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Extralevator abdominoperineal excision versus abdominoperineal excision for low rectal cancer: a meta-analysis

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Abstract

Background: Extralevator abdominoperineal excision (ELAPE) has become a popular procedure for low rectal cancer as compared with abdominoperineal excision (APE). No definitive answer has been achieved whether one is superior to the other. This study aimed to evaluate the safety and efficacy of ELAPE for low rectal cancer with meta-analysis.

Methods: The Web of Science, Cochrane Library, Embase, and PubMed databases before September 2019 were comprehensively searched to retrieve comparative trials of ELAPE and APE for low rectal cancer. Pooled analyses of the perioperative variables, surgical complications, and oncological variables were performed. Odds ratio (OR) and mean differences (MD) from each trial were pooled using random or fixed effects model depending on the heterogeneity of the included studies. A subgroup analysis or a sensitivity analysis was conducted to explore the potential source of heterogeneity when necessary.

Results: This meta-analysis included 17 studies with 4049 patients, of whom 2248 (55.5%) underwent ELAPE and 1801 (44.5%) underwent APE. There were no statistical differences regarding the circumferential resection margin positivity (13.0% *vs.* 16.2%, OR = 0.69, 95% CI = 0.42–1.14, $P = 0.15$) and post-operative perineal wound complication rate (28.9% *vs.* 24.1%, OR = 1.21, 95% CI = 0.75–1.94, $P = 0.43$). The ELAPE was associated with lower rate of intraoperative perforation (6.6% *vs.* 11.3%, OR = 0.50, 95% CI = 0.39–0.64, $P < 0.001$) and local recurrence (8.8% *vs.* 20.5%, OR = 0.29, 95% CI = 0.21–0.41, $P < 0.001$) when compared with APE.

Conclusions: The ELAPE was associated with a reduction in the rate of intra-operative perforation and local recurrence, without any increase in the circumferential resection margin positivity and post-operative perineal wound complication rate when compared with APE in the surgical treatment of low rectal cancer.

Keywords: Extralevator abdominoperineal excision; Abdominoperineal excision; Low rectal cancer; Surgical complications

Introduction

Abdominoperineal excision (APE) has been the standard surgery for advanced low rectal cancer for over a century. An alternative procedure, extralevator abdominoperineal excision (ELAPE), was first described by Holm *et al*[1] in 2007 and has gained popularity among colorectal surgeons. Several studies reported that ELAPE has better outcomes regarding the rate of intra-operative perforation (IOP), circumferential resection margin (CRM) positivity, and local recurrence (LR) as compared to APE.[2-4] This improved performance of ELAPE may result from the absence of the surgical "waist," located where the abdominal and perineal dissections meet, that remained after APE.[1] However, other studies reported comparable outcomes for APE and ELAPE.[5,6] Thus, whether one of these methods is superior to the other remains uncertain.

Reviewing the past seven meta-analyses of ELAPE and APE studies,[7-13] we found many contradictory results with respect to oncological variables: four indicated that ELAPE was superior with respect to CRM positivity, IOP, and LR rates;[7,8,11,13] one reported that ELAPE and APE were equivalence with respect to CRM positivity and IOP rates;[9] one reported that ELAPE was superior with respect to LR and IOP rates;[10] and one reported the superiority of ELAPE with respect to the IOP rate alone.[12] However, five of these meta-analyses, conducted between

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2013 and 2015, were not registered with the International Prospective Register of Systematic Review (PROSPERO) or Cochrane, failed to use the Newcastle-Ottawa Scale correctly, and simply used the random effects model without further analyzing the source of high heterogeneity.[7-11] The meta-analysis by Zhang *et al*[13] barely investigated oncological variables. In addition, five high-quality studies[14-18] that questioned the benefits of ELAPE as a standard operation have been published in the past 3 years.

The conflicting conclusions and shortcomings of previous meta-analyses necessitate further investigation using a larger number of patients and rigorous statistical methods. This meta-analysis aims to compare perioperative variables, surgical complications, and oncological variables between the ELAPE and APE for low rectal cancer.

Methods

This review protocol has been registered and published in PROSPERO (CRD42019118433) and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Data sources

To acquire all cited publications, a comprehensive search of the Web of Science, Cochrane Library, Embase, and PubMed databases was conducted between 2007 and 2019. We chose to start in 2007 because ELAPE was first presented by Holm *et al*[1] at that time. The literature search used various combinations of the subject words and free words related to ELAPE and APE in low rectal cancer, using the following keywords: rectal neoplasm, rectum neoplasm, rectum cancer, rectal tumor, cancer of the rectum, rectal cancer, extra-levator abdominoperineal, extralevator abdominoperinea, extended abdominoperineal, extralevator abdominoperineal, cylindrical abdominoperineal, abdominoperineal prone position, standard abdominoperineal, conventional abdominoperineal, excision, or resection. Articles were also identified using the "related articles" function. The most recent study retrieved by this search was published on August 25, 2019.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) Randomized controlled trials (RCTs) and non-randomized controlled trials (non-RCTs); (2) published as a full paper about low rectal cancer in English; (3) compared ELAPE and APE in the same study, including open, laparoscopic, and robotic approaches; (4) included a minimum of 20 patients undergoing ELAPE and APE; (5) reported patients' clinical and pathologic parameters, such as age, sex, and tumor differentiation; (6) if the same data had been published more than once, the higher quality or latest study was included; (7) evaluated at least one of the outcomes of interest mentioned below. Nonhuman studies, experimental trials, review articles, editorials, letters, and case reports were excluded.

Data extraction

Studies were finally included by reviewers independently. To resolve discrepancies, a third experienced gastrointestinal surgery professor participated in the decision-making process. The following variables were extracted from each study: first author, year of publication, country, study type, matching criteria, sample size, and outcomes of interest. For cases with missing or incomplete data, the primary authors were contacted requesting further information, but none was provided.

Outcomes of interest and definitions

1. Perioperative variables: operating time, estimated blood loss, and length of hospital stay (LOS).
2. Surgical complications: post-operative perineal herniation, post-operative abdominal infection, post-operative urinary dysfunction, post-operative chronic perineal pain, post-operative urinary infection, post-operative parastomal hernia, post-operative intestinal obstruction, and post-operative perineal wound complication (PWC). The PWC includes perineal wound infection, dehiscence, breakdown, wound healing problems, and sinus formation.
3. Oncological variables: Rates of IOP, LR, and CRM positivity. Any tumor located less than 1 mm from the circumferential margin was defined as positive according to previous evidence.[19] LR, CRM positivity, IOP, and PWC rates were evaluated as the main outcomes of interest for this review.

