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ORIGINAL ARTICLE

Oncological superiority of extralevator abdominoperineal resection over conventional abdominoperineal resection: a meta-analysis

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Abstracts

Purpose The oncological superiority, i.e., lower circumferential resection margin (CRM) involvement, lower intraoperative perforation (IOP), and local recurrence (LR) rates, of extralevator abdominoperineal resection (EAPR) over conventional abdominoperineal resection (APR) for rectal cancer is inconclusive. This meta-analysis systematically compared the rates of CRM involvement, IOP, and LR of rectal cancer patients treated by EAPR and APR, respectively.

Methods An electronic literature search of MEDLINE, EMBASE, and Cochrane Library through May 2013 was performed by two investigators independently to identify studies evaluating the CRM involvement, IOP, and LR rates of EAPR and APR, and search results were cross-checked to reach a consensus. Data was extracted accordingly. A Mantel–Haenszel random effects model was used to calculate the odds ratio (OR) with 95 % confidence intervals (95 % CI).

Results Six studies with a total of 881 patients were included. Meta-analysis of CRM involvement and IOP data from all six studies demonstrated significant lower CRM involvement (OR, 0.36; 95%CI, 0.23–0.58; $P<0.0001$) and IOP (OR, 0.31; 95%CI, 0.12–0.80; $P=0.02$) rates of EAPR. Data from four studies also showed that EAPR was associated with a lower LR rate than APR (OR, 0.27; 95%CI, 0.08–0.95; $P=0.04$). No differences of between-study heterogeneity or publication bias were seen in any of the meta-analyses.

Conclusions Extralevator abdominoperineal resection could achieve better CRM involvement outcome and lower IOP and LR rates, demonstrating an oncological superiority over conventional abdominoperineal resection.

Keywords Extralevator abdominoperineal resection (EAPR) · Abdominoperineal resection (APR) · Circumferential resection margin involvement (CRM) · Intraoperative perforation (IOP) · Local recurrence (LR)

Introduction

Despite advances in adjuvant therapy [1], surgery remains to be the primary treatment for rectal cancer [2]. The abdominoperineal resection (APR) has been the standard operation for advanced low rectal cancer [3]. However, compared with anterior resection (AR), the local control and survival of which have been greatly improved with the technical development of total mesorectal excision (TME) [4–8], APR still bears a relatively worse outcome, i.e., greater circumferential resection margin (CRM) positivity, higher local recurrence (LR) and intraoperative perforation (IOP) rate, and shorter overall and disease free survival [9–11]. These disadvantages could be partially attributed to that more cases of lower [12] and advanced tumors [13] that are treated by APR instead of by AR. However, it is noteworthy that specimens removed by APR often have less tissue surrounding the tumor, which results in a narrow waist around the levator level in tissue morphometry [14], and it is reported that a wider

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resection surrounding the levator would provide additional clinic benefits for patients [15]. Thus technical improvement in APR is required [16].

Recently, a more extended approach, which was later called extralevator abdominoperineal resection (EAPR), has been introduced by T. Holm [17]. This procedure aims at removing more tissues surrounding the tumor, including the mesorectum, the striated sphincter, and levator ani, to leave with a cylindrical specimen rather than the one with a surgical waist by conventional APR. After its initial introduction, this technique has spread among surgeons: several studies have reported lower CRM involvement, IOP, and LR rates by EAPR than conventional APR, showing a favorable oncological outcome for EAPR [18–21]. However, the conclusion is not clear: literature have also reported comparable results by conventional APR, demonstrating its non-inferiority to EAPR [22–24]. Moreover, there still lacks large multicenter prospective randomized controlled trials to systematically compare outcomes of these two surgical techniques, especially the oncological outcomes. Therefore, to more conclusively evaluate whether there exists an oncological superiority of EAPR to APR, namely lower CRM positivity and IOP and LR rates, we carried out this meta-analysis.

Methods

Data source

To identify potential publications, a comprehensive search of the MEDLINE (through PubMed), EMBASE, and Cochrane Library through May 2013 was separately performed by two researchers (Ao Huang and Hongchao Zhao) using the following terms: cylindrical abdominoperineal resection/excision, extralevator/extra-levator abdominoperineal resection/excision, extended abdominoperineal resection/excision, CRM, perforation, local recurrence as well as their combinations. All related articles were retrieved and evaluated to avoid omitting any possible studies. References of all relevant researches were manually searched and assessed. Search results were cross-checked until no more publications were found. Disagreements were resolved by consensus. This meta-analysis was conducted under the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 [25].

