Meta-Analysis of the Impact of the Learning Curve in Robotic Rectal Cancer Surgery on Histopathologic Outcomes

Meta-Analysis of the Impact of the Learning Curve in Robotic Rectal Cancer Surgery on Histopathologic Outcomes

Mahir Gachabayov, MD, PhD
Research Scholar
Section of Colorectal Surgery, New York Medical College
Westchester Medical Center
Valhalla, NY

Karen You, BS
Research Assistant
Department of Physiology and Biophysics
State University of New York
Stony Brook, NY

Seon-Hahn Kim, MD, PhD
Professor of Surgery, Director of Cancer Center
Korea University Anam Hospital
Seoul, Korea

Tomohiro Yamaguchi, MD, PhD
Head
Division of Colon and Rectal Surgery
Shizuoka Cancer Center Hospital
Shizuoka, Japan

Rosa Jimenez-Rodriguez, MD, PhD
Associate Head
Section of Colorectal Surgery
Hospital Universitario Virgen del Rocio
Sevilla, Spain

Li-Jen Kuo, MD
Head
Division of Colorectal Surgery
Department of Surgery
Taipei Medical University Hospital
Taipei, Taiwan

Fabio Cianchi, MD, PhD
Professor and Chief
Department of Surgery and Translational Medicine
Carreggi Hospital
University of Florence
Florence, Italy

Fabio Staderini, MD
Surgery Resident
Department of Surgery and Translational Medicine
Carreggi Hospital
University of Florence, Florence, Italy

Roberto Bergamaschi, MD, PhD
Professor of Surgery and Chief
Section of Colorectal Surgery
New York Medical College
Westchester Medical Center
Valhalla, NY

ABSTRACT

Introduction: Although the process of learning robotic surgery for rectal cancer is associated with a prolonged operating time and higher complication rates, its impact on histopathologic outcomes is unknown. The aim of this meta-analysis was to evaluate the impact of the learning curve in robotic surgery for rectal cancer on histopathologic outcomes.

Methods: The PubMed, EMBASE, Cochrane Library, MEDLINE via Ovid, CINAHL, and Web of Science databases were systematically searched. The inclusion criterion was any clinical study comparing the

outcomes of robotic surgery for rectal cancer between different phases of the learning curve (LC) including competence (C). The primary endpoint was the circumferential resection margin (CRM) involvement rate defined as CRM ≤1 mm. The Mantel-Haenszel method with odds ratios with 95% confidence intervals (OR (95%CI)) was used for dichotomous variables.

Results: Ten studies including a total of 907 patients (521 LC and 386 C) were selected. Nine studies were found to have a low risk of bias, and one had a moderate risk of bias. The CRM involvement rate was 2.9% (13/441) for learning curve vs. 4.6% (13/284) for competence. This difference was not significant (OR (95%CI) = 0.70 (0.30, 1.60); p=0.39; I2=0%).

Conclusion: A surgeon's learning curve seems to have no impact on CRM involvement rates compared to surgeon competence in robotic surgery for rectal cancer.

INTRODUCTION

At the turn of this century, the U.S. Food and Drug Administration (FDA) approved a robotic surgical system (RSS), which has since been used in thousands of operations.[1] However, questions have arisen in the literature about patient safety and the appropriate utilization of RSS.[2] In fact, a sudden increase in RSS-related adverse events was reported to the FDA's database between 2012 and 2013.[3] In 2013, the Emergency Care Research Institute included RSSs among the top 10 health technology hazards, blaming insufficient training.[4] In addition to training considerations, a small-sample FDA survey reminded everyone of the learning curve associated with RSSs. In fact, all participating surgeons who were experienced with RSSs confirmed that experience with several cases was required to achieve competence.[5] In the specific case of rectal cancer, attempts have been made to structure training [6] as well as to define the learning curve [7] in robotic rectal cancer surgery. The few reports that have analyzed the learning curve in robotic proctectomy for cancer have only studied operating time. Accordingly, it has been suggested that the learning curve should include 20 to 23 cases for surgeons with previous experience in conventional surgery.[8,9] However, a recent retrospective study suggested that skills acquired in laparoscopic rectal cancer surgery might have a beneficial impact on the learning curve in robotic rectal cancer surgery.[10] Moreover, a recent study found no association between prolonged operating time and morbidity rates.[11] Histopathology, rather than surrogate metrics, should guide our understanding of whether RSS may be in the best interest of patients with rectal cancer. It has been suggested that a potential benefit of robotic proctectomy may be the achievement of high rates of uninvolved circumferential resection margin (CRM), thanks to the ability of RSS wristed instruments to overcome the fulcrum effect created by the trocars and the confined space of the pelvis.[12]

In this study, we performed a meta-analysis to evaluate the impact of the learning curve in robotic surgery for rectal cancer on histopathologic outcomes.

MATERIALS AND METHODS

This systematic review was performed according to the Cochrane Handbook for Systematic Reviews of Interventions[13] and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[14,15] The protocol of this systematic review was developed *a priori* and registered in PROSPERO, the international prospective register of systematic reviews (CRD42018086633). The literature search, screening of full-text articles, inclusion and exclusion of screened records, quality assessment, data extraction and analysis, followed by critical appraisal, were performed by two independent researchers (MG and KY). Any disagreements during this process were discussed and resolved by the senior authors. The research question was formulated within the PICOTS framework as follows:

(P) Population: Adults older than 18 years old
(I) Intervention: Robotic surgery for rectal cancer during a surgeon's learning curve (LC)
(C) Comparator intervention: Robotic surgery for rectal cancer after a surgeon has achieved competence (C)
(O) Outcomes: Pathologic and clinical outcomes.
(T) Time: Short-term
(S) Setting: In- and outpatient

Eligibility criteria, Definitions and Endpoints

The inclusion criterion for this systematic review was all clinical studies that compared the outcomes of robotic surgery for rectal cancer between different phases of the learning curve. Exclusion criteria were any studies involving the same subjects, technical notes and summary design studies, and studies that compared any of the interventions of interest to an intervention irrelevant to this study, such as laparoscopic surgery for rectal cancer.

The learning curve was defined as any phase of the learning process preceding competence. The learning curve could have two or more phases, such as the initial learning phase and plateau

Supplement 1.
Search strategy. PubMed

("robotics"[MeSH Terms] OR "robotics"[All Fields] OR "robotic"[All Fields]) AND ("rectal neoplasms"[MeSH Terms] OR ("rectal"[All Fields] AND "neoplasms"[All Fields]) OR "rectal neoplasms"[All Fields] OR ("rectal"[All Fields] AND "cancer"[All Fields]) OR "rectal cancer"[All Fields]) AND ("learning curve"[MeSH Terms] OR ("learning"[All Fields] AND "curve"[All Fields]) OR "learning curve"[All Fields])
Records found: 77

phase. Circumferential resection margin was determined microscopically and expressed in mm. CRM was considered to be involved if it was ≤1 mm. Quality of total mesorectal excision (TME) was assessed macroscopically by pathologists and based on the number and size of defects in the mesorectal fascia. Surgical site infections (SSI) were defined according to the Centers for Disease Control (CDC) National Nosocomial Infections Surveillance System.[16] Anastomotic leak was defined as clinical features of peritoneal irritation with bowel content, direct visualization of bowel content in draining tubes, and/or radiological extravasation of intraluminal contrast through an anastomotic defect.

The primary endpoint of this systematic review was the CRM involvement rate.

Secondary endpoints were

- Pathologic endpoints: Number of lymph nodes harvested, distal margin, CRM in mm, and TME quality.
- Clinical endpoints: Intraoperative (operating time, docking time, surgeon console time, conversion rate, estimated blood loss) and postoperative (postoperative complication rate, anastomotic leak rate, time to first flatus, time to soft diet resumption, length of hospital stay, and readmission rate).

Search strategy and study selection

The PubMed, EMBASE, Cochrane Library, MEDLINE via Ovid, CINAHL, and Web of Science databases were systematically searched using the following MeSH terms: 'robotic', 'rectal cancer', and 'learning curve' combined with the Boolean operator 'AND' and all synonyms combined with the Boolean operator 'OR'. In addition, clinicaltrials.gov was searched for any ongoing studies. Relevant articles were identified, and the results of the search were

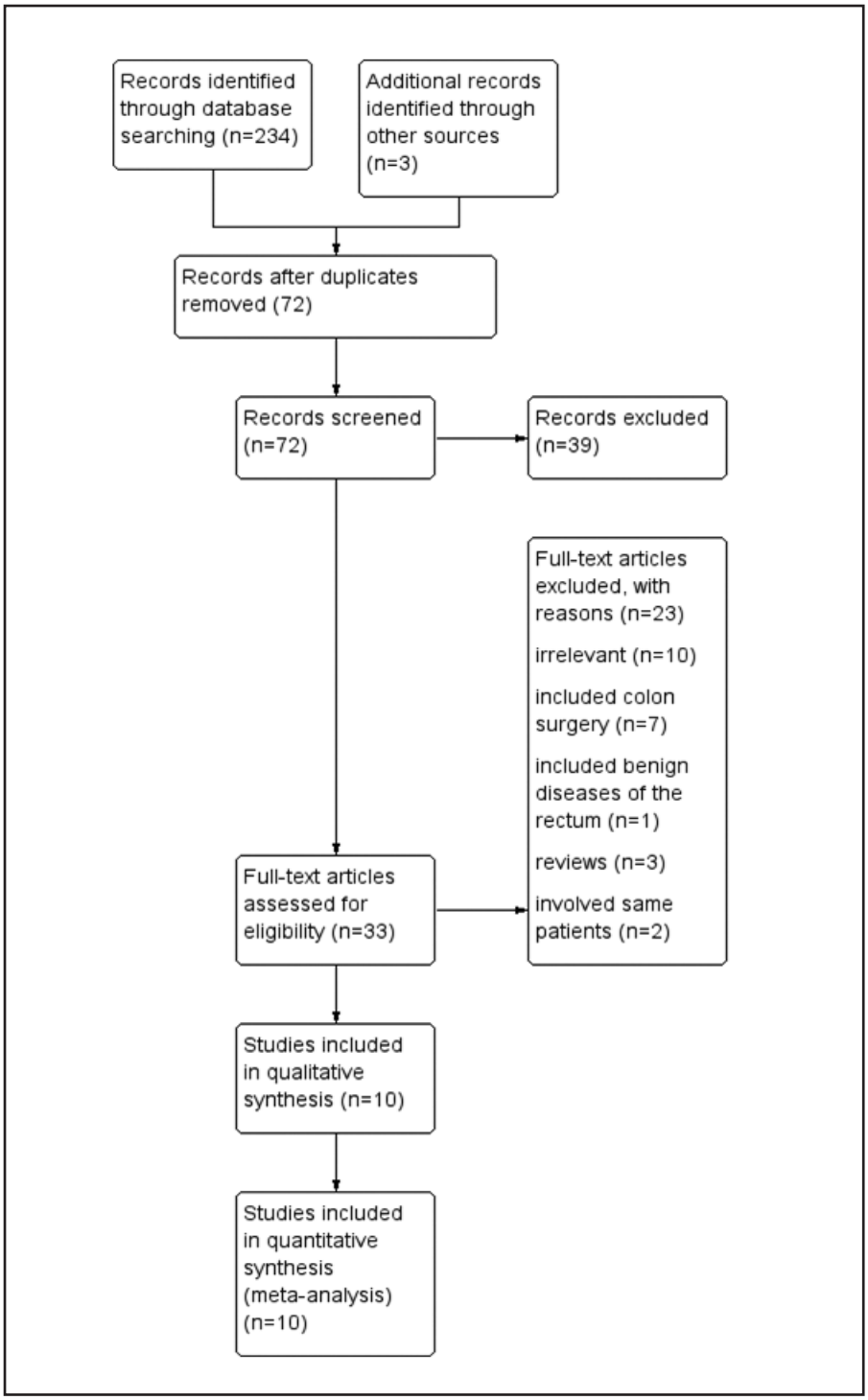


Figure 1. PRISMA flow diagram.

