 to -0.37; $p=0.001$) (Figure 2B). Because there was no evidence of heterogeneity among

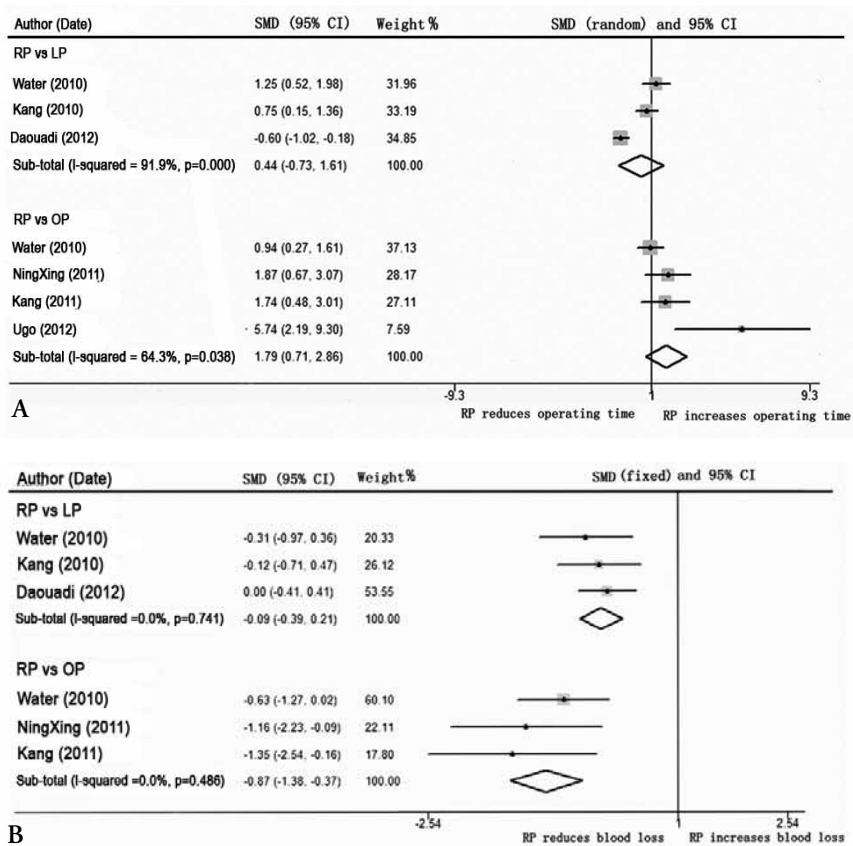


Figure 2 - Results of the meta-analysis regarding operating time and estimated blood loss comparing RP with LP and OP. A) Results of the meta-analysis regarding operating time; B) results of the meta-analysis regarding estimated blood loss. CI - confidence intervals, RP - robotic-assisted pancreatectomy, LP - laparoscopic pancreatectomy, OP - open pancreatectomy, SMD - standardized mean difference

studies ($p=0.486$, $I^2=0.00\%$), a fixed effects model was used.

Duration of hospitalization. In group 1, all of the studies provided information on hospital stay (days). For patients undergoing RP, the mean hospital stay was 5.9 days and for LP was 6.8 days. There was no significant statistical difference for hospital stay between RP and LP (SMD -0.17; 95% CI -0.47 to 0.13; $p=0.274$) (Figure 3A). Because there was no evidence of heterogeneity among studies ($p=0.734$, $I^2=0.00\%$), a fixed effects model was used. In group 2, all of the articles reported the length of postoperative hospitalization (days). For patients undergoing RP, the mean hospital stay was 9 days and, for OP was 14.4 days. There was a significant statistical difference for hospital stay between RP and OP (SMD -0.82; 95% CI -1.3 to -0.35; $p=0.001$) (Figure 3A). Because there was no evidence of heterogeneity among studies ($p=0.291$, $I^2=19.8\%$), a fixed effects model was used.