Study selection and data extraction

To be included in this meta-analysis, studies had to meet the following criteria: (a) studies must report at least one of the three outcomes, i.e., CRM involvement, IOP, and LR events/rates and (b) studies had to compare EAPR with APR. Figure 1 is the flowchart of the study selection process. Two investigators (Ao Huang and Hongchao Zhao) independently extracted the following data: number of patients operated with EAPR and APR in each study, case numbers and/or rates of CRM involvement, IOP, and LR; in the case of only rates provided, numbers of CRM involvement, IOP, and LR events were calculated manually. Other information, i.e., primary author's name, publication time, study design, number of patients enrolled, total surgeries performed, and patient characteristics, including sex, age, and preoperative chemoradiotherapy status, were also collected. Discrepancies were resolved by cross-checking data to reach consensus.

Statistical analysis

The Review Manager (RevMan) Version 5.2 (http://ims.cochrane.org/revman) was used for meta-analysis. The heterogeneity among the included studies was first assessed by

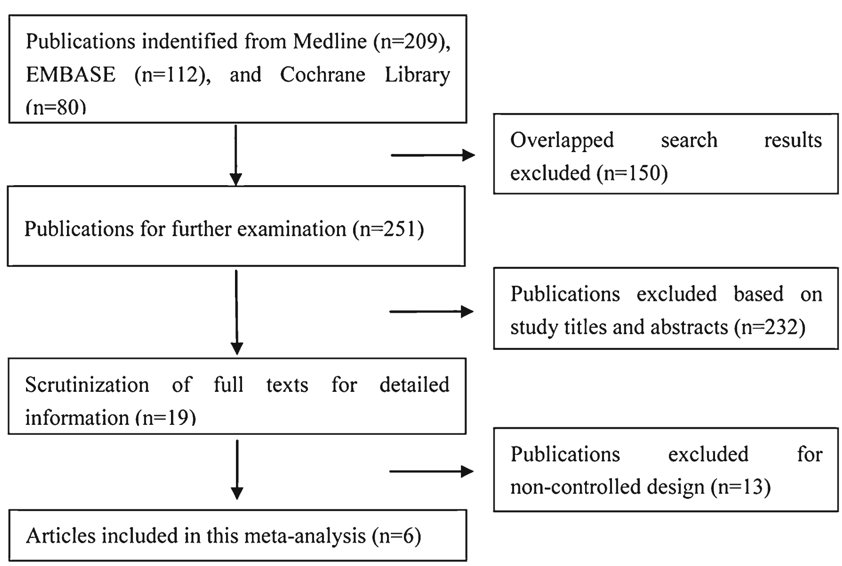

Fig. 1 The flowchart of data search and extract procedure

the Cochran's $\chi 2$ and the I^2 test. According to the heterogeneity and the varying risk profiles of patients undergoing surgeries treated in different centers as well as the different indication for each surgical technique, a Mantel–Haenszel random effects model was used to calculate the pooled odds ratio (OR), along with the 95 % confidence intervals (95 % CI); $P<0.05$ was considered to be statistically significant. Subgroup analysis of CRM involvement, IOP, and LR rates were performed with studies which presented data of patients who all had neoadjuvant therapy. Egger's linear regression test and Begg's adjusted rank correlation test using Stata program (version 10.0; Stata Corporation, College Station, TX) were applied to assess the publication bias.

Results

Study characteristics

A comprehensive search of the electronic databases identified 401 potential studies. Among them, 150 overlapped search results were first excluded; then, 232 studies were excluded based on irrelevant titles and abstracts. After scrutinizing full texts of the rest articles, a further 13 studies were excluded for uncontrolled design or unrelated study objectives. Finally, six studies, including a total of 881 patients, were included in this meta-analysis [23, 26–30]. Of the 881 patients, 468 cases received EAPR and 413 underwent APR. The included studies were conducted during 1997–2011 and published between 2010 and 2012; all studies had compared the CRM involvement and IOP rates of EAPR and APR, while four studies also reported LR rate [23, 26–28]; only one study reported long-term survival information [26]. Of the six studies, two were prospective [26, 29] and four were retrospective [23, 27, 28, 30]; of the prospective studies, one was randomized, open-label, parallel controlled study [26]; five were carried out in a single center manner [23, 26–29] and one in multicenter [30]; five studies originated from Europe [23, 27–30] and one from China [26].