Statistical analysis

For statistical analysis, this review used Review Manager Software 5.3 (The Cochrane Collaboration, London, UK). The mean difference (MD) with the 95% confidence interval (CI) was chosen as the effect measure for continuous data and odds ratio (OR) for dichotomous data. For continuous data presented as the median with quartile or range, the mean and standard deviation were estimated according to the methods described previously.[20] The Chi-square test and I^2 statistics were used for assessing study heterogeneity, reflecting the total variation between the studies generated by differences between the trials rather than sample error. For $I^2 > 50\%$, which indicated heterogeneity, a random effects model was used. Otherwise, the fixed-effect model was used to analyze the outcomes of interest. For cases in which the outcomes of interest showed high heterogeneity, the reasons for the statistical heterogeneity were explored using subgroup and sensitivity analysis. Publication bias was evaluated using funnel plots. The pooled effects were determined using the Z test, and $P < 0.05$ was considered statistically significant. The quality of randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias Tool.[21] The quality of non-RCTs was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I).[22]

Results

Description of eligible studies

Seventeen studies[14-18,23-34] published from 2007 to 2018 fulfilled the inclusion criteria and were included in the meta-analysis [Figure 1]. The characteristics of the

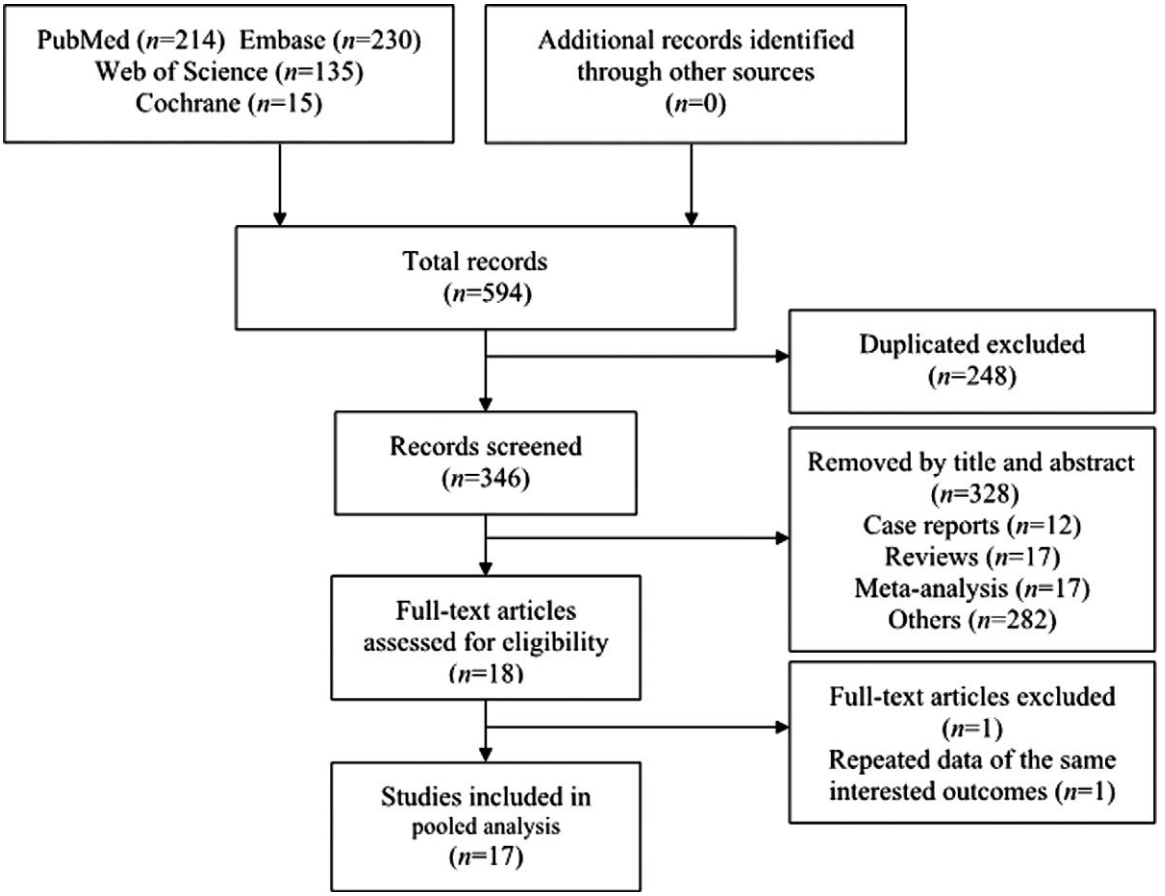

Figure 1: Flow diagram of the meta-analysis literature search and study selection.

included studies are shown in Table 1. A total of 4049 patients (ELAPE, 2248; APE, 1801) from 17 studies were included. One RCT (from China) and 16 non-RCTs (12 from Europe, 3 from Asia, and 1 from South America) were included in the meta-analysis. Two studies by Stelzner *et al*[3,33] included two apparently overlapping patient cohorts. To avoid duplicate ion bias, only the latter study was included.[33]

Methodological quality of included studies

Using the Cochrane Risk of Bias Tool to assess the quality of the RCT, we found that the RCT did not calculate the sample size and provided no information about the blinding method. Using the ROBINS-I, all non-RCT were assessed with low or moderate risk (Supplementary Table 1, http://links.lww.com/CM9/A103).

Meta-analysis of perioperative variables

Operating time

Pooled data from nine studies[14,17,23,26-30,32] that reported operating time showed significantly longer operating time for ELAPE than APE (MD = 57.05, 95% CI = 28.61–85.48, $P < 0.001$, Table 2) with high heterogeneity ($P < 0.001$, $I^2 = 90\%$). The subgroup analysis revealed ELAPE has longer operating time in Europe ($P < 0.001$, $I^2 = 87\%$), and no significant statistically difference in Asia ($P = 0.13$, $I^2 = 92\%$). When excluding one highly heterogeneous study[23] by sensitivity analysis, we still found longer operating time in ELAPE (MD = 49.63, 95% CI = 22.17–77.08, $P < 0.001$), indicating that the above-mentioned result was stable.

Estimated blood loss

Pooled data from eight studies[14,15,17,23,26,27,29,32] that reported estimated blood loss showed lower blood loss for ELAPE than APE (MD = −82.98, 95% CI = −122.06 to −43.90, $P < 0.001$, Table 2) with high heterogeneity ($P < 0.001$, $I^2 = 72\%$). The subgroup analysis revealed ELAPE has lower blood loss in Europe ($P = 0.002$, $I^2 = 59\%$) and Asia ($P = 0.008$, $I^2 = 59\%$). When excluding one highly heterogeneous study[15] by sensitivity analysis, we still found lower blood loss in ELAPE (MD = −81.35, 95% CI = −131.93 to −30.76, $P = 0.002$), indicating that the above-mentioned result was stable.