Table I
Characteristics of included studies

Author	Publication	Country	Study design	Sample size (LC vs C) 521 vs. 386	Number of surgeons	CUSUM analysis employed	Procedures	Tumor distance from AV	CRM involvement	Oxford CEBM evidence level
Akmal	Surg Endosc 2012	USA	Prospective cohort (2004-2009)	40 vs. 40	1	No	LAR, APR	Mid and low rectum	Not involved/ Involved	2b
Foo	World J Surg 2016	Hong Kong	Prospective cohort (2013-2014)	25 vs. 14	1	Yes	LAR, APR, HP	7.5 (1.0-12.0) cm*	Not involved/ Involved	2b
Huang	Medicine 2017	Taiwan	Prospective cohort (2012-2015)	20 vs. 20	NR (same team)	No	LAR, ULAR, ISR	Within 10 cm from the AV	1 mm	2b
Jimenez-Rodriguez	Int J Colorectal Dis 2013	Spain	Retrospective cohort (2009-2012)	21 vs. 22	3	Yes	AR, APR	9.1 ± 4.1 cm#	1 mm	2b
Kim	Surg Laparosc Endosc Percutan Tech 2012	South Korea	Retrospective cohort (2004-2010)	20 vs. 42	1	No	LAR, ULAR, APR, HP	23% high rectum, 77% mid and low rectum	1 mm	2b
Kim	Int J Colorectal Dis 2014	South Korea	Prospective cohor t	120 vs. 80	2	No	LAR	9.7 and 8.8 cm#	1 mm	2b
Kuo	Int J Colorectal Dis 2014	Taiwan	Prospective cohort (2009-2013)	19 vs. 17	1	Yes	ISR	3.8 cm*	1 mm	2b
Park	Surg Endosc 2014	South Korea	Prospective cohort (2006-2011)	78 vs. 52	1	Yes	LAR	29% high, 45% mid, and 26% low rectum	1 mm	2b
Sng	Surg Endosc 2013	South Korea	Prospective cohort (2006-2011)	128 vs. 69	1	Yes	AR, LAR, ULAR, ISR, APR	6 (0-15) cm*	1 mm	2b
Yamaguchi	Surg Endosc 2015	Japan	Prospective cohort (2011-2013)	50 vs. 30	1	Yes	AR, LAR, ISR, APR	16% high, 15% mid, and 69% low rectum	0 mm	2b

* median; # mean; NR, not reported; LC, learning curve; C, competence; CUSUM, cumulative sum analysis; AV, anal verge; CRM, circumferential resection margin; AR, anterior resection of the rectum; LAR, low anterior resection of the rectum; ULAR, ultra-low anterior resection of the rectum; ISR, intersphincteric resection of the rectum; APR, abdominoperineal excision of the rectum; HP, Hartmann's procedure; NOS, Newcastle-Ottawa Quality Assessment Scale for cohort studies; S, selection; C, comparability; O, outcome; CEBM, Center for Evidence-Based Medicine.

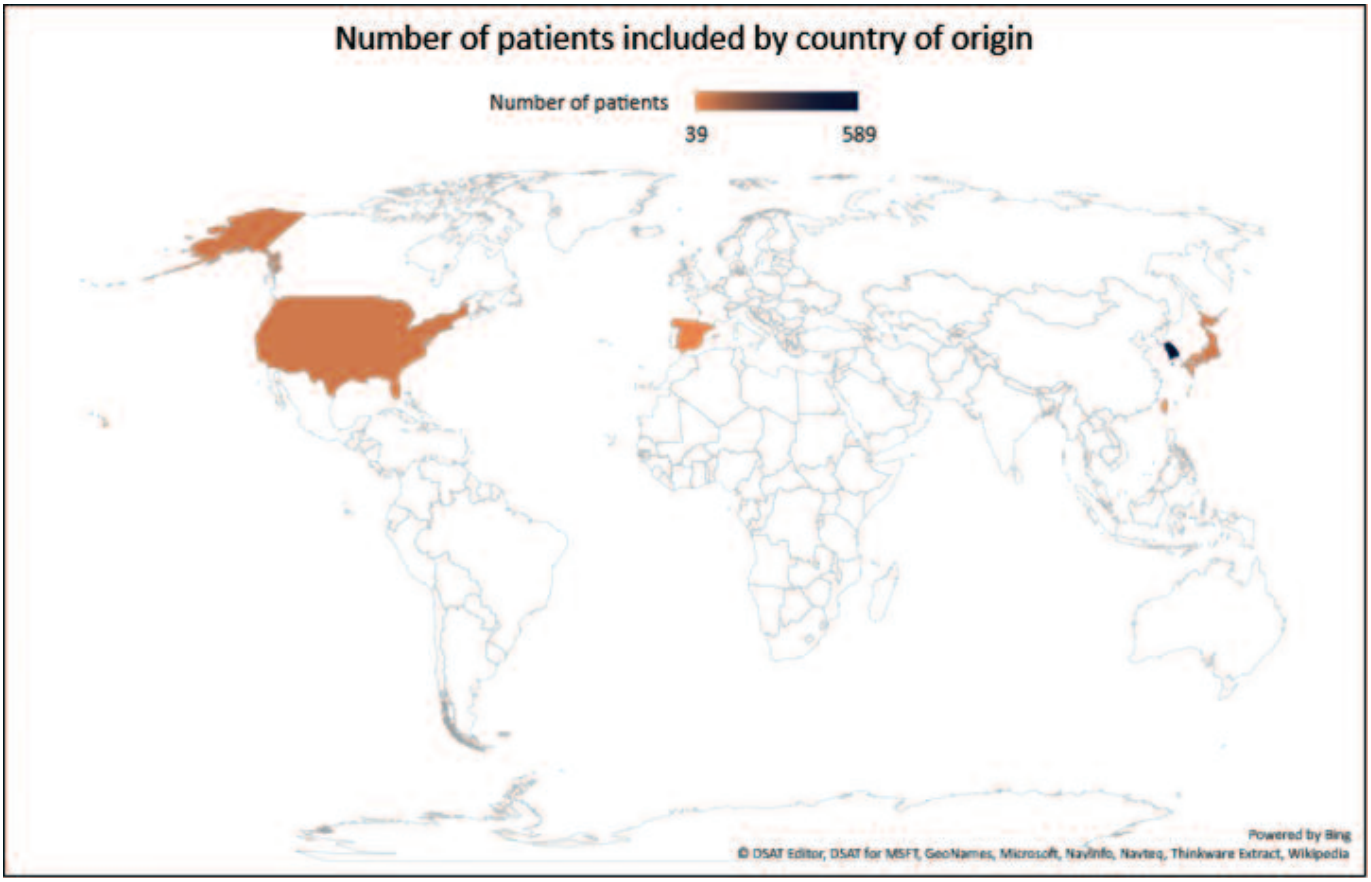


Figure 2. Number of included patients by country.

screened through the title, abstract and/or full-text article. The sensitivity of the search strategy was assessed by screening the references of included articles for additional publications.

Data extraction and quality assessment

The data from the included articles were extracted to predefined Microsoft Excel (Microsoft Inc., Redmond, WA, USA) spreadsheets and studies were assessed for validity by two researchers independently. Collected data included author, year of publication, study design, sample size, definition of learning curve, pathologic data (CRM involvement rate, CRM, TME quality, distal margin, number of lymph nodes harvested), and clinical data (operating time, docking time, surgeon console time, postoperative morbidity, anastomotic leak rate, SSI rate, length of hospital stay, readmission rate). The quality of each individual study was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions in terms of the following items: selection, performance, detection, attrition, selective reporting, and other bias risks.[13] In cases where additional data were needed, the senior authors of the included studies were contacted and asked for deidentified patient-level data.

Statistical analysis

The inverse variance method with point estimates for standardized mean differences and 95% confidence intervals (MD (95%CI)) was used for continuous variables, whereas the Mantel-Haenszel method with odds ratios with 95% confidence intervals (OR (95%CI)) was used for dichotomous variables. In cases where continuous variables were reported in median and interquartile range, mean and standard deviation (SD) were estimated using Hozo's formula.[17] Statistical heterogeneity among effect estimates was assessed using Cochran Chi^2 and I^2, and between-study variance was assessed using the Tau^2 statistic when I^2 was 50% or greater.[18] A random-effects model of meta-analysis was used to synthesize the meta-data. The results of the meta-analysis were illustrated on forest plots. To assess the clinical significance of the results, relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat/harm (NNT) with 95%CI were calculated. Funnel plots of standard error, funnel plots of precision by log OR, Egger's test, and Begg and Mazumdar rank correlation tests were used to evaluate for publication bias. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using RevMan (version 5.3; Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark) and CMA Software (Version 3; Biostat, Englewood, NJ, USA).

RESULTS

Literature search and study selection

The details of the search strategy are shown in Supplement 1 and the details of study selection are presented in a PRISMA flowchart (Figure 1). The six searched databases revealed 234 records. Three additional articles were found among the references of eligible studies. Ten articles were included after excluding duplicates, irrelevant articles,

Supplement 2
Studies included in the quantitative analysis of different endpoints.