Table 1 described the characteristics of the six included studies. Patients enrolled in each study ranged from 36 to 300. Asplund et al., Han et al., and Stelzner et al. presented actual numbers of CRM involvement, IOP, and LR events; Vaughan-Shaw et al. reported case numbers of CRM involvement and IOP; Martijnse et al. reported rates of CRM involvement, IOP, and LR events,while West et al. reported CRM and IOP rates. In case of no accurate number of events available, we calculated the number of patients who developed CRM involvement, IOP, and/or LR events based on their rates and the total number of patients in each study. Three studies presented data of the events stratified by neoadjuvant therapy status [27, 28, 30]. The data extracted from the included studies was shown in Table 2.

Table 1 Characteristics of included studies

Reference (year)	Country (institutions)	Design (period)	Surgeries performed (EAPR/APR)	Age (range)	Gender (M/F)	Neoadjuvant therapy				Primary outcome
						Chemoradiotherapy		Radiotherapy		
						EAPR	APR	EAPR	APR	
West et al. [30]	UK and Sweden (multiple)	RCS (1997–2008)	176/124	67.9 (58–76)	203/91	NA	NA	130/165 (76.8 %)	90/114 (78.9 %)	CRM, IOP
Vaughan-Shaw et al. [29]	UK (single)	PCS (2009–2011)	16/20	71.7 (49–89)	20/16	9/16 (56.3 %)	7/20 (35 %)	7/16 (43.7 %)	9/20 (45 %)	Short-term outcome, QOL
Asplund et al. [23]	Sweden (single)	RCS (2004–2009)	79/79	67.5 (35–89)	99/59	15/79 (19 %)	5/79 (6 %)	60/79 (76 %)	66/79 (84 %)	CRM, IOP, LR, short-term complication
Han et al. [26]	China (single)	PRCT (2008–2010)	35/32	65.4 (32–84)	41/26	EAPR vs APR: 10/35vs 9/32				Surgical outcome, CRM, LR
Martijnse et al. [27]	Netherlands (single)	RCS (2000–2010)	134/112	63 (NA)	163/83	All underwent				CRM, IOP, wound abscess
Stelzner et al. [28]	Germany (single)	RCS (1997–2010)	28/46	64.8 (44–82)	56/18	All underwent				CRM, IOP

RCS retrospective cohort study, *PRCT* prospective randomized controlled study, *PCS* prospective cohort study, *NA* not available, *CRM* circumferential resection margin, *IOP* intraoperative perforation, *LR* local recurrence, *QOL* quality of life

Table 2 CRM involvement, IOP, and LR events/rates of EAPR and APR

Reference (year)	Surgeries included (EAPR/APR)	CRM involvement		IOP		LR	
		EAPR	APR	EAPR	APR	EAPR	APR
West et al. [30]	176/124	20.3 %	49.6 %	28.2 %	8.2 %	NA	NA
Vaughan-Shaw et al. [29]	16/20	0	3	0	1	NA	NA
Asplund et al. [23]	79/79	13	15	8	10	7	7
Han et al. [26]	35/32	2	9	2	5	1	6
Martijnse et al. [27]	134/112	14.2 %	29.5 %	0.7 %	9.8 %	1.7 %	11.5 %
Stelzner et al. [28]	28/46	0	2	0	7	1	7

Effects of EAPR and APR for CRM involvement, IOP, and LR rates

All six included studies contributed to the meta-analysis of the CRM involvement rate of EAPR compared to APR (Fig. 2). All study obeyed the 1-mm rule of CRM positivity and applied TME technique. The total positive CRM rate was 22.1 % (184 of 831). The rates for the EAPR and APR group were 14.6 % (63 of 432) and 30.3 % (121 of 399), respectively. No evidence of between-study heterogeneity was shown (P=0.24; I^2=26 %). Pooled analysis of OR by the random effects model demonstrated a superiority of EAPR to APR in reducing the CRM involvement rate (OR=0.36, 95%CI=0.23–0.58; P<0.0001). No significant publication bias was seen (Egger's test, P=0.271; Begg's test, P=0.308).