Length of stay

Pooled data from six studies[15,23,24,26,28,29] that reported LOS showed there was no significant statistically difference between ELAPE and APE (MD = −0.58, 95% CI = −2.18

Table 1: Characteristics of included studies.

Author	Year	Country	Group	Patients, *n*	Study type	Inclusion period	Clinical stage	Neoadjuvant			Mean follow-up time (months)	Outcomes of interest*
								RaCT	RT	CT		
West *et al*[23]	2010	UK	ELAPE	176	Non-RCT	1997–2008	T0–T4	NA	130	84	Unclear	1, 2, 3, 4, 6, 8, 11, 12, 13, 14
			APE	124				NA	90	48	Unclear	
Asplund *et al*[24]	2012	Sweden	ELAPE	79	Non-RCT	2004–2009	T0–T4	15	60	NA	26	3, 11, 12, 13, 14
			APE	79				5	66	NA	45	
Martijnse *et al*[25]	2012	Dutch	ELAPE	134	Non-RCT	2000–2010	T0–T4	NA	NA	NA	36	12, 13, 14
			APE	112				NA	NA	NA	>36	
Han *et al*[26]	2012	China	ELAPE	35	RCT	2008–2010	T3–T4	10	7	NA	29	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
			APE	32				9	1	NA	22	
Ortiz *et al*[16]	2014	Spanish	ELAPE	457	Non-RCT	2008–2013	T0–T4	348	NA	NA	24	11, 12, 13
			APE	457				346	NA	NA	24	
Perdawood *et al*[28]	2014	Denmark	ELAPE	68	Non-RCT	2006–2012	T0–T4	NA	NA	58	50	1, 3, 11, 12, 13, 14
			APE	39				NA	NA	19	80	
Wang *et al*[29]	2015	China	ELAPE	23	Non-RCT	2010–2013	T3–T4	5	5	NA	20	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12,13, 14
			APE	25				5	5	NA	22	
Shen *et al*[14]	2015	China	ELAPE	36	Non-RCT	2011–2013	T1–T4	10	NA	NA	18	1, 2, 5, 6, 8, 10, 11, 12, 13, 14
			APE	33				4	NA	NA	18	
Klein *et al*[15]	2015	Denmark	ELAPE	301	Non-RCT	2009–2012	T0–T4	114	NA	NA	Unclear	2, 3, 12, 13
			APE	253				211	NA	NA	Unclear	
Colov *et al*[31]	2016	Denmark	ELAPE	245	Non-RCT	2009–2012	T0–T4	174	NA	NA	36	4, 5, 7, 11
			APE	200				82	NA	NA	36	
Hanif *et al*[30]	2016	UK	ELAPE	24	Non-RCT	2010–2014	T1–T4	NA	5	NA	12	1, 11, 12, 13, 14
			APE	48				NA	9	NA	12	
Nessar *et al*[32]	2016	Turkey	ELAPE	25	Non-RCT	2008–2011	T1–T4	9	NA	NA	44.7	1, 2, 11, 12, 13, 14
			APE	26				6	NA	NA	70.6	
Stelzner *et al*[33]	2016	Germany	ELAPE	36	Non-RCT	1997–2012	T1–T4	32	3	1	63.6	11, 12, 13, 14
			APE	36				35	NA	1	126.3	
Habr–Gama *et al*[34]	2017	Brazil	ELAPE	22	Non-RCT	1998–2014	T0–T4	8	NA	NA	14.0	4, 9, 10, 11, 12, 13, 14
			APE	50				23	NA	NA	49.4	
Kamali *et al*[18]	2017	UK	ELAPE	27	Non-RCT	2009–2015	T0–T4	NA	NA	NA	26	11, 13, 14
			APE	21				3	NA	NA	59	
Carpelan *et al*[17]	2018	Finland	ELAPE	42	Non-RCT	2004–2016	T2–T4	28	11	NA	38.4	1, 2, 11, 12, 13, 14
			APE	27				19	6	NA	69.6	
Prytz *et al*[27]	2014	Sweden	ELAPE	518	Non-RCT	2007–2009	T0–T4	159	456	NA	Unclear	1, 2, 12, 13
			APE	209				32	144	NA	Unclear	

* Meaning of numbers for outcomes of interest: 1: Operating time; 2: Estimated blood loss; 3: Length of stay; 4: Post-operative perineal herniation; 5: Post-operative abdominal infection; 6: Post-operative urinary dysfunction; 7: Post-operative chronic perineal pain; 8: Post-operative urinary infection; 9: Post-operative peristomal hernia; 10: Post-operative intestinal obstruction; 11: Perineal wound complication; 12: Intra-operative perforation; 13: Circumferential resection margin positive; 14: Local recurrence; APE: Abdominoperineal excision; ELAPE: Extralevator abdominoperineal excision; RaCT: Radiochemotherapy; RCT: Randomized controlled trial; RT: Radiotherapy; CT: Chemotherapy; NA: Not applicable; UK: United Kingdom.

Table 2: Results of the meta-analysis in interested outcomes.

Outcome of interest	*n*	No. of patients (ELAPE/APE)	Statistical method	MD/OR (95% CI)	*P*	Study heterogeneity χ^2	df	I^2 (%)	*P*
Perioperative variables									
Operating time	9	947/593	IV, Random, MD (95% CI)	57.05 (28.61–85.48)	<0.001	81.17	8	90	<0.001
Estimated blood loss	8	1156/759	IV, Random, MD (95% CI)	−82.98 (−122.06 to −43.90)	<0.001	25.21	7	72	<0.001
LOS	6	682/552	IV, Random, MD (95% CI)	−0.58 (−2.18 to 1.01)	0.480	18.44	5	73	0.002
Surgical complications									
Post-operative perineal herniation	5	501/431	MH, Fixed, OR (95% CI)	1.41 (0.67–2.94)	0.360	4.07	4	2	0.400
Post-operative abdominal infection	4	394/274	MH, Fixed, OR (95% CI)	0.30 (0.11–0.81)	0.020	1.18	3	0	0.760
Post-operative urinary dysfunction	4	270/214	MH, Fixed, OR (95% CI)	2.16 (1.07–4.39)	0.030	0.55	3	0	0.910
Post-operative chronic perineal pain	3	303/257	MH, Random, OR (95% CI)	6.10 (1.49–24.95)	0.010	8.11	2	75	0.020
Post-operative urinary infection	3	247/189	MH, Fixed, OR (95% CI)	0.60 (0.19–1.89)	0.380	3.20	2	38	0.200
Post-operative parastomal hernia	3	80/107	MH, Fixed, OR (95% CI)	1.25 (0.59–2.66)	0.560	0.89	2	0	0.640
Post-operative intestinal obstruction	3	81/108	MH, Fixed, OR (95% CI)	2.64 (0.65–10.68)	0.170	0.87	2	0	0.650
PWC	14	1295/1227	MH, Random, OR (95% CI)	1.21 (0.75–1.94)	0.430	55.86	13	77	<0.001
Oncological variables									
IOP	15	1976/1580	MH, Fixed, OR (95% CI)	0.50 (0.39–0.64)	<0.001	27.37	14	49	0.020
CRM positive	16	1989/1589	MH, Random, OR (95% CI)	0.69 (0.42–1.14)	0.150	60.93	15	75	<0.001
LR	13	727/682	MH, Fixed, OR (95% CI)	0.29 (0.21–0.41)	<0.001	13.80	12	13	0.310