Pathologic endpoints	
CRM involvement rate	Foo 2016, Jimenez-Rodriguez 2013, Kim 2014, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Number of lymph nodes harvested	Foo 2016, Jimenez-Rodriguez 2013, Kim 2012, Kim 2014, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Distal margin	Foo 2016, Jimenez-Rodriguez 2013, Kim 2012, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Incomplete TME quality rate	Foo 2016, Jimenez-Rodriguez 2013, Kuo 2014, Yamaguchi 2015
CRM	Jimenez-Rodriguez 2013, Kuo 2014
Local recurrence rate	Jimenez-Rodriguez 2013, Kuo 2014, Park 2014, Sng 2013
CRM, circumferential resection margin; TME, total mesorectal excision.	
Clinical endpoints: Intraoperative variables	
Operating time	Foo 2016, Huang 2017, Jimenez-Rodriguez 2013, Kim 2012, Kim 2014, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Docking time	Foo 2016, Jimenez-Rodriguez 2013, Park 2014, Yamaguchi 2015
Surgeon console time	Foo 2016, Jimenez-Rodriguez 2013, Kim 2012, Park 2014, Yamaguchi 2015
Conversion rate	Akmal 2012, Foo 2016, Jimenez-Rodriguez 2013, Kim 2012, Kim 2014, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Estimated blood loss	Foo 2016, Huang 2017, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Intraoperative complication rate	Jimenez-Rodriguez 2013, Yamaguchi 2015
Clinical endpoints: Postoperative variables	
Overall postoperative morbidity	Akmal 2012, Foo 2016, Huang 2017, Jimenez-Rodriguez 2013, Kim 2012, Kim 2014, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Anastomotic leak rate	Akmal 2012, Jimenez-Rodriguez 2013, Kim 2014, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Time to first flatus	Huang 2017, Jimenez-Rodriguez 2013, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Time to soft diet resumption	Huang 2017, Jimenez-Rodriguez 2013, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Length of hospital stay	Foo 2016, Huang 2017, Jimenez-Rodriguez 2013, Kuo 2014, Park 2014, Sng 2013, Yamaguchi 2015
Readmission rate	Foo 2016, Jimenez-Rodriguez 2013, Kuo 2014, Sng 2013, Yamaguchi 2015

and articles that did not report the outcome of interest.

Description of the included studies

Ultimately, 10 studies were selected from among 33 potentially eligible studies[19-28] totaling 907 patients (521 LC and 386 C). The characteristics of the included studies are provided in Table I. All 10 studies were cohort studies with an evidence level of 2b (8 prospective and 2 retrospective cohort studies).[19-28] All of the included studies were published after 2012. Eligible articles that reported the outcomes of patients operated on by the same surgeon or in the same institution with an overlapping study span were excluded.[29,30] Studies involving patients with benign disease or colon cancers along-

Supplement 3
NHLBI quality assessment tool for before-after (pre-post) studies with no control group: criteria

Criteria	Scale Items
Was the study question or objective clearly stated?	1
Were eligibility/selection criteria for the study population pre-specified and clearly described?	2
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	3
Were all eligible participants that met the pre-specified entry criteria enrolled?	4
Was the sample size sufficiently large to provide confidence in the findings?	5
Was the test/service/intervention clearly described and delivered consistently across the study population?	6
Were the outcome measures pre-specified, clearly defined, valid, reliable, and assessed consistently across all study participants?	7
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	8
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	9
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	10
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	11
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level? *If this question is not applicable, total score is out of 11, not 12.	12
Y = Yes, N = No, NR = Not reported, CD = Cannot determine, NA = Not applicable, M = Moderate Add scores for each criterion together and divide by 12. Risk of bias rating (Low (75-100%), Moderate (25-75%), or High (0-25%))* OVERALL SCORE:	

Table II
Quality assessment of included studies using NHLBI quality assessment tool for before-after (pre-post) studies with no control group

NHLBI criterion	Akmal 2012	Fooű 2016	Huang 2017	Jimenez-Rodriguez 2013	Kim ű2012	Kim 2014	Kuo 2014	Park 2014	Sng 2013	Yamaguchi 2015
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Y	N	Y	Y	Y	Y	N	Y	Y	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	N	NR	NR	Y	NR	NR	Y	NR	Y	Y
9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10	N	N	Y	Y	N	N	N	N	N	N
11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Risk of bias rating	80% Low	70% Mod.	90% Low	100% Low	80% Low	80% Low	80% Low	80% Low	90% Low	90% Low

NHLBI, National Heart, Lung, and Blood Institute; Y, yes; N, no; NR, not reported; NA, not applicable; Mod., moderate.

side those with rectal cancer were also excluded.[31-34]

Description of the study populations and interventions

The patients in the 10 included studies were adults from 6 countries (USA, Hong Kong, Taiwan, Spain, South Korea, and Japan) (Figure 2). The patients had similar baseline characteristics. The studies stratified according to the reported endpoints are shown in Supplement 2. In seven of the 10 included studies, all procedures were performed by the same surgeon.[19,20,23,25-28] The procedures were performed by two surgeons in one study,[24] and by three surgeons in another study.[22] In one study, all procedures were performed by the same team, but the number of surgeons was not reported.[21] The learning curve was found to consist of 3 phases in six studies,[20,22,24,26-28] 2 phases in three studies,[19,21,25] and 6 phases in one study.[23] Anterior, low anterior, and ultralow anterior resection of the rectum was performed in nine of the 10 studies.[19-24,26-28] One study included only patients with intersphincteric resection of the rectum.[25] Six studies included patients with abdominoperineal resection of the rectum[19,20,22,23,27,28] and two studies included patients with Hartmann's procedure.[20,23] The number of surgeons, phases of the learning curve, and procedures are summarized in Table I.

Quality assessment

All of the included studies provided a 2b level of evidence according to the Oxford Centre for Evidence Based Medicine (CEBM) (Table I). The National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool for before-after (pre-post) studies with no control group was used. Criteria and scoring principles of the NHLBI quality assessment tool are provided in Supplement 3. Quality assessment findings are presented in Table II. Nine studies had a low risk of bias,[19,21-28] and one had a moderate risk of bias.[20] Figure 3 summarizes the risk of bias and presents a graph of the included studies. The selection bias in pre-post design studies was considered to be low when an objective criterion was used to allocate patients between the LC and C groups. The objective criterion in our study was a cumulative sum (CUSUM) analysis. The risk of selection bias was low in six studies,[20,22,23,25,27,28] and was considered to be high in the remaining four studies.[19,21,24,26] The risk of performance and detection bias was high in almost all of the studies. It is impractical to try to prevent performance and detection bias by blinding surgeons to the intervention and assessment of the outcome. Attrition, reporting, and other bias risks were either low or unclear.

META-ANALYSIS

CRM involvement rate

CRM involvement was defined as CRM of ≤1 mm. The CRM involvement rate was reported in 7 studies (441 LC vs. 284 C).[20,22,24-28] In a study from Japan, a positive resection margin was considered to be involved CRM.[28] Statistical among-study heterogeneity was low (I^2=0%). The CRM involvement rate was 2.9% (13/441) in LC vs. 4.6% (13/284) in C. This difference was neither statistically nor clinically significant (OR (95%CI) = 0.70 (0.30, 1.60); p=0.39; NNT (95%CI) = 62 (> 22.1 to benefit, > 78.8 to harm)) (Figure 4) (Table III).

Number of lymph nodes harvested

The number of lymph nodes harvested was reported in 8 studies (461 LC vs. 326 C).[20,22-28] Statistical among-study heterogeneity was low (I^2=3%). No statistically significant difference was found between LC and C (MD (95%CI) = 0.04 (-1.30, 1.39); p=0.95) (Figure 5a).

Distal margin

The distal margin was reported in 7 studies (341 LC vs. 246 C).[20,22,23,25-28] Statistical among-study heterogeneity was low (I^2=25%). No statistically significant difference was found between LC and C (MD (95%CI) = 0.03 (-0.32, 0.38); p=0.87) (Figure 5b).

Operating time, docking time, and surgeon console time

Operating time was reported in 9 studies (481 LC vs. 346 C).[20-28] Statistical among-study heterogeneity was high (I^2=89%; Tau^2=1746.70). Operating time was significantly longer in LC compared to C (MD (95%CI) = 52.81 (23.49, 82.14); p=0.0004) (Figure 6a).

Docking time was reported in 4 studies (174 LC vs. 118 C).[20,22,26,28]

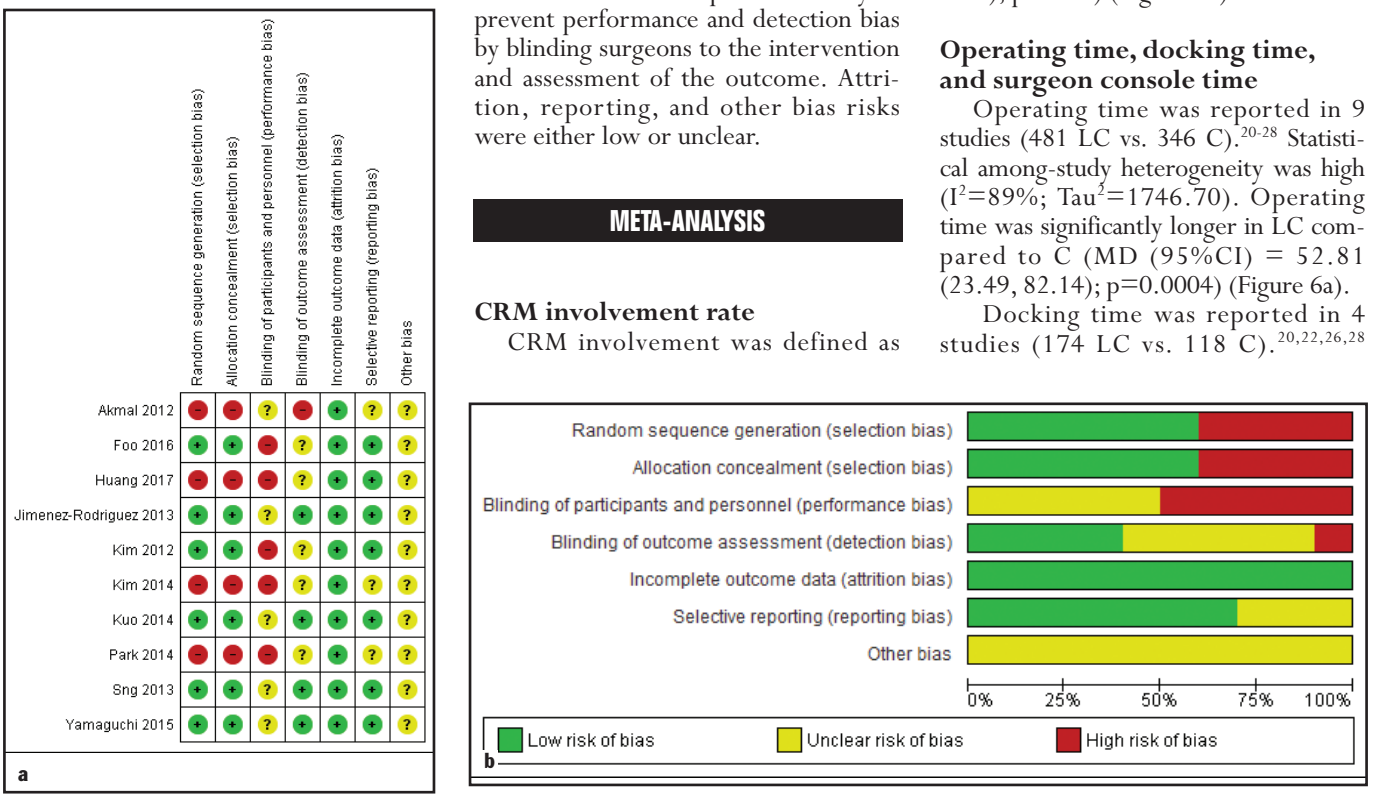


Figure 3. Quality assessment. (a) Risk of bias summary. (b) Risk of bias graph.