Pancreatic fistula. In group 1, only 2 studies provided information on pancreatic leak. Overall, 29.8% of patients (14/47) undergoing RP and 36.6%

of patients (41/112) undergoing LP experienced a pancreatic fistula (pooled RD 1.02; 95% CI 0.65 to 1.60; $p=0.929$) (Figure 3B). Because of the low heterogeneity among studies ($p=0.261$, $I^2=20.7\%$), a fixed effects model was used. In group 2, all of articles reported the rate of pancreatic leakage. Overall, 15.2% of patients (5/33) undergoing RP and 31.1% of patients (14/45) undergoing OP experienced a pancreatic fistula (pooled RD 0.539; 95% CI 0.237 to 1.223; $p=0.139$) (Figure 3B). Because of the low heterogeneity among studies ($p=0.446$, $I^2=0.0\%$), a fixed effects model was used.

Microscopic negative margins of resection (R0). In group 1, only 2 studies provided information on R0 resection. Overall, 80.8% of patients (38/47) undergoing RP and 46.4% of patients (52/112) undergoing LP had a surgery of R0 resection (pooled RD 1.935; 95% CI 1.355 to 2.746; $p=0.000$) (Figure 4A). In group 2, 2 articles reported the rate of R0 resection. Overall, 100% patients (25/25) undergoing RP and 76.7% patients (23/30) undergoing OP had a surgery of R0 resection (pooled RD 1.294; 95% CI 1.042 to 1.607; $p=0.02$)

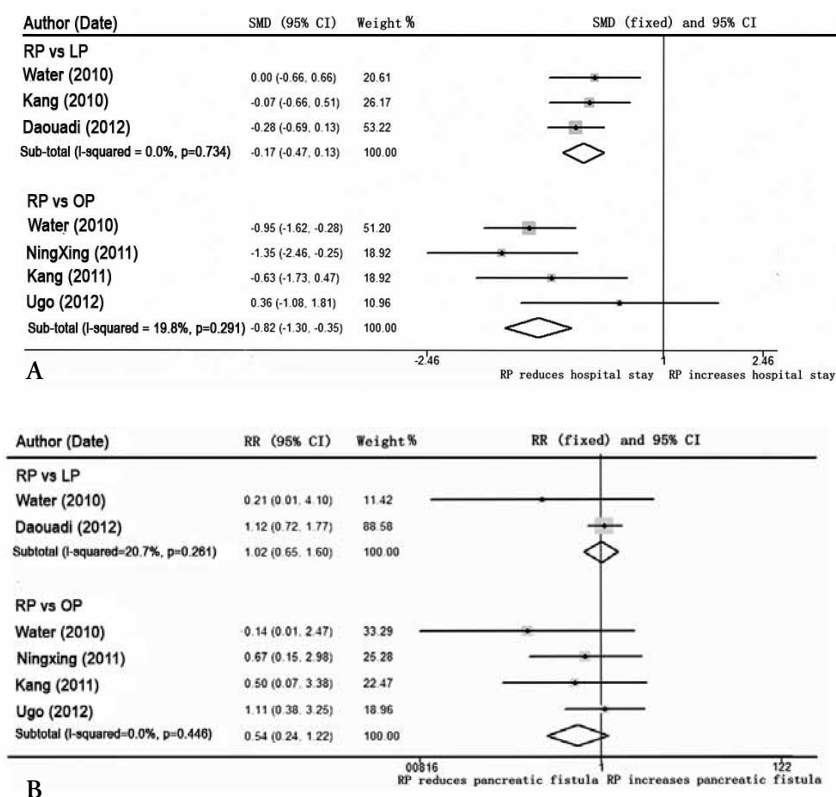


Figure 3 - Results of the meta-analysis regarding pancreatic leak and hospital stay comparing RP with LP and OP. A) Results of the meta-analysis regarding hospital stay; B) results of the meta-analysis regarding pancreatic leak. CI - confidence intervals, RP - robotic-assisted pancreatectomy, LP - laparoscopic pancreatectomy, OP - open pancreatectomy; SMD - standardized mean difference