APE: Abdominoperineal excision; CI: Confidence interval; CRM: Circumferential resection margin; ELAPE: Extralevator abdominoperineal excision; IOP: Intra-operative perforation; IV: Inverse-variance statistical method; LOS: Length of hospital stay; LR: Local recurrence; MD: Mean difference; MH: Mantel-Haenszel statistical method; OR: Odds ratio; PWC: Perineal wound complication.

to 1.01, $P = 0.48$, Table 2) with high heterogeneity ($P = 0.002$, $I^2 = 73\%$). The subgroup analysis revealed ELAPE has shorter LOS in Asia, and no significant statistically difference in Europe ($P = 0.59$, $I^2 = 47\%$). When excluding one highly heterogeneous study[15] by sensitivity analysis, we found shorter LOS in ELAPE (MD = −1.34, 95% CI = −2.59 to −0.09, $P = 0.04$) with lower heterogeneity ($P = 0.25$, $I^2 = 26\%$), indicating that the above-mentioned result was unstable.

Meta-analysis of surgical complications

Post-operative perineal herniation

Pooled data from five studies[23,26,29,31,34] that reported the post-operative perineal herniation rate showed there was no significant statistically difference between ELAPE and APE (3.6% *vs.* 2.8%, OR = 1.41, 95% CI = 0.67–2.94, $P = 0.36$, Table 2) with lower heterogeneity ($P = 0.40$, $I^2 = 2\%$).

Post-operative abdominal infection

Pooled data from four studies[14,15,26,29] that reported the post-operative abdominal infection rate showed ELAPE was associated with lower rate of post-operative abdominal infection (1.3% *vs.* 5.1%, OR = 0.30, 95% CI = 0.11–0.81, $P = 0.02$, Table 2) with lower heterogeneity ($P = 0.76$, $I^2 = 0\%$).

Post-operative urinary dysfunction

Pooled data from four studies[14,23,26,29] that reported the post-operative urinary dysfunction rate showed ELAPE was associated with higher post-operative urinary dysfunction (11.1% *vs.* 7.0%, OR = 2.16, 95% CI = 1.07–4.39, $P = 0.03$, Table 2) with lower heterogeneity ($P = 0.91$, $I^2 = 0\%$).

Post-operative chronic perineal pain

Pooled data from the three studies[26,29,31] that reported the rate of post-operative chronic perineal pain showed ELAPE was associated with high rate of post-operative chronic perineal pain (40.6% *vs.* 18.3%, OR = 6.10, 95% CI = 1.49–24.95, $P = 0.01$, Table 2) with high heterogeneity ($P = 0.02$, $I^2 = 75\%$).

Post-operative urinary infection

Pooled data from the three studies[14,23,26] that reported post-operative urinary infection showed there was no significant statistically difference between ELAPE and APE (1.6% *vs.* 3.2%, OR = 0.60, 95% CI = 0.19–1.89, $P = 0.38$, Table 2) with lower heterogeneity ($P = 0.20$, $I^2 = 38\%$).

Post-operative parastomal hernia

Pooled data from the three studies[26,29,34] that reported the rate of post-operative parastomal hernia showed there was no significant statistically difference between ELAPE and APE (27.5% *vs.* 18.7%, OR = 1.25, 95% CI = 0.59–2.66, $P = 0.56$, Table 2) with lower heterogeneity ($P = 0.64$, $I^2 = 0\%$).

Post-operative intestinal obstruction

Pooled data from the three studies[14,29,34] that reported the rate of intestinal obstruction showed there was no significant statistically difference between ELAPE and APE (7.4% *vs.* 2.7%, OR = 2.64, 95% CI = 0.65–10.68, $P = 0.17$, Table 2) with lower heterogeneity ($P = 0.65$, $I^2 = 0\%$).

Perineal wound complication

The PWC rate was reported by 14 studies[14,16-18,23,24,26,28-34] (ELAPE group, $n = 1295$; APE group, $n = 1227$). No significant statistically difference was observed in PWC rate between ELAPE and APE (28.9% *vs.* 24.1%, OR = 1.21, 95% CI = 0.75–1.94, $P = 0.43$, Table 2) with high heterogeneity ($P < 0.001$, $I^2 = 77\%$, Figure 2). The subgroup analysis showed that there was no significant statistically difference in Asia ($P = 0.90$, $I^2 = 68\%$) and Europe ($P = 0.10$, $I^2 = 78\%$) [Figure 3]. When excluding two highly heterogeneous studies[23,31] by sensitivity analysis, we still found there was no significant statistically difference between ELAPE and APE (25.9% *vs.* 26.4%, OR = 0.97, 95% CI = 0.60–1.55, $P = 0.89$), indicating that the above-mentioned result was stable.

Meta-analysis of oncological variables

Circumferential resection margin positivity

The CRM positivity rate was reported by 16 studies[14-18,23-30,32-34] (ELAPE group, $n = 1989$; APE group, $n = 1589$). No significant statistically difference was observed in CRM positivity rate between ELAPE and APE (13.0% *vs.* 16.2%, OR = 0.69, 95% CI = 0.42–1.14, $P = 0.15$, Table 2) with high heterogeneity ($P < 0.001$, $I^2 = 75\%$, Figure 4), which was consistent with the high quality meta-analysis of Negoi *et al.*[12] The subgroup analysis revealed there was no statistically significant difference in Europe ($P = 0.53$, $I^2 = 81\%$), but lower CRM positivity in Asia ($P = 0.004$, $I^2 = 0\%$) [Figure 5]. When excluding one high heterogeneous study[23] by sensitivity analysis, we still found there was no statistically significant difference between ELAPE and APE (12.4% *vs.* 13.3%, OR = 0.80, 95% CI = 0.50–1.26, $P = 0.34$), indicating that the above-mentioned result was stable.