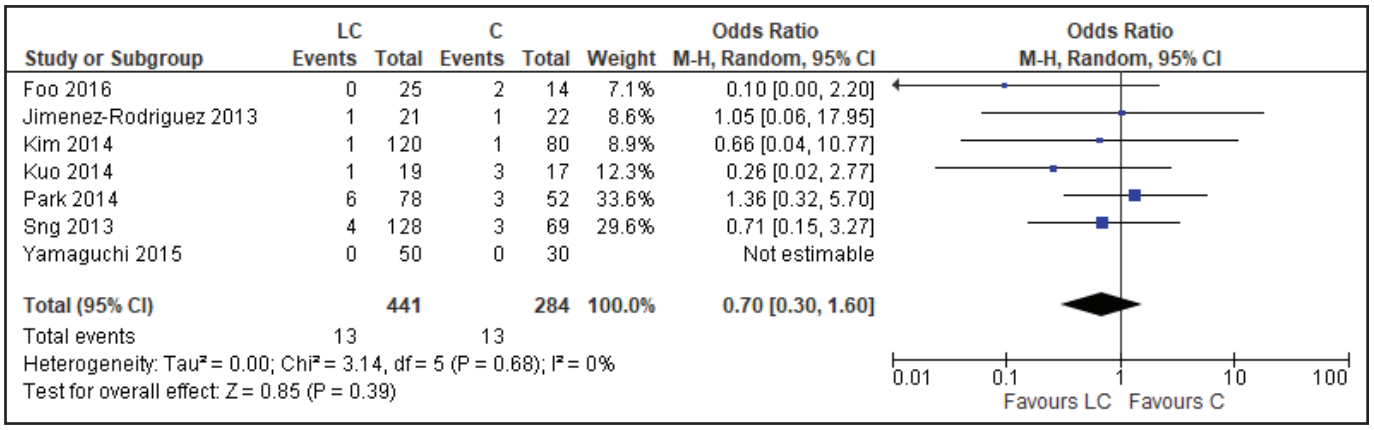


Figure 4. Meta-analysis of LC vs. C: CRM involvement rate (primary endpoint).

Statistical among-study heterogeneity was high (I^2=96%; Tau^2=14.63). Docking time was significantly longer in LC compared to C (MD (95%CI) = 7.83 (3.34, 12.32); p=0.0006) (Figure 6b).

Surgeon console time was reported in 5 studies (194 LC vs. 160 C).[20,22,23,26,28] Statistical among-study heterogeneity was high (I^2=78%; Tau^2=343.42). Surgeon console time was also significantly longer in LC compared to C (MD (95%CI) = 29.58 (10.40, 48.77); p=0.003) (Figure 6c).

Conversion rate

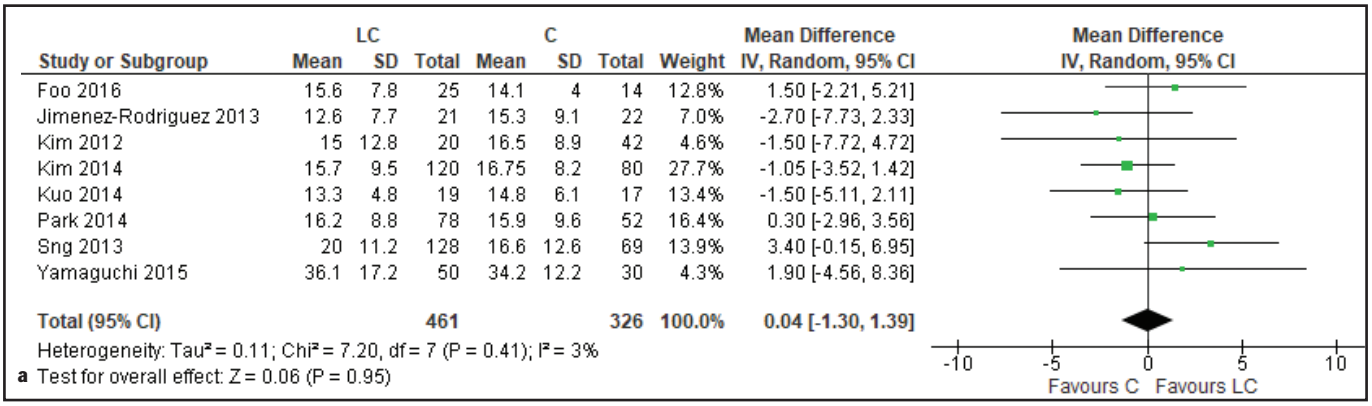
The conversion rate was reported in 9 studies (501 LC vs. 366 C).[19,20,22-28] Statistical among-study heterogeneity was low (I^2=41%). The conversion rate was 1.8% (9/501) in LC vs. 1.4% (5/366) in C. This difference was neither statistically nor clinically significant (OR (95%CI) = 1.65 (0.54, 5.10); p=0.38; NNT (95%CI) = 233 (> 47.8 to benefit, > 81.1 to harm)) (Figure 6d) (Table III).

Estimated blood loss

Estimated blood loss (EBL) was reported in 6 studies (320 LC vs. 202 C).[20,21,25-28] Statistical among-study heterogeneity was low (I^2=0%). No statistically significant difference in EBL was found between LC and C (MD (95%CI) = 12.61 (-3.06, 28.29); p=0.11) (Figure 6e).

Postoperative complication rate

The postoperative complication rate was reported in all 10 studies (521 LC vs. 386 C).[19-28] Statistical among-study heterogeneity was low (I^2=37%). The postoperative complication rate was 19% (99/521) in LC vs. 24.6% (5/366) in C. This difference was not statistically significant (OR (95%CI) =



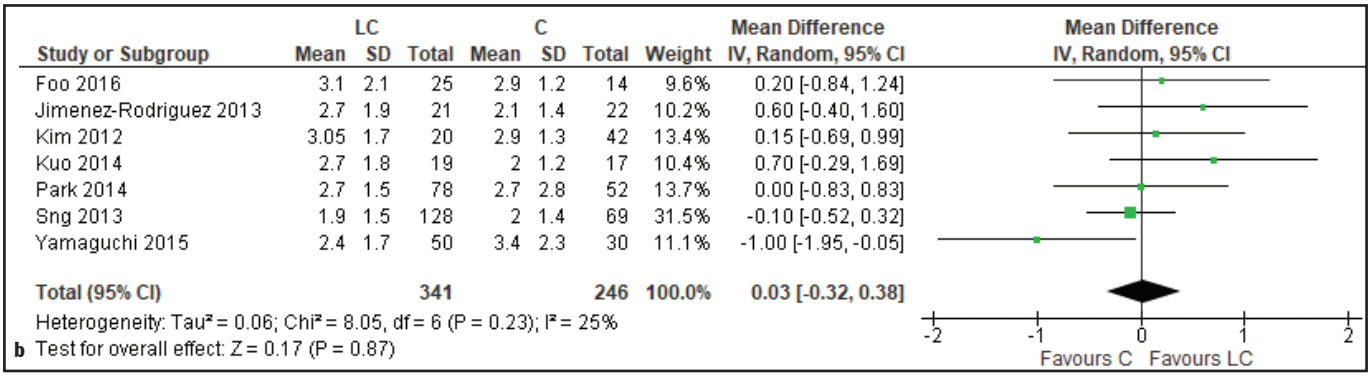
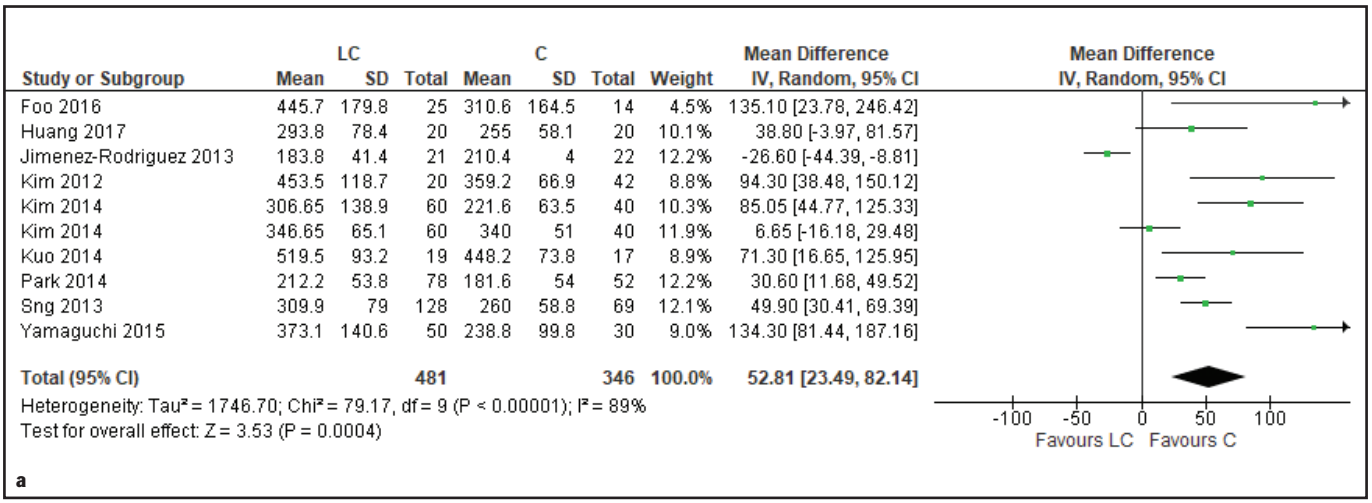
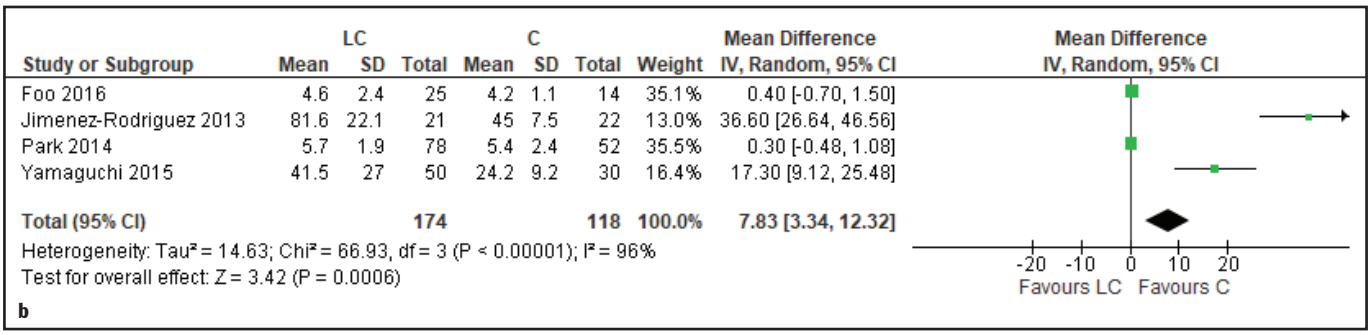
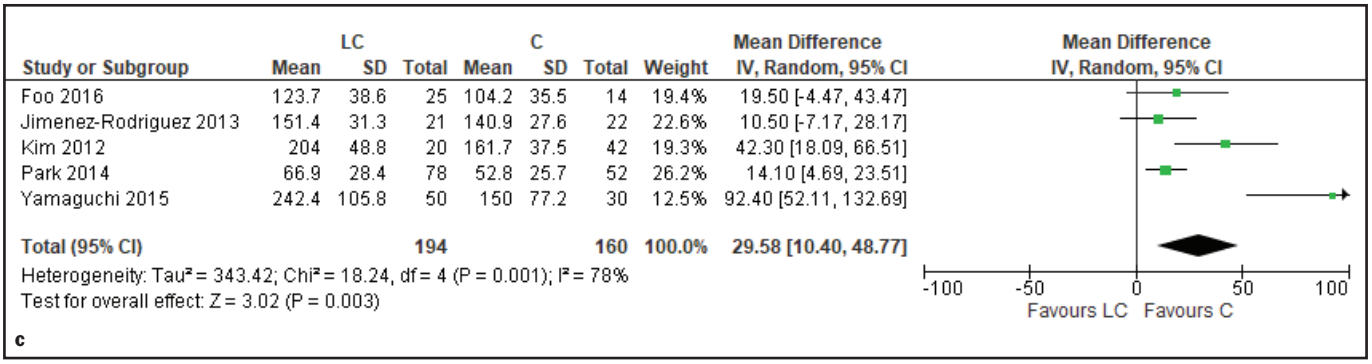