The six included studies also provided data for the meta-analysis of IOP rate (Fig. 3). The total IOP rate for all patients was 10.7 % (94 of 876). For the EAPR group, the IOP rate was 5.8 % (27 of 463) and for APR group, it was 16.2 % (32 of 289). Meta-analysis of all six studies showed a significant decrease of IOP rate in the EAPR group compared with APR group (OR=0.31, 95%CI=0.12–0.80; P=0.02). No significant between-study heterogeneity (P=0.04; I^2=57 %) or publication bias was observed (Egger's test, P=0.143; Begg's test, P=0.308).

Of all included studies, four studies reported data on LR (Fig. 4). The total LR rate was 8.1 % (44 of 545). LR rates of the EAPR and APR group were 4.0 % (11 of 276) and 12.3 % (33 of 269), respectively. Meta analysis of the four studies revealed a significantly decreased LR rate for EAPR (OR=0.27, 95%CI=0.08–0.95; P=0.04). Neither between-study heterogeneity (P=0.08; I^2=56 %) nor publication bias (Egger's test, P=0.507; Begg's test, P=0.308) was observed.

Subgroup analysis for the effects of EAPR and APR on CRM involvement, IOP, and LR rates

Neoadjuvant therapy plays an important role in downstaging tumor [31] and is associated with an improved local control [32]. Thus, we made a subgroup analysis to exclude the confounding interference of preoperative chemoradiotherapy by analyzing patients with the same neoadjuvant therapy status. Of the six studies, two (Martijnse et al. and Stelzner et al.) comprised of patients who all received neoadjuvant therapy, while one study (West et al.) provided number of patients who had been given such treatment. The remaining three studies included mixed patients with or without neoadjuvant therapy; however, the precise case numbers were not available. Thus, the former three studies were analyzed, and as shown in Table 3, the CRM involvement, IOP, and LR rates in

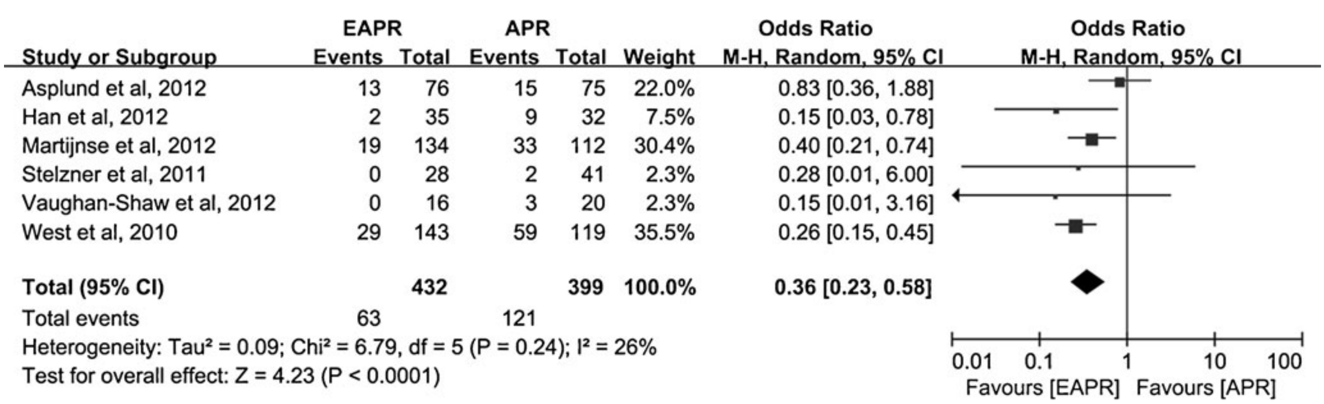

Fig. 2 Forest plot of the weighted odds ratio of CRM involvement rate. The estimates of the weighted odds ratio in each study correspond to the *middle of each square* and the *horizontal line* gives the 95 % confidence intervals. The summary odds ratio is represented by the *middle of the solid diamond*