Intra-operative perforation

The IOP rate was reported by 15 studies[14-17,23-30,32-34] (ELAPE group, $n = 1976$; APE group, $n = 1580$). Fixed-effect model analysis revealed significantly lower IOP rate for ELAPE than APE (6.6% *vs.* 11.3%, OR = 0.50, 95% CI = 0.39–0.64, $P < 0.001$, Table 2) with lower heterogeneity ($P = 0.02$, $I^2 = 49\%$, Figure 6), which was consistent with a high quality meta-analysis by Negoi *et al.*[12]

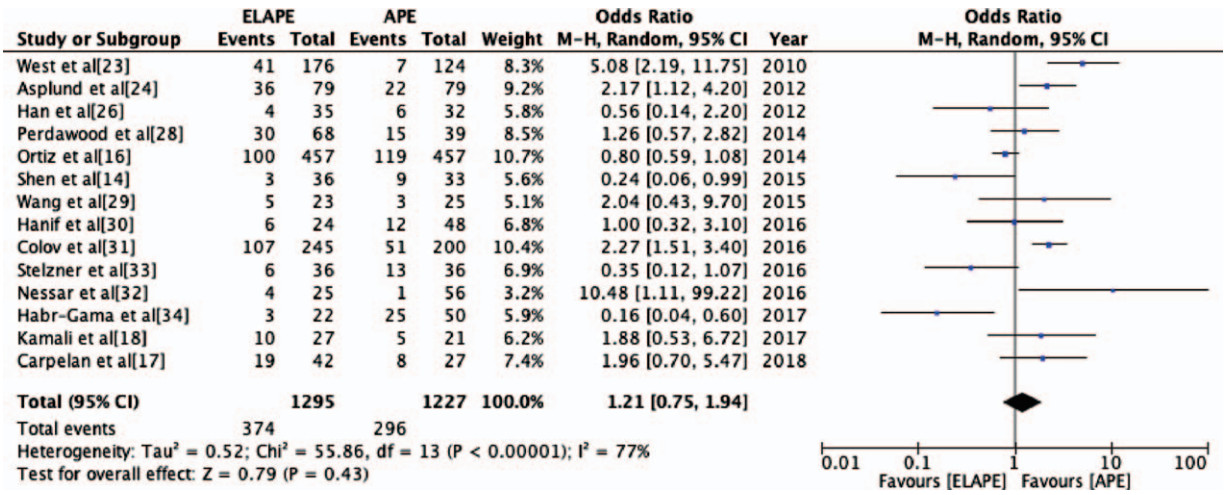

Figure 2: Odds Ratio for perineal wound complication from fourteen included studies. APE: Abdominoperineal excision; CI: Confidence interval; ELAPE: Extralevator abdominoperineal excision; MH: Mantel-Haenszel.

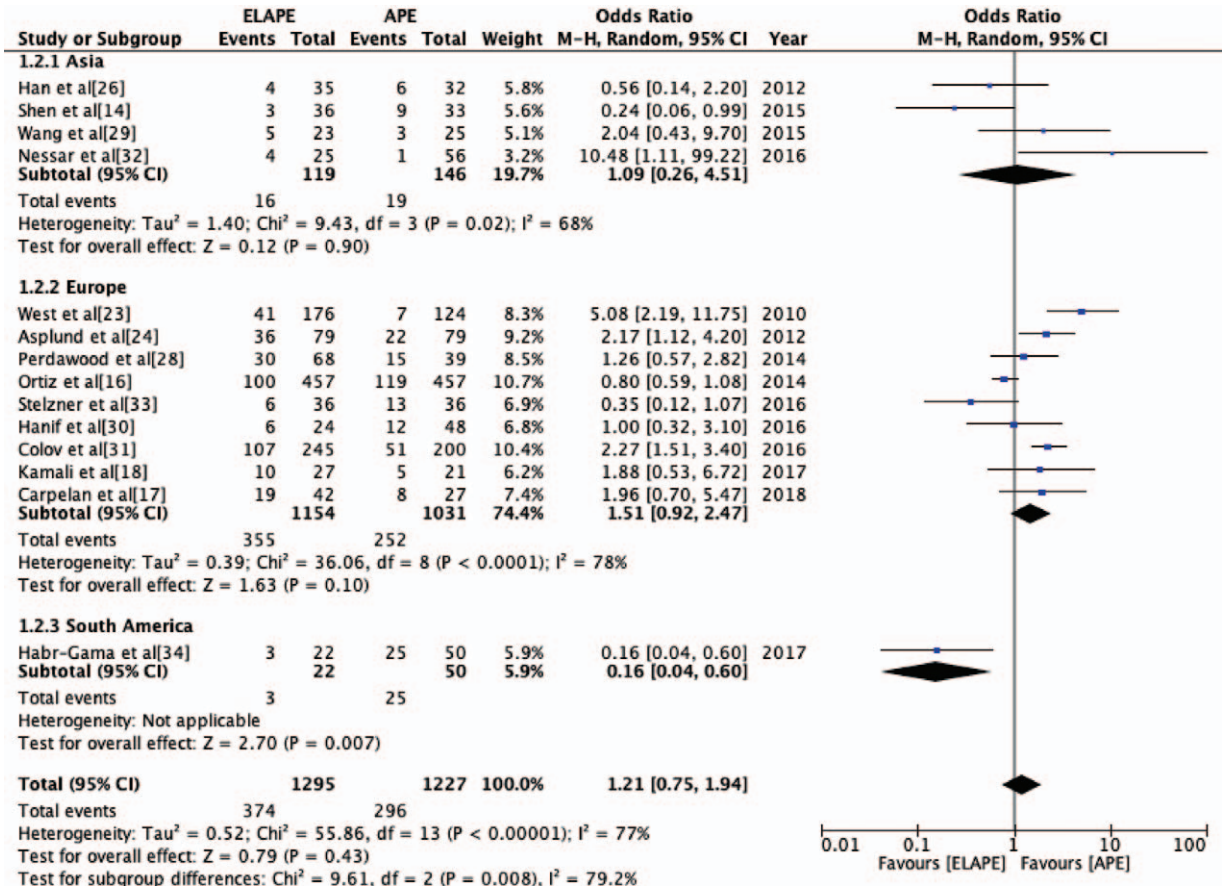

Figure 3: Odds Ratio for perineal wound complication grouped by Asia, Europe, and South America. APE: Abdominoperineal excision; CI: Confidence interval; ELAPE: Extralevator abdominoperineal excision; MH: Mantel-Haenszel.