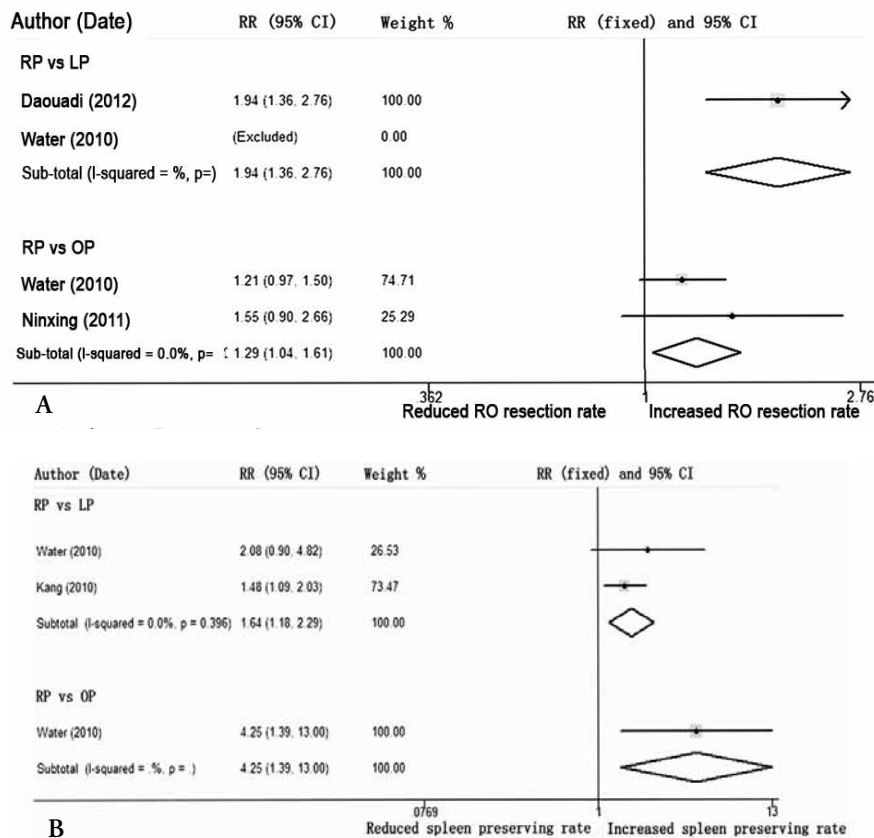


Figure 4 - Results of the meta-analysis regarding spleen preserving and R0 resection. A) Results of the meta-analysis regarding R0 resection; and B) results of the meta-analysis regarding spleen preserving. CI - confidence intervals, RP - robotic-assisted pancreatectomy, LP - laparoscopic pancreatectomy, OP - open pancreatectomy, SMD - standardized mean difference

(Figure 4A). Because of the low heterogeneity among studies ($p=0.79$, $I^2=0.00\%$), a fixed effects model was used.

Spleen-preserving. In group 1, 2 of the studies provided information on spleen-preserving. Overall, 76.9% of patients (30/39) undergoing RP and 51.2% of patients (21/43) undergoing LP had a spleen-preserving surgery (pooled RD 1.643; 95% CI 1.180 to 2.289; $p=0.003$) (Figure 4B). Because of the evidence of heterogeneity among studies ($p=0.72$, $I^2=0.00\%$), a fixed effects model was used. In group 2, only one article reported the rate of spleen preserving (RD 4.246; 95% CI 1.386 to 13.004; $p=0.011$) (Figure 4B).

Discussion. Pancreatic surgery has always been seen as a challenge for both the patient and the general surgeon. There are some important details surgeons should consider, such as retroperitoneal location, proximity to major vascular structures and meticulous surgical technique.²⁶ Although a laparoscopic pancreatic surgery has become accepted practice, it is

still a challenge for pancreatic surgeons for inherent limitations of the laparoscopic platform. The advent of robotic surgery has made it possible to perform more complex procedures, including pancreatic and biliary anastomoses, under good conditions of feasibility and safety.^{10,27} As an emerging field, RP has shown advantages over other surgical approaches, such as laparoscopic pancreatectomy and open pancreatectomy.^{12,27} Dimitrios et al reported that pancreatic robotic-assisted surgery can offer many practical advantages over other “classic” approaches.¹² Therefore, though the robotic surgery platform is costly, RP is performed with ever-increasing frequency worldwide.