Figure 5. Secondary pathologic endpoints of the meta-analysis of LC vs. C. (a) Number of lymph nodes harvested. (b) Distal margin (cm).







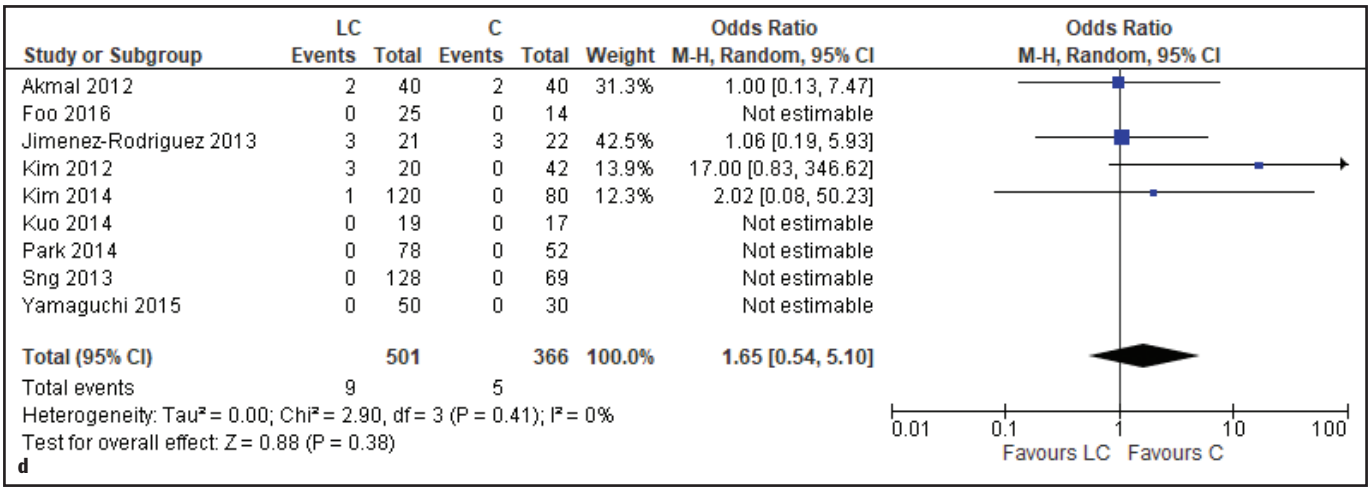
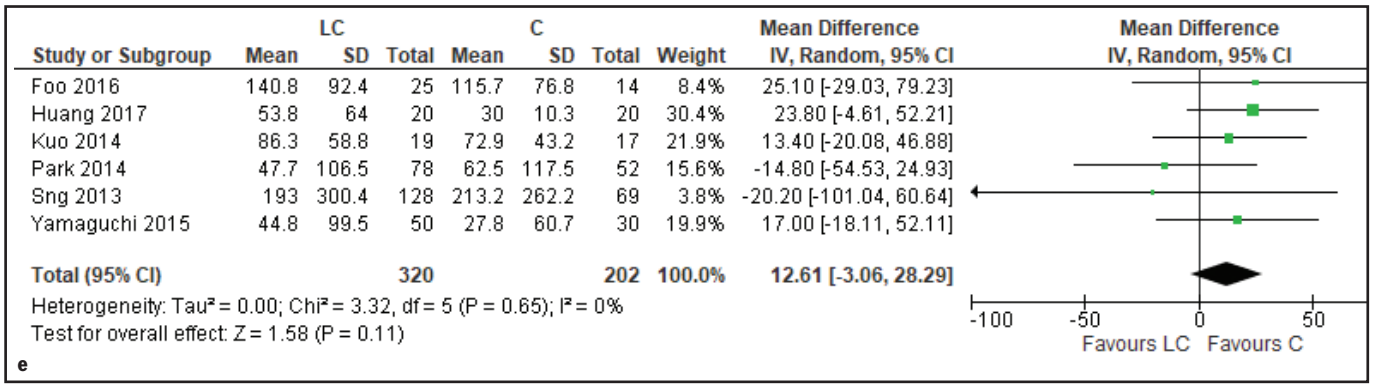
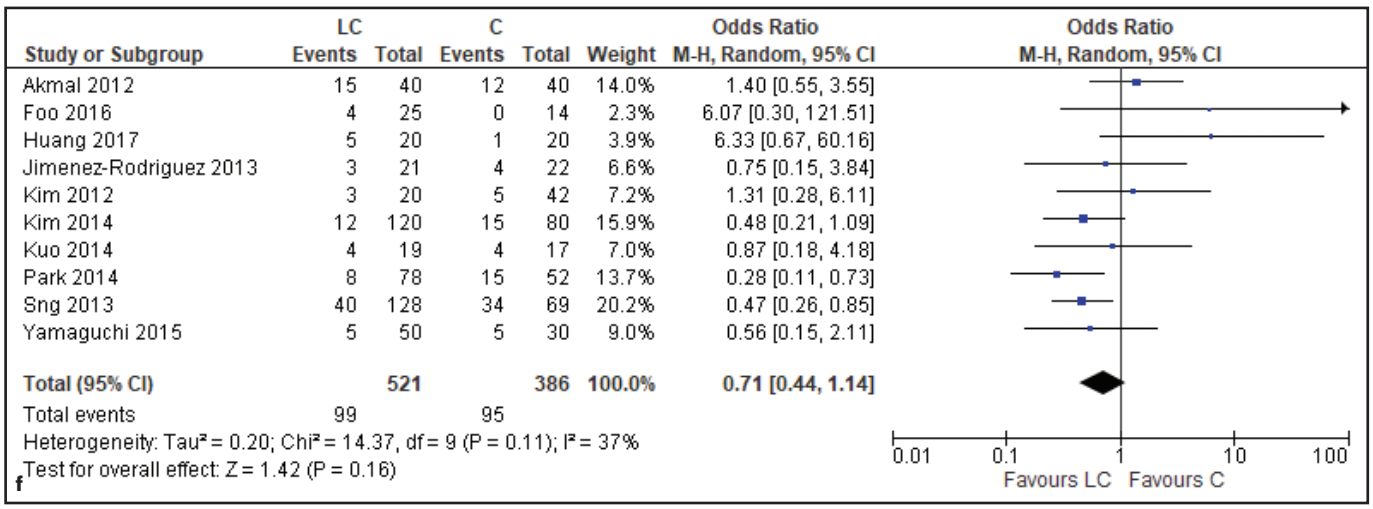
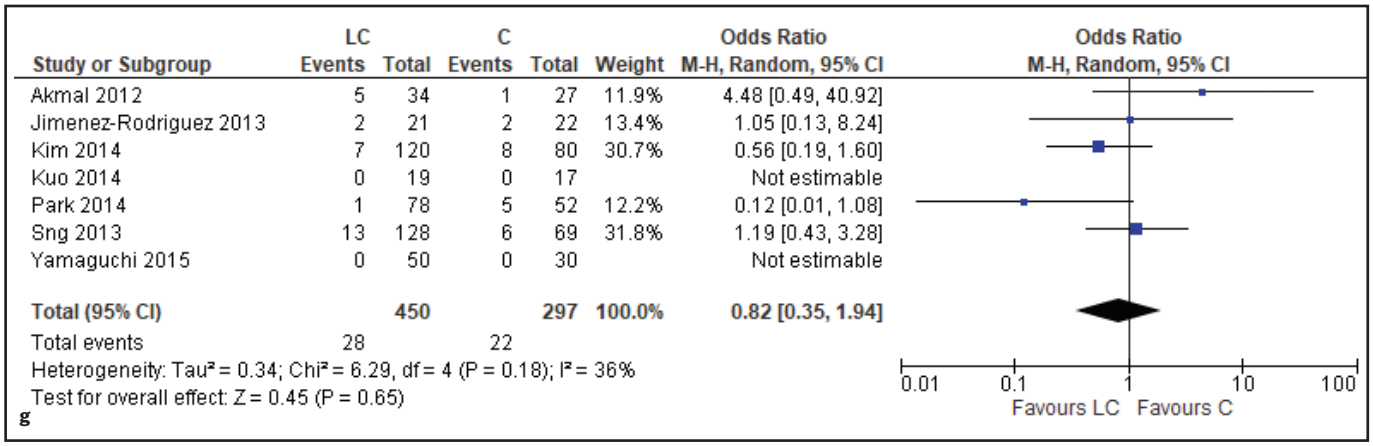


Figure 6. Secondary clinical endpoints of the meta-analysis of LC vs. C. (a) Operating time. (b) Docking time. (c) Surgeon console time. (d) Conversion rate.