Local recurrence

The LR rate was reported by 13 studies[14,17,18,23-26,28-30,32-34] (ELAPE group, $n = 727$; APE group, $n = 682$). Fixed-effect model analysis revealed significantly lower LR rate for ELAPE than APE (8.8% *vs.* 20.5%, OR = 0.29, 95% CI = 0.21–0.41, $P < 0.001$, Table 2) with lower heterogeneity ($P = 0.31$, $I^2 = 13\%$, Figure 7), which was inconsistent with a high quality meta-analysis by Negoi *et al*.[12]

Subgroup and sensitivity analyses

Subgroup (according to the geographical location) and sensitivity analyses were implemented to investigate operating time, estimated blood loss, LOS, PWC rate,

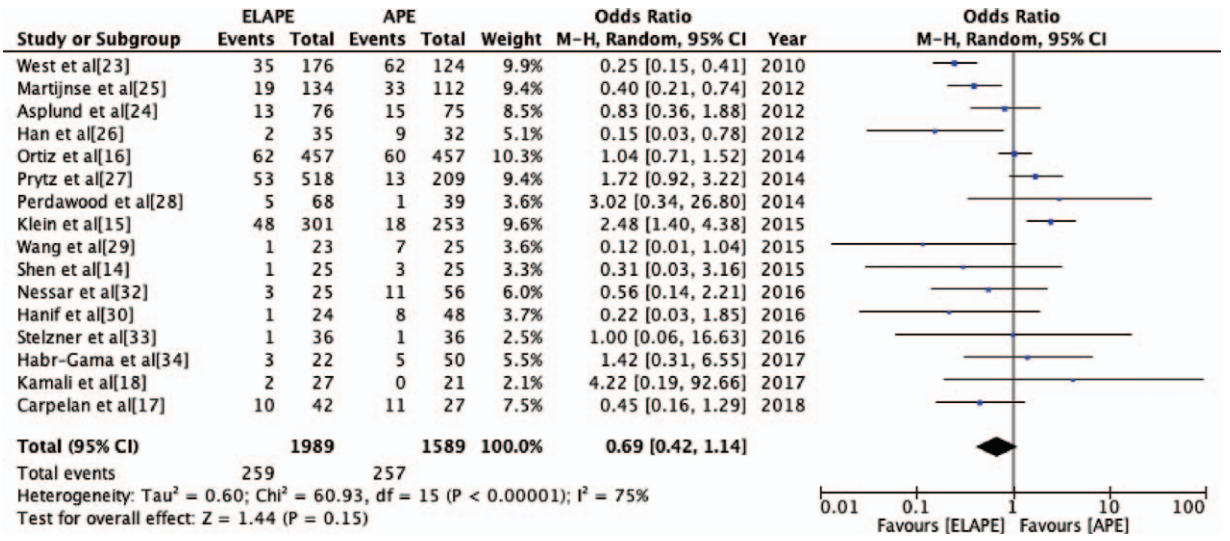

Figure 4: Odds Ratio for circumferential resection margin positivity from sixteen included studies. APE: Abdominoperineal excision; CI: Confidence interval; ELAPE: Extralevator abdominoperineal excision; MH: Mantel-Haenszel.

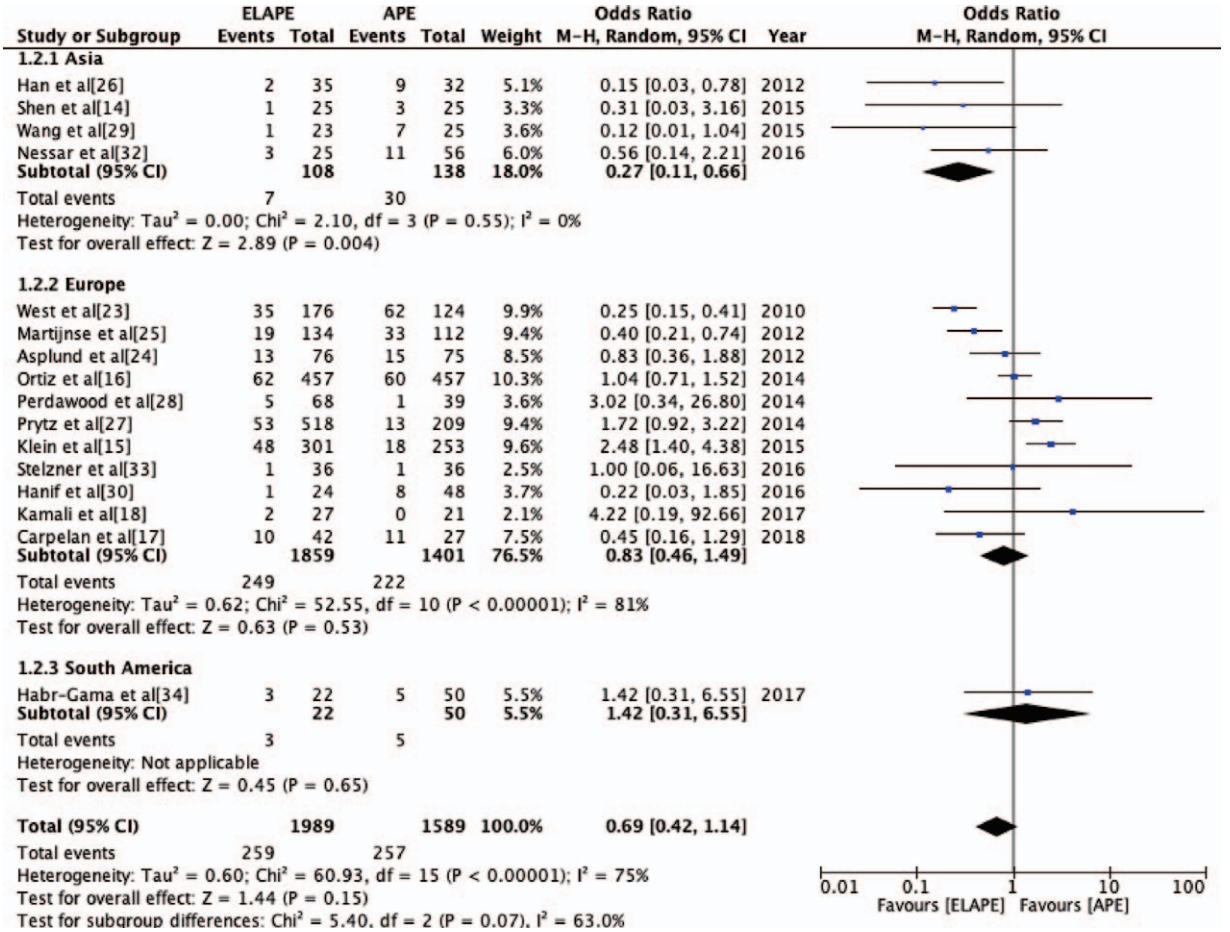

Figure 5: Odds Ratio for circumferential resection margin positivity grouped by Asia, Europe, and South America. APE: Abdominoperineal excision; CI: Confidence interval; ELAPE: Extralevator abdominoperineal excision; MH: Mantel-Haenszel.

and CRM positivity rate. Studies by Klein *et al*[15] and West *et al*[23] were the main drivers of heterogeneity in this review. Furthermore, sensitivity analysis revealed that the inclusion of the South American study[34] had little effect on the heterogeneity or stability of the variables.