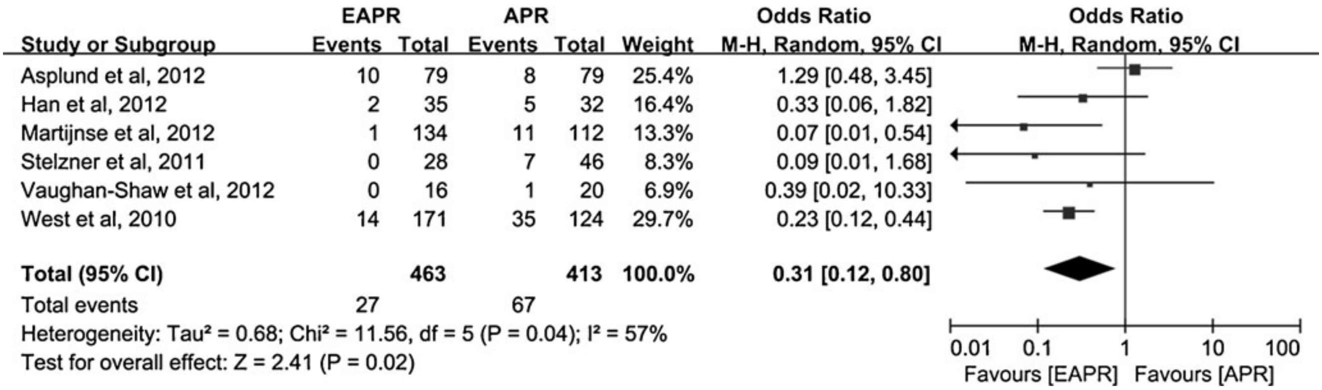

Fig. 3 Forest plot of the weighted odds ratio of IOP rate

EAPR group were significantly lower than that of APR group. In addition, we compared the perineal complication (wound infection or abscess) between the two groups and found a slightly increased, yet nonsignificant postoperative morbidity of EAPR (21.8 vs 18.3 %, P=0.67; heterogeneity: P=0.05, I^2=63 %).

Discussion

This study provides the first meta-analysis to compare the oncological outcomes between EAPR and APR. Six studies with a total of 881 patients were included. Results showed that CRM involvement, IOP, and LR rates of patients treated by EAPR were significantly lower than those of APR. Furthermore, meta-analyses of these measurements after homogenizing neoadjuvant therapy status all demonstrated significant benefits of EAPR.

With the introduction of TME, the outcome of rectal cancer patients treated by conventional APR had been improved; however, the CRM involvement, LR, and IOP rates of APR still remained high and also inferior to those of AR [10, 16]. Importantly, CRM involvement as an alternative predictor for local recurrence and inadvertent intraoperative perforation as a prognostic factor for adverse oncologic outcome were well-established [33]. In this meta-analysis, the overall CRM involvement, IOP, and LR rates of EAPR were lower than those of the conventional APR. The pooled rate of CRM involvement for EARP was 14.6 %, which was lower than that of the APR (30.3 %) and roughly equivalent to rates reported for AR (range, 5–12 %) [10, 34], indicating an advantage of EAPR in reducing CRM positivity. Consistently, pooled rates of IOP and LR for EAPR were also lower than those of APR. Considering the definition of CRM involvement, tumor, or lymph nodes within the resection margin of less than 1 mm [35], the benefit of more tissues removed in EAPR would greatly reduce the chance of CRM involvement, which would consequently lower the possibility of local recurrence. Also, the ease of excising more tissues around tumor reduced the chance of perforation. In the conventional APR surgery, the perineal procedure and anterior dissection are prone to be sites of perforation [30], whereas the EAPR removed tumor and the levator en bloc to avoid such incidents without forming a waist on the specimen [17]. On the tissue morphometry, specimens of EAPR have larger cross-sectional areas and more tissues surrounding the internal sphincter and muscularis propria [26, 30], which may yield additional chance to avoid perforation. This could be well explained by the significant decrease of IOP rate from 9.8 to 0.7 % in the study conducted by Martijnse et al. [27], of which the same group of surgeons performed APR during 2000–2005 and transferred to EAPR after then.