To assess the safety, feasibility, and efficacy of RP, we tried to pool analysis of data comparing RP with LP and OP. Many clinical experiences with robotic surgery were reported, however, they mainly focused on surgical skills and retrospective clinical parameters. The prospective or case-matched study designs are few in number. Although this meta-analysis identified

numerous articles, we only identified 7 case-matched studies that fulfilled all the same inclusion criteria. We included 6 studies, 3 studies comparing RP and LP and 4 comparing RP and OP (one study compared both RP with LP and RP with OP). We found that operating time in patients undergoing pancreatic surgery was significantly longer for RP than for OP. The longer operating time for RP may in part reflect the early learning curve because this is a relatively new procedure that requires extensive experience in laparoscopic and open pancreatic surgery. As surgeons become more experienced, their time required for RP will decrease. There are other possible reasons, such as an increased set up time, difficult trocar positioning, and interruption by camera motion. When 2 minimally-invasive pancreatectomies were compared, RP, and LP which all need a set up time, and trocar positioning, difference for operating time was not observed. We found that estimated intraoperative blood loss was significantly less in patients undergoing RP than OP. Robotic-assisted pancreatectomy also caused less estimated blood loss than LP, but this difference did not reach statistical significance. In addition, the duration of hospitalization was shorter for patients undergoing RP than OP, but did not differ between RP and LP. Maybe the high-resolution 3-D imaging and the magnification of the operative field allow for more accurate dissection and surgical precision.^{28,29} More precise operative techniques may cause less blood loss and reduce duration of hospitalization. Another principle advantages stemming from a minimally-invasive approach may be a decrease in postoperative pain, (subsequently resulting in decreased use of narcotics, ileus, and morbidity from poor mobility).

A R0 (complete resection) resection is important for long-term oncologic outcomes and is always a main concern for many surgeons.²⁵ Besides, recently, the role of the spleen has been emphasized, and spleen-preserving distal pancreatectomy is thought to be a quite adequate surgery for pancreatic tumors.^{20,30} Based on our data, we observed that compared with LP, and OP, RP had a higher R0 resection rate and spleen-preserving rate. The unique properties of the robotic surgical system, such as increased maneuverability and 3-D visualization, may play an important role during the processes of R0 resection and preservation of the spleen.

A postoperative pancreatic fistula represents a major concern after pancreatectomy. Our meta-analysis showed, for pancreatic fistulas, no significant statistical differences between RP, OP, and LP. We also observed

no significant differences in intraoperative conversion rates between RP and LP. It should be noted that, after years of improvement of surgical techniques, there are many methods designed to prevent pancreatic fistulas in the processes of OP and LP.³¹ As an emerging technique, the rate of pancreatic fistula formation for RP is similar to LP and OP.

This study has a number of limitations that deserve attention. First, the number of studies and patients involved were relatively small, making it hard to perform subgroup analysis. Although this systematic review identified numerous case series, we only identified 7 case-matched studies that fulfilled all the inclusion criteria. Second, it is subject to the inherent bias of this study design. Included studies consisted only of non-randomized, case-matched studies. Most of these studies were biased, thus biasing the interpretation of their results. The comparison of robotic to laparoscopic and open pancreatectomy is fraught with selection bias. This is also true for whether patients had spleen preservation and/or margin negative resection since patient-specific factors that affect these variables will also guide the operative approach utilized by the pancreatic surgeon. Third, because of rare data, other important parameters, such as lymph nodes harvesting, morbidity rate, and operation cost, could not be included and pooled in this meta-analysis.

In conclusion, the current meta-analysis suggested that RP may be able to increase R0 resection and spleen preserving rates. Moreover, RP can reduce estimated blood loss and duration of hospitalization in comparison to OP. However, it should be noted that robotic minimally-invasive surgery increases the cost and adds to the operation time. A robotic approach to pancreatectomy has many advantages as compared with traditional surgery. However, these findings should be validated by more multicenter, randomized trials comparing RP with OP and LP.

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