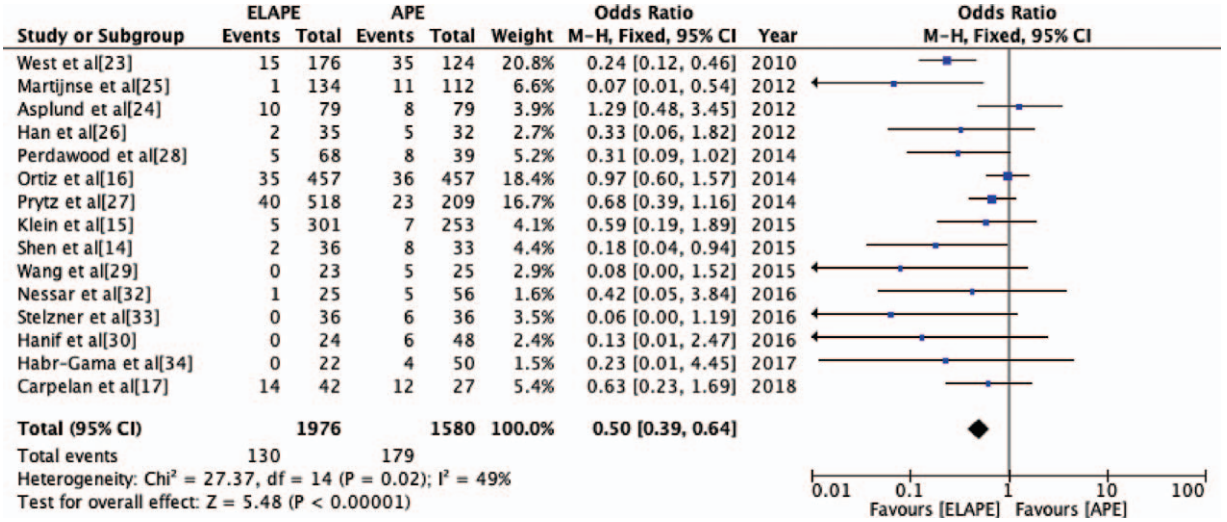

Figure 6: Odds Ratio for intra-operative perforation from 15 included studies. APE: Abdominoperineal excision; CI: Confidence interval; ELAPE: Extralevator abdominoperineal excision; MH: Mantel-Haenszel.

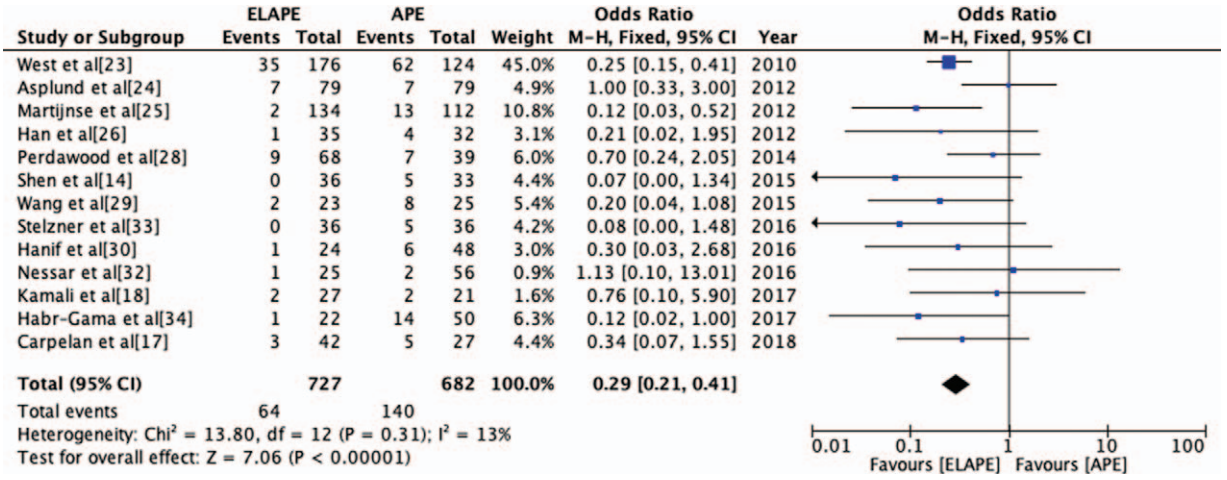

Figure 7: Odds Ratio for local recurrence from included 13 studies. APE: Abdominoperineal excision; CI: Confidence interval; ELAPE: Extralevator abdominoperineal excision; MH: Mantel-Haenszel.

Publication bias

The only RCT[26] in this study was removed. The funnel plots showed that all data within the 95% CI are distributed symmetrically for all outcomes of interest except the LR rate [Supplementary Figure 1, http://links.lww.com/CM9/A103], indicating that the publication bias was minimal.

Discussion

The present study showed that compared to APE, ELAPE had a longer operating time, lower estimated blood loss, lower incidence of abdominal infection, but a higher incidence of urinary dysfunction and chronic perineal pain. No significant difference was observed in the rate of PWC, perineal herniation, urinary infection, parastomal hernia, or intestinal obstruction between the two surgical approaches. Finally, this study showed that the IOP and LR rates were lower for ELAPE than those for APE, while the CRM positivity rate did not differ significantly between them.

We speculate that the increased operating time observed for ELAPE maybe because this technology was recently adopted and had a long learning curve for beginners. Other factors contributing to the difference in operation time and blood loss between ELAPE and APE included differences in patient positioning, removal of the coccyx, the type of perineal reconstruction, and the type of technology used (open, laparoscopic, or robotic surgery). However, the prone Jack-Knife position and the application of minimally invasive techniques can provide excellent exposure of the perineal structures and direct visualization of the operative field, which may reduce blood loss during surgery. A shorter LOS after ELAPE was observed after removing the highly heterogeneous study reported by Klein *et al*.[15] However, several significant limitations were present in the study of Klein *et al*[15] and are discussed in the following section.