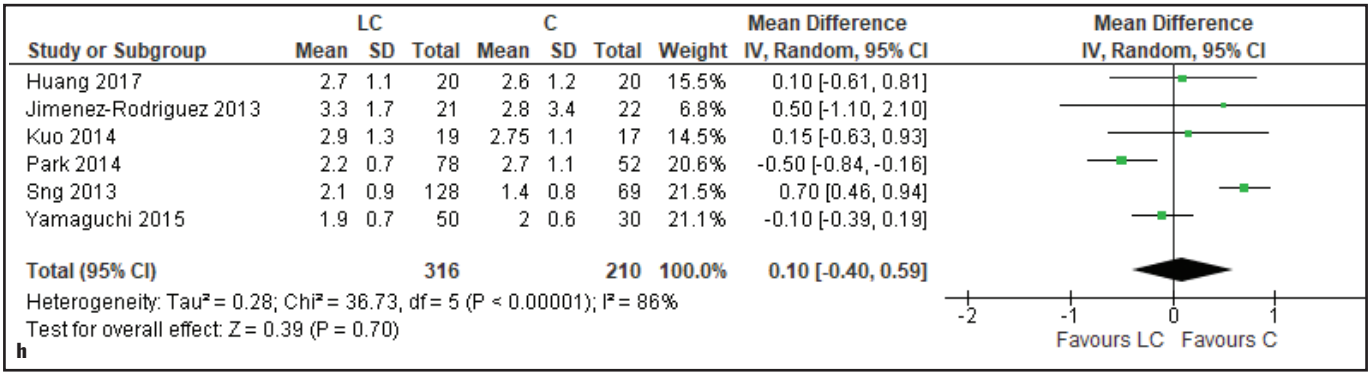
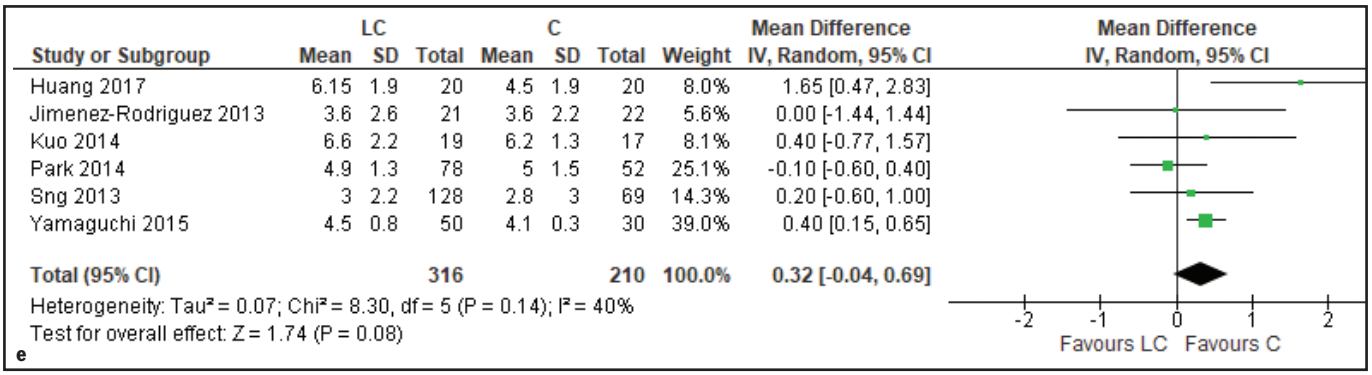
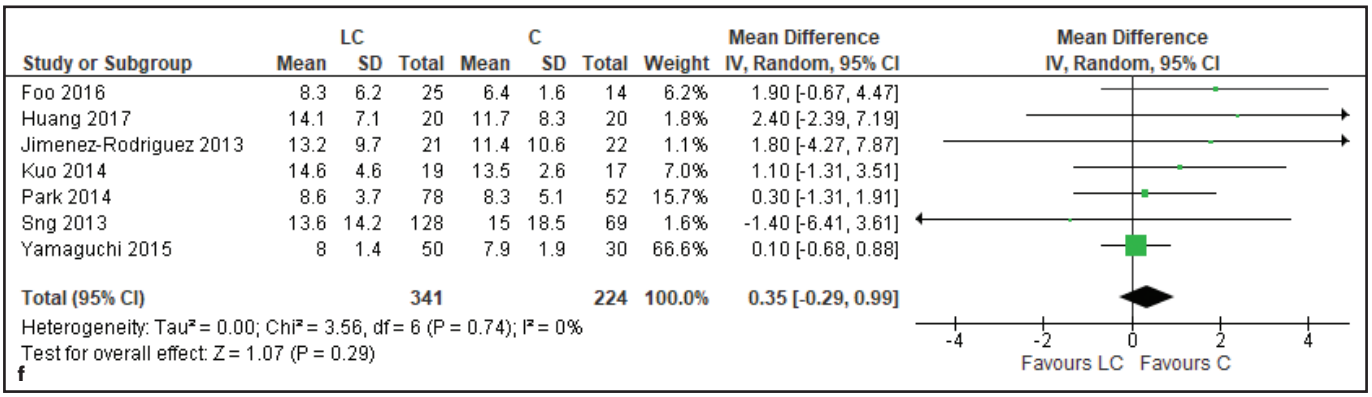


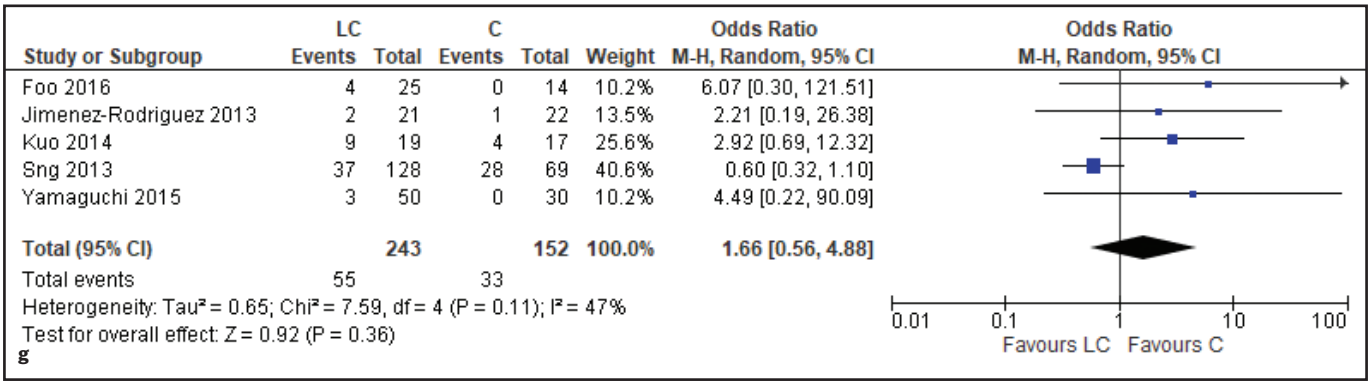
Figure 6 (cont). Secondary clinical endpoints of the meta-analysis of LC vs. C. (e) Estimated blood loss. (f) Postoperative complication rate. (g) Anastomotic leak rate. (h) Time to first flatus.



e



f



g

Figure 6 (cont). Secondary clinical endpoints of the meta-analysis of LC vs. C. (i) Time to soft diet resumption. (j) Length of hospital stay (days). (k) Readmission rate.

Table III
Clinical significance of the statistical difference between LC and C

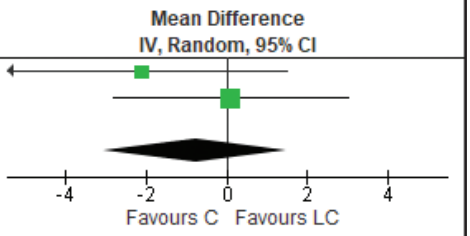
Endpoints	RRR	ARR (95%CI)	NNT (95%CI)
CRM involvement rate	0.37	0.016 (-0.012, 0.045)	62 (> 22.1 to benefit, > 78.8 to harm)
Incomplete TME quality rate	0.16	0.018 (-0.075, 0.113)	54 (> 8.8 to benefit, > 13.2 to harm)
Conversion rate	0.05	0.004 (-0.012, 0.021)	233 (> 47.8 to benefit, > 81.1 to harm)
Postoperative complication rate	0.23	0.056 (0.001, 0.111)	18 (9.0, 669.7)
Readmission rate	0.04	0.009 (-0.075, 0.093)	109 (> 10.7 to benefit, > 13.4 to harm)

RRR, relative risk reduction; ARR, absolute risk reduction; NNT, numbers needed to treat; 95%CI, 95% confidence interval; CRM, circumferential resection margin; TME, total mesorectal excision.