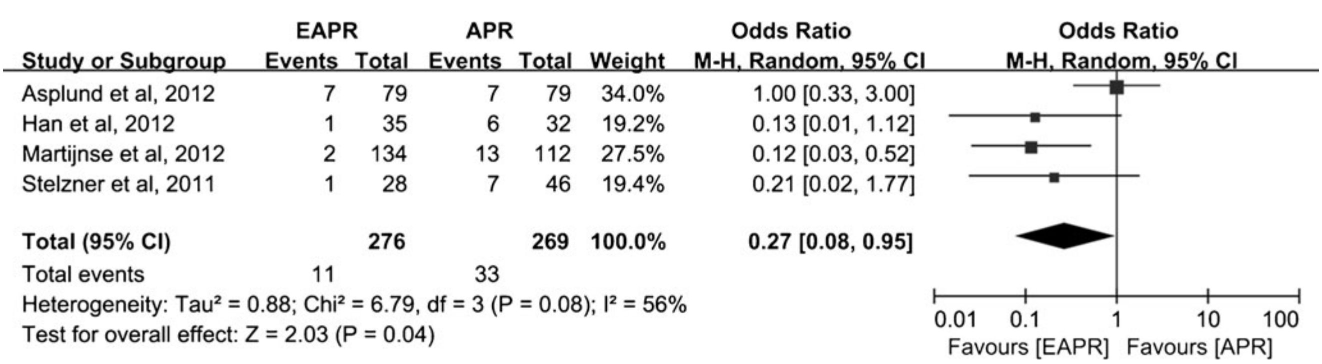

Fig. 4 Forest plot of the weighted odds ratio of LR rate

Table 3 Subgroup analysis for the effects of EAPR and APR on CRM involvement, IOP, and LR rates

Subgroup analysis	Included studies	No. of events		OR	95%CI	*P* value	Heterogeneity	
		EAPR	APR				I^2 (%)	*P* value
CRM involvement	3	28/223	60/196	0.24	0.10–0.60	=0.002	51	0.13
IOP	3	6/245	36/206	0.10	0.04–0.24	<0.00001	0	0.93
LR	2	3/162	20/158	0.14	0.04–0.48	=0.002	0	0.66

In the subgroup analysis, we first examined the pooled rates of these three parameters in studies composed of patients with the same neoadjuvant therapy status. Preoperative chemoradiotherapy could induce tumor regression and lead to tumor downstage, and it was demonstrated to be associated with increased resectability and improved local control rate [36]. Hence, difference of neoadjuvant therapy status among patients treated by EAPR and APR could be a variable that potentially influenced the surgery outcomes. To exclude the interference caused by heterozygous chemoradiotherapy status, we extracted the data of patients with homogeneous preoperative status, either all had undergone chemoradiotherapy or none. Clearly, the pooled results demonstrated the superiority of EAPR to APR in decreasing the CRM involvement, IOP, and LR rates in patients who had undergone neoadjuvant therapy. However, we could not know whether and to what extent the neoadjuvant therapy exerts an impact on these outcomes as a subgroup analysis of patients without preoperative chemoradiotherapy was unavailable. We also compared postoperative complications (perineal would infection or abscess) of EAPR and APR. EAPR showed a nonsignificant but higher postoperative perineal wound complication frequency. Yet, this result may need further validation as cases included in this analysis were not large enough, and it is generally considered that EAPR tends to be a more invasive technique [17].

Several limitations in this meta-analysis need to be considered. First, one study was conducted in a multicenter manner and the other five studies were all single center-based; additionally, only one study was prospectively conducted and designed with randomized control. Second, patients enrolled in each study were not in a large scale and this may weaken the significance of differences. Third, confounding bias caused by neoadjuvant therapy should be taken into account in interpreting our findings. More importantly, data presented in this meta-analysis only demonstrated the oncological superiority of EAPR to APR. Due to a deficiency of trials comparing the side effects, complications, and long-term survival outcomes of these two surgeries, it was impossible to identify whether EAPR should be recommended and thus, cautions should be made to further extend our conclusions.

In summary, we provided convincing evidences showing that rectal cancer treated by EAPR was associated with lower CRM involvement, IOP, and LR rates compared with conventional APR. These findings demonstrated the oncological superiority of EAPR for rectal cancer patients. In the future, prospective randomized controlled trials are warranted to systematically compare the complication and survival outcomes of EAPR and conventional APR.

Conflict of interest The authors declare that they have no conflicts of interest.

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