Regarding surgical complications, lower rate of abdominal infection after ELAPE may attribute to the application of more minimally invasive techniques (laparoscopic or robotic surgery) in abdominal surgery. Differences in the experience of chronic perineal pain may result from the wider excision of the levator ani muscles and ischiorectal fossa fat. Han *et al*[26] and Wang *et al*[29] demonstrated that coccyx preservation significantly reduced the occurrence of chronic perineal pain in a study with a small number of patients, and Han *et al*[26] even proposed that coccygectomy may be the main cause of chronic perineal pain. However, it is well known that the frequency of coccygectomy is lower for the perineal method. Thus, this issue deserves further discussion. Genitourinary function is innervated by the pelvic autonomic nervous plexuses and can be influenced by injury in the region of the hypogastric plexus before it joins the parasympathetic nerves at the level of the inferior hypogastric plexus.[35,36] A recent anatomic dissection study[36] also showed that clear identification of pelvic anatomic landmarks during surgery might be useful for both achieving CRM negativity and preserving urogenital function. The intra-operative separation and dissection by ELAPE are performed using the two-plane method. The plane of the mesorectum is separated in the abdominal surgery, and the perineum is separated along the lateral plane of the levator ani muscle. Together, these procedures improve the visibility of the surgical plane and anatomy, leading to lower rates of CRM positivity, IOP, and genitourinary injury. Unfortunately, the results of this study indicated that of these three outcomes, only the IOP rate was improved by ELAPE. The higher rate of PWCs in ELAPE (ELAPE, 28.9%; APE, 24.1%) may result from the ELAPE approach and the type of closure used to repair the perineal defect after surgery (primary closure or reconstruction). One national study[31] of PWCs reported a high rate of PWC (75%) in patients who underwent APE. From an anatomical point of view, APE involves removal of structures of the mesorectum, while ELAPE uses an expanded scope of resection as compared to APE. Thus, both techniques ultimately create a large perineal defect, which can result in a high PWC rate, especially with the ELAPE approach. Primary closure was reported to have a higher rate of PWC after APE,[37] and many medical centers are placing greater efforts into the reconstruction of the pelvic floor. A high-quality meta-analysis[38] of pelvic floor reconstruction reported that the PWC rate was equivalent between 255 patients undergoing flap repair and 85 patients undergoing biological mesh repair. The latest statement[39] also reported that myocutaneous flaps and biological mesh were both effective for use in ELAPE closure. However, the evidence is insufficient to allow recommendation of one particular method of perineal closure until now. In addition, pre-operative irradiation and neo-adjuvant therapy were also defined as risk factors for PWCs.[40] A meta-analysis reported that the PWC rate after ELAPE and APE was 37.6% and 30.2%, respectively, with chemoradiation as compared to 14.8% and 15.3% without chemoradiation.[41] In view of the higher rate of PWC after ELAPE, Han *et al*[26] first proposed the new concept of individualized APE, which aimed to preserve normal tissue, achieve local radical excision, minimize operative trauma of the perineal wound, and minimize damage to the nerves supplying the genital organs. However, the outcomes of individualized APE should be further explored in future studies.

With respect to oncological variables, the rates of CRM positivity and IOP have been demonstrated to correlate with a poor prognosis in patients with low rectal cancer.[42,43] Because of the poor prognosis resulting from the surgical waist remaining after APE, separation of the levators close to the surgical waist in ELAPE approach. As a result, the extent of resection and the thickness of the excised tissue are undoubtedly superior with ELAPE and should theoretically reduce the rates of CRM positivity and IOP. Previous studies have shown that the IOP rate correlates significantly to the tumor level, advanced T and M stage, and quality of mesorectum excision.[16] In ELAPE, en bloc removal of the tumor and levators clearly reduced the IOP rate, as indicated by numerous studies.[14,26,29,30,32,33] However, one nationwide database study by Klein *et al*[15] reported opposing results. Upon careful review, obvious selection bias was present in their study. First, patients who underwent ELAPE in their study were more likely to have received neo-adjuvant therapy. Second, although ELAPE is now applied to tumors of both low and high stages, more high T-stage tumors were included in the ELAPE group in their study. Third, their lack of standardization of surgical techniques and indications was also unacceptable. Moreover, two studies from Europe[17,23] and the only RCT, from China[26] investigating advanced low rectal cancer showed the perforation is most often located anteriorly; this observation should be considered in surgical plans. Several factors, including the body mass index, tumor stage, and pre-operative therapies, also have been proven to affect the CRM positivity rate.[19,44] Neo-adjuvant therapy has been widely used and may improve the tumor stage and change the treatment strategy to some extent. A recent study reported that 10.3% of patients showed a pathological complete response to neoadjuvant therapy in a single UK tertiary center, further confirming the influence of neo-adjuvant therapy.[45] Thus, the CRM positivity rate in the two groups might not be accurate, given the effects of neoadjuvant therapy. Further studies are needed to elucidate the effects of neo-adjuvant therapy ion the CRM positivity rate. Moreover, ELAPE might not be advantageous for tumors located away from the surgical waist. How *et al*[46] concluded that ELAPE might be more appropriate for tumors located above and below the puborectalis sling and anteriorly at the level of the prostate. Another recent study from a tertiary-care center concluded that ELAPE should be the preferred approach for low rectal tumors with involvement of the levators and that current evidence is insufficient to recommend ELAPE over APE for patients in whom the levators are not involved.[47] In the present study, we observed that the LR rate was significantly lower after ELAPE (9%) than after APE (21%). Further analysis revealed a certain bias in the funnel plot for LR rate, which may result from differences in tumor stages, pre-operative neoadjuvant therapy, and post-operative chemotherapy. Missing data also may be a contributing factor.

Compared with the previous seven meta-analyses, this study has several advantages. First, using rigorous statistical

methods, this study is a registered meta-analysis with a large sample size aiming to explicitly compare the perioperative variables, surgical complications, and oncological variables between ELAPE and APE. Second, this study showed that compared to APE, ELAPE has a lower incidence of abdominal infection but a higher incidence of urinary dysfunction. The latter complication was not expected by clinicians and requires attention in surgery. Third, using subgroup and sensitivity analysis, we conclude that the higher heterogeneity observed in this study undoubtedly come from two studies in Europe,[15,23] likely resulting from their multicenter and the lack of standardization of surgical techniques and indications in one study. Therefore, the surgical indications for ELAPE deserve further discussion in the future. Meanwhile, several limitations of this meta-analysis should also be considered. First, only one small-scale RCT was included in the cohort of 17 studies, which may decrease the reliability of the results. Second, a majority of patients in the ELAPE group received neoadjuvant treatment, which could affect the long-term results. Whether this factor compared CRM positivity and the PWC rate was unknown.

In conclusion, for the surgical treatment of low rectal cancer, ELAPE was associated with decreased rates of IOP and LR, with no increase in CRM positivity or postoperative PWC rate as compared to those of APE.

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Conflicts of interest

None.

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