Supplement 4
Meta-analysis of LC vs. C: Circumferential resection margin (mm)

Study or Subgroup	LC Mean	LC SD	LC Total	C Mean	C SD	C Total	Weight	Mean Difference IV, Random, 95% CI
Jimenez-Rodriguez 2013	9.7	6.2	21	11.8	5.8	22	39.8%	-2.10 [-5.69, 1.49]
Kuo 2014	6.9	3.1	19	6.8	5.4	17	60.2%	0.10 [-2.82, 3.02]
Total (95% CI)			**40**			**39**	**100.0%**	**-0.78 [-3.04, 1.49]**

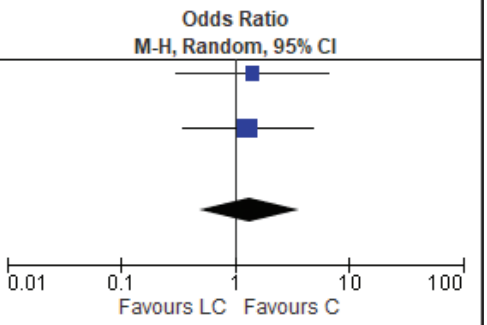
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)



Supplement 5
Meta-analysis of LC vs. C: Incomplete TME quality rate

Study or Subgroup	LC Events	LC Total	C Events	C Total	Weight	Odds Ratio M-H, Random, 95% CI
Foo 2016	7	25	3	14	42.2%	1.43 [0.30, 6.70]
Jimenez-Rodriguez 2013	0	21	0	22		Not estimable
Kuo 2014	9	19	7	17	57.8%	1.29 [0.34, 4.82]
Yamaguchi 2015	0	50	0	30		Not estimable
Total (95% CI)		**115**		**83**	**100.0%**	**1.34 [0.49, 3.67]**
Total events	16		10			

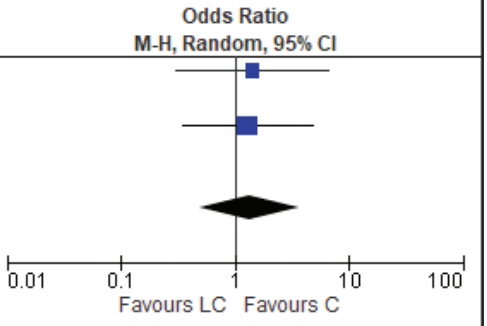
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)



Supplement 6
Meta-analysis of LC vs. C: Local recurrence rate

Study or Subgroup	LC Events	LC Total	C Events	C Total	Weight	Odds Ratio M-H, Random, 95% CI
Foo 2016	7	25	3	14	42.2%	1.43 [0.30, 6.70]
Jimenez-Rodriguez 2013	0	21	0	22		Not estimable
Kuo 2014	9	19	7	17	57.8%	1.29 [0.34, 4.82]
Yamaguchi 2015	0	50	0	30		Not estimable
Total (95% CI)		**115**		**83**	**100.0%**	**1.34 [0.49, 3.67]**
Total events	16		10			

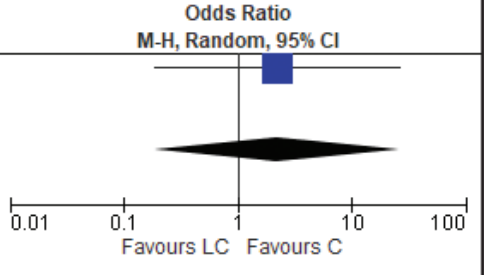
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)



Supplement 7
Meta-analysis of LC vs. C: Intraoperative complication rate

Study or Subgroup	LC Events	LC Total	C Events	C Total	Weight	Odds Ratio M-H, Random, 95% CI
Jimenez-Rodriguez 2013	2	21	1	22	100.0%	2.21 [0.19, 26.38]
Yamaguchi 2015	0	50	0	30		Not estimable
Total (95% CI)		**71**		**52**	**100.0%**	**2.21 [0.19, 26.38]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)



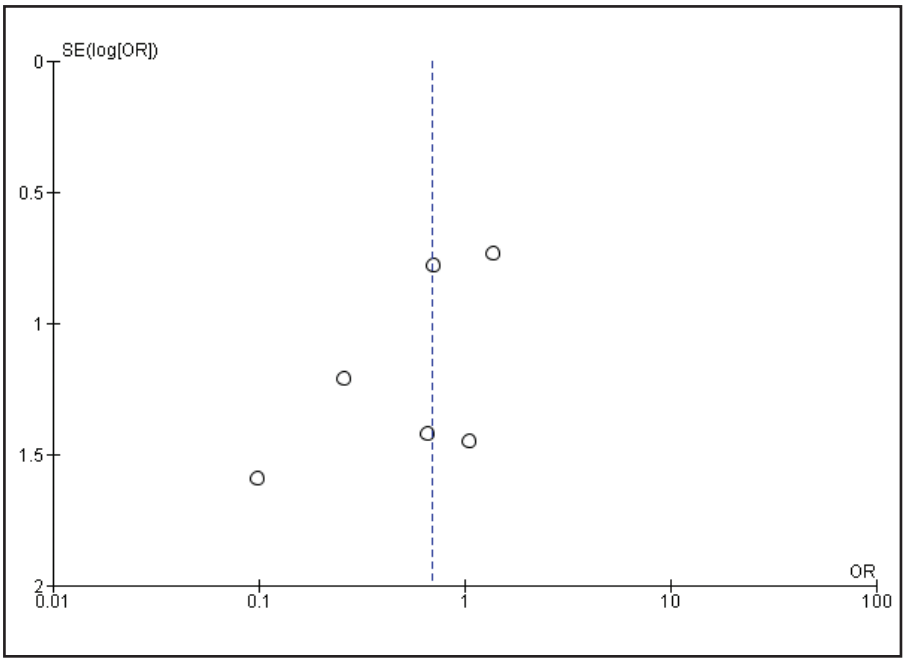


Figure 7. Meta-analysis of LC vs. C: Funnel plot (primary endpoint).

0.71 (0.44, 1.14); p=0.16). However, the difference was clinically significant (NNT (95%CI) = 18 (9.0, 669.7)) (Figure 6f).

Anastomotic leak rate

The anastomotic leak rate was reported in 7 studies (450 LC vs. 297 C).[19,22,24-28] Statistical among-study heterogeneity was low (I^2=36%). The anastomotic leak rate was 6.2% (28/450) in LC vs. 7.4% (22/297) in C. This difference was not statistically significant (OR (95%CI) = 0.82 (0.35, 1.94); p=0.65) (Figure 6g).

Time to first flatus

Time to first flatus was reported in 6 studies (316 LC vs. 210 C).[21,22,25-28] Statistical among-study heterogeneity was high (I^2=86%; Tau^2=0.28). Time to first flatus was not significantly different between LC and C (MD (95%CI) = 0.10 (-0.40, 0.59); p=0.70) (Figure 6h).

Time to soft diet resumption

Time to soft diet resumption was reported in 6 studies (316 LC vs. 210 C).[21,22,25-28] Statistical among-study heterogeneity was low (I^2=40%). Time to soft diet resumption was not significantly different between LC and C (MD (95%CI) = 0.32 (-0.04, 0.69); p=0.08) (Figure 6i).

Length of hospital stay

Length of stay (LOS) was reported in 7 studies (341 LC vs. 224 C) [20-22,25-28]. Statistical among-study heterogeneity was low (I^2=0%). LOS was not significantly different between LC and C (MD (95%CI) = 0.35 (-0.29, 0.99); p=0.29) (Figure 6j).

Readmission rate

The readmission rate was reported in 5 studies (243 LC vs. 152 C).[20,22,25,27,28] Statistical among-study heterogeneity was moderate (I^2=47%; Tau^2=0.65). The readmission rate was 22.6% (55/243) in LC vs. 21.7% (33/152) in C. This difference was neither statistically nor clinically significant (OR (95%CI) = 1.66 (0.56, 4.88); p=0.36; NNT (95%CI) = 109 (> 10.7 to benefit, > 13.4 to harm)) (Figure 6k) (Table III).

Other endpoints

The results of the meta-analysis for additional endpoints (incomplete TME quality rate, circumferential resection margin, local recurrence rate, and intraoperative complication rate) are presented in Supplements 4, 5, 6, and 7.

Clinical significance

Relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT) for primary and some secondary endpoints are shown in Table III. The only endpoint with clinical significance was the postoperative complication rate.

Sensitivity analysis and publication bias

A sensitivity analysis of the included studies was performed by excluding studies with the highest risk of bias. This did not affect the findings. Publication bias was evaluated by a visual assessment of symmetry in the funnel plot (Figure 7), the funnel plot of precision by log OR, Egger's test (t= 1.72; p= 0.16), and Begg and Mazumdar rank correlation tests (Tau= -0.4; p= 0.26) (Supplement 8). No publication bias was found.

DISCUSSION

This meta-analysis was designed to evaluate whether the learning curve in robotic surgery for rectal cancer has any impact on histopathologic outcomes.

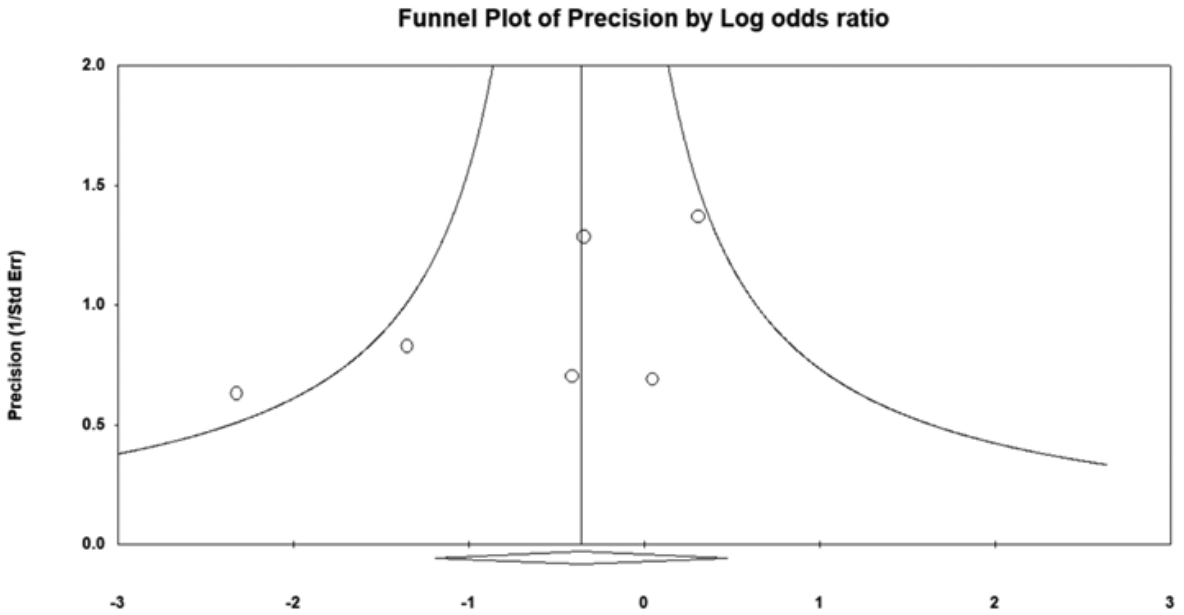
Interpretation of the results

The lack of a significant difference in CRM involvement rates between LC and C suggests that the six degrees of freedom of the RSS instruments (rather than the surgeon's competence) are the limiting factors that determine CRM involvement rates. Furthermore, the surgeon's learning curve did not affect either the number of lymph nodes harvested or the distal margin. Additional pathologic endpoints such as CRM, incomplete TME quality rates, and local recurrence rates (Supplements 4, 5, and 6) did not allow us to draw robust conclusions due to the insufficient number of studies (two studies) reporting the outcome or high heterogeneity.

The findings of significantly decreased total operating time, docking time, and surgeon console time were as expected. However, there was high heterogeneity across the studies, since only 6 studies used a CUSUM analysis.[20,22,23,25,27,28] The findings of this meta-analysis allow us to draw reliable conclusions because the learning curve did not affect conversion rates or EBL. Since only two studies reported intraoperative complication rates,[22,28], we could not draw any clinically sound conclusions.

There were no statistically significant differences in postoperative complication rates between LC and C (19% vs. 25%, respectively). However, NNT analysis showed that experience with 18

Supplement 8
Evaluation of publication bias risk: funnel plot of precision, results of Egger's test, and Begg and Mazumdar rank correlation tests



Egger's regression intercept		Begg and Mazumdar rank correlation	
Intercept	-1.52838	**Kendall's S statistic (P-Q)**	-7.00000
Standard error	0.89084	**Kendall's tau without continuity correction**	
95% lower limit (2-tailed)	-4.00175	Tau	-0.46667
95% upper limit (2-tailed)	0.94499	z-value for tau	1.31507
t-value	1.71566	p-value (1-tailed)	0.09424
df	4.00000	p-value (2-tailed)	0.18849
p-value (1-tailed)	0.08068	**Kendall's tau with continuity correction**	
p-value (2-tailed)	0.16137	Tau	-0.40000
		z-value for tau	1.12720
		p-value (1-tailed)	0.12983
		p-value (2-tailed)	0.25966

cases during LC could prevent one postoperative complication during C. A higher postoperative complication rate could be explained by increased case complexity and surgeon confidence. LC did not affect anastomotic leak or readmission rates, time to soft diet resumption, or LOS. Although the time to first flatus was similar among the studies, high heterogeneity did not allow us to draw robust and clinically sound conclusions.

The finding that the tumor distance from the anal verge was a risk factor for CRM involvement was expected. However, while male gender and high BMI were also expected to be risk factors, they did not yield significant results.

Existing evidence

Robotic surgery for rectal cancer is controversial for several reasons, including (but not limited to) operating time, learning curve, and cost. This meta-analysis is in line with previous studies suggesting that learning is associated with a prolonged operating time. Nonetheless, a recent study found that an operating time over 300 minutes was not a risk factor for postoperative complications.[11] Aside from operating time, this meta-analysis shows that learning has no detrimental impact on histopathologic outcomes. In fact, this meta-analysis supports previous evidence[12] suggesting that CRM involvement is not affected by learning. Histopathologic outcomes and recurrence rates (rather than only cost)[32] should play the key roles in the era of value-based care.

Strengths and limitations

This meta-analysis was based on a literature search in several databases and an evaluation of metrics of clinical significance (relative and absolute risk reduction, numbers needed to treat/harm).

However, it has several limitations. All of the eligible studies were observational studies that included only a small number of patients. Nonetheless, the pre-post design of the studies with the allocation of patients based on a CUSUM analysis decreased the overall risk of bias. There was some heterogeneity in study interventions: 6 studies included patients with abdominoperineal resection of the rectum, and 2 studies included patients with Hartmann's procedure. An overall lack of details regarding key outcomes was a common limitation of most studies, which precludes us from drawing conclusions about the root causes of some important outcomes, such as CRM and TME quality. Insufficient information about the previous experience of participating surgeons with laparoscopic surgery was an additional limitation of this meta-analysis.

Clinical and scientific implications

The evidence provided in this meta-analysis is sufficient to constitute level 1a evidence that the learning curve for robotic surgery for rectal cancer has no impact on histopathologic outcomes. However, the limitations of this meta-analysis, e.g., lack of evidence regarding TME quality, should be taken into account. Further studies on the impact of the learning curve for robotic rectal cancer surgery on histopathologic outcomes are required. However, any further research should use a CUSUM analysis to identify phases of the learning curve and include more details on histopathologic outcomes, such as CRM and TME quality.

CONCLUSION

This meta-analysis found that learning had no detrimental impact on CRM involvement rates compared to the surgeon's competence in robotic surgery for rectal cancer. More detailed reporting on other histopathologic metrics is necessary to improve our understanding of the role of the learning curve in robotic rectal cancer surgery. STI

REFERENCES

1. Lowers R. Complications of robotic surgery underreported, study says. Medscape; 2013. https://www.medscape.com/ viewarticle/ 810490 (Accessed August 5, 2018).
2. Peters JD. Robots holding the scalpel. Trial 2012;48(5):36-40.
3. Alemzadeh H, Raman J, Leveson N, Kalbarczyk Z, Iyer RK. Adverse events in robotic surgery: a retrospective study of 14 years of FDA data. PLoS One 2016 Apr 20;11(4):e0151470.
4. ECRI Institute. Top 10 health technology hazards for 2014. https://www.ecri.org/ Resources/Whitepapers_and_reports/2014_ Top_10_Hazards_Executive_Brief.pdf (Accessed March 13, 2019)
5. U.S. Food and Drug Administration (FDA), Medical Product Safety Network. (2013, November). Small sample survey – final report. https://www.fda.gov/downloads/medicaldevices/productsandmedicalprocedures/surgeryandlifesupport/computerassistedsurgicalsystems/ucm374095.pdf (Accessed August 5, 2018)
6. Tou S, Bergamaschi R, Heald RJ, Parvaiz A. Structured training in robotic colorectal surgery. Colorectal Dis 2015;17(3):185.
7. Szold A, Bergamaschi R, Broeders I, et al. European Association of Endoscopic Surgeons consensus statement on the use of robotics in general surgery. Surg Endosc 2015;29(2): 253-88.
8. Huang CW, Yeh YS, Ma CJ, et al. Robotic colorectal surgery for laparoscopic surgeons with limited experience: preliminary experiences for 40 consecutive cases at a single medical center. BMC Surg 2015;15:73.
9. Jiménez-Rodríguez RM, Rubio-Dorado-Manzanares M, Díaz-Pavón JM, et al. Learning curve in robotic rectal cancer surgery: current state of affairs. Int J Colorectal Dis 2016;31(12):1807-15.
10. Duchalais E, Machairas N, Kelley SR, et al. Does prolonged operative time impact postoperative morbidity in patients undergoing robotic-assisted rectal resection for cancer? Surg Endosc 2018;32(8):3659-66.
11. Odermatt M, Ahmed J, Panteleimonitis S, Khan J, Parvaiz A. Prior experience in laparoscopic rectal surgery can minimise the learning curve for robotic rectal resections: a cumulative sum analysis. Surg Endosc 2017;31(10):4067-76.
12. Barnajian M, Pettet D III, Kazi E, Foppa C, Bergamaschi R. Quality of total mesorectal excision and depth of circumferentialresection marginin rectal cancer: A matched comparison offirst 20 robotic cases. Colorectal Dis 2014;16(8):603-9.
13. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Vol. 4. Chichester, UK: John Wiley & Sons; 2011.
14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.
15. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283(15):2008-12.
16. Horan TC, Gaynes RP, Martone WJ, et al. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 1992;13:606-8.
17. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
18. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
19. Akmal Y, Baek JH, McKenzie S, Garcia-Aguilar J, Pigazzi A. Robot-assisted total mesorectal excision: is there a learning curve? Surg Endosc 2012;26(9):2471-6.
20. Foo CC, Law WL. The learning curve of robotic-assisted low rectal resection of a novice rectal surgeon. World J Surg 2016; 40(2):456-62.
21. Huang YM, Huang YJ, Wei PL. Outcomes of robotic versus laparoscopic surgery for mid and low rectal cancer after neoadjuvant chemoradiation therapy and the effect of learning curve. Medicine (Baltimore) 2017;96(40):e8171.
22. Jiménez-Rodríguez RM, Díaz-Pavón JM, de la Portilla de Juan F, Prendes-Sillero E, Dussort HC, Padillo J. Learning curve for robotic-assisted laparoscopic rectal cancer surgery. Int J Colorectal Dis 2013;28(6):815-21.
23. Kim YW, Lee HM, Kim NK, Min BS, Lee KY. The learning curve for robot-assisted total mesorectal excision for rectal cancer. Surg Laparosc Endosc Percutan Tech 2012;22(5):400-5.
24. Kim IK, Kang J, Park YA, Kim NK, Sohn SK, Lee KY. Is prior laparoscopy experience required for adaptation to robotic rectal surgery?: Feasibility of one-step transition from open to robotic surgery. Int J Colorectal Dis 2014;29(6):693-9.
25. Kuo LJ, Lin YK, Chang CC, Tai CJ, Chiou JF, Chang YJ. Clinical outcomes of robot-assisted intersphincteric resection for low rectal cancer: comparison with conventional laparoscopy and multifactorial analysis of the learning curve for robotic surgery. Int J Colorectal Dis 2014;29(5):555-62.
26. Park EJ, Kim CW, Cho MS, et al. Multidimensional analyses of the learning curve of robotic low anterior resection for rectal cancer: 3-phase learning process comparison. Surg Endosc 2014;28(10):2821-31.
27. Sng KK, Hara M, Shin JW, Yoo BE, Yang KS, Kim SH. The multiphasic learning curve for robot-assisted rectal surgery. Surg Endosc 2013;27(9):3297-307.
28. Yamaguchi T, Kinugasa Y, Shiomi A, et al. Learning curve for robotic-assisted surgery for rectal cancer: use of the cumulative sum method. Surg Endosc 2015;29(7):1679-85.
29. Park EJ, Kim CW, Cho MS, et al. Is the

learning curve of robotic low anterior resection shorter than laparoscopic low anterior resection for rectal cancer?: a comparative analysis of clinicopathologic outcomes between robotic and laparoscopic surgeries. Medicine (Baltimore) 2014;93(25):e109.
30. Melich G, Hong YK, Kim J, et al. Simultaneous development of laparoscopy and robotics provides acceptable perioperative outcomes and shows robotics to have a faster learning curve and to be overall faster in rectal cancer surgery: analysis of novice MIS surgeon learning curves. Surg Endosc 2015; 29(3): 558-68.
31. Bokhari MB, Patel CB, Ramos-Valadez DI, Ragupathi M, Haas EM. Learning curve for robotic-assisted laparoscopic colorectal surgery. Surg Endosc 2011;25(3):855-60.
32. Byrn JC, Hrabe JE, Charlton ME. An initial experience with 85 consecutive robotic-assisted rectal dissections: improved operating times and lower costs with experience. Surg Endosc 2014;28(11):3101-7.
33. Guend H, Widmar M, Patel S, et al. Developing a robotic colorectal cancer surgery program: understanding institutional and individual learning curves. Surg Endosc 2017;31(7):2820-8.
34. Shaw DD, Wright M, Taylor L, et al. Robotic colorectal surgery learning curve and case complexity. J Laparoendosc Adv Surg Tech A 2018 May 7. doi: 10.1089/lap.2016.0411. (Epub ahead of print).