Systematic review

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Robotic *vs* laparoscopic total mesorectal excision for rectal cancers: has a paradigm change occurred? A systematic review by updated meta-analysis

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Abstract

Aim The debate about the oncological adequacy, safety and efficiency of robotic *vs* laparoscopic total mesorectal excision for rectal cancers continues. Therefore, an updated, traditional and cumulative meta-analysis was performed with the aim of assessing the new evidence on this topic.

Method A systematic search of the literature for data pertaining to the last 25 years was performed. Fixed- and random-effects models were used to cumulatively assess the accumulation of evidence over time.

Results Patients with a significantly higher body mass index (BMI), tumours located approximately 1 cm further distally and more patients undergoing neoadjuvant therapy were included in the robotic total mesorectal excision (RTME) cohort compared with those in the laparoscopic total mesorectal excision (LTME) cohort [RTME, mean difference (MD) = 0.22 (0.07, 0.36), $P = 0.005$; LTME, MD = −0.97 (−1.57, 0.36), $P < 0.002$; OR = 1.47 (1.11, 1.93), $P = 0.006$]. Significantly lower conversion rates to open surgery were observed in the RTME cohort than in the LTME cohort [OR = 0.33 (0.24, 0.46), $P < 0.001$]. Operative time in the LTME cohort was significantly reduced (by 50 min) compared with the RTME cohort. Subgroup analysis of the three randomized controlled trials (RCTs) challenged all the significant results of the main analysis and demonstrated nonsignificant differences between the RTME cohort and LTME cohort.

Conclusion Although the RTME cohort included patients with a significantly higher BMI, more distal tumours and more patients undergoing neoadjuvant therapy, this cohort demonstrated lower conversion rates to open surgery when compared with the LTME cohort. However, subgroup analysis of the RCTs demonstrated nonsignificant differences between the two procedures.

Keywords Robotic, laparoscopic, total mesorectal excision, rectal cancer, meta-analysis, colorectal surgery, colorectal cancer, colorectal research, robotic surgery, MIS colorectal, systematic review

Introduction

Total mesorectal excision (TME) was first described by Richard (Bill) Heald and is now the gold standard procedure for rectal cancer surgery because of its low recurrence rate and prolonged survival outcomes [1]. However, intense debate continues to rage around the oncological adequacy, efficiency and safety of laparoscopic TME (LTME) and robotic TME (RTME) as well the indications and feasibility of laparoscopy *vs* a robotic approach, especially for ultra-low rectal cancers [2]. Two large randomized controlled trials (RCTs) have supported the oncological adequacy of LTME [3,4]. However, two other RCTs demonstrated that LTME

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failed to meet the criterion for noninferiority in pathological outcomes compared with open TME [5,6]. An assistant-dependent and unstable camera platform, traction, and steep and long learning curves are limitations that can influence the outcomes [7]. Robotic rectal surgery claimed to overcome these limitations but its effectiveness is still to be demonstrated. One RCT including surgeons with varying experience concluded that RTME had no advantage over LTME [8]. In 2014, a meta-analysis based on eight retrospective studies reported that RTME had a lower conversion rate to open surgery and a lower rate of positive circumferential resection margins (CRMs) when compared with LTME [9].

There has been concern of bias in some of these studies, with Patel *et al.* reporting evidence of biased opinion in 82% of the studies that assessed robotic colorectal surgery [10]; Boutron *et al.* [11] defined spin as 'a specific reporting that could distort the interpretation of results and mislead readers'.

This contradictory evidence demonstrates the need for an updated meta-analysis. Furthermore, a cumulative meta-analysis would help reveal the accumulation of evidence over time, pinpoint the turning points, and detect those studies which had a particular influence on results.

The aim of this study was to perform an updated and cumulative meta-analysis to determine whether one procedure was superior to the other.

Method

The systematic review and meta-analysis were carried out in accordance with the guidelines set out in the Preferred Reporting in Systematic Review and Meta-Analysis (PRISMA) checklist [12].

Literature search

A systematic literature search of articles published during the last 25 years was performed in Embase, MEDLINE (PubMed), Cochrane Library and Google Scholar databases using free text and MeSH terms (robotic total mesorectal excision; laparoscopic total mesorectal excision; rectal cancer or cancers; rectal adenocarcinoma; retrospective studies; randomised or randomized controlled trial). A grey literature search on https://www.clinicaltrials.gov/ was also performed. References cited in the retrieved articles were manually checked for further analysis. Disagreements between authors were resolved by a consensus-based discussion.

Study selection and inclusion and exclusion criteria

Randomized controlled trials, retrospective studies and case-matched studies that compared RTME with LTME for rectal cancers were included in this study. All non-comparative studies, reviews or narrative articles were excluded.

Data extraction and outcomes

Two reviewers (PG and NA) independently extracted the following data and outcomes for the patients in the included studies: age, sex, body mass index (BMI), neoadjuvant treatment, T3 and T4 tumours, distance from the anal verge, previous surgery, operative time, estimated blood loss, conversion to open surgery, protective stoma, major morbidity, time to oral intake, number of lymph nodes harvested, distal resection margin, CRM, positive CRM, length of stay, readmission, local recurrence, erectile dysfunction, overall survival and 3-year disease-free survival (DFS). The names of the authors of these studies were also noted.

Risk of bias assessment of included studies

The methodological quality of all included studies was assessed based on the validated Newcastle–Ottawa scale (NOS) [13]. The NOS is an assessment tool used to measure the quality of retrospective studies that are included in a systematic review and meta-analysis. Using this tool, each study was assessed for eight parameters and categorized into three groups: first, the selection of the study groups; second, the comparability of the groups; and third, the ascertainment of either the exposure or outcome of interest for case–control studies. One point was awarded for each quality item. High-quality studies were awarded up to 9 points. Studies that scored ≥ 7 were considered to be of high quality [13]

Statistical analysis

Statistical analyses were conducted using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Heterogeneity was assessed through the I^2 statistic, and cut-off values of 25%, 50% and 75% were considered low, moderate and high, respectively [14,15]. Both fixed- and random-effects models were produced, and the conclusions were compared; the latter was used preferentially in cases where there were discrepancies between the two models. In cases of I^2 values less than 25%, fixed-effects models were used throughout.

Dichotomous variables were analysed based on odds ratios (OR) with a 95% confidence interval (CI). For the analysed outcomes, reference categories were selected so that an OR < 1 favoured RTME. Continuous variables were combined based on both the mean difference (MD) and the standardized mean difference (SMD). The studies were then combined using the Mantel–Haenszel method in the first instance and the Peto approach when the cross-table had a zero cell [14]. For studies that did not report the means and variances for the two groups, these values were estimated from the median, range and size of the sample, when possible, using the technique described by Hozo *et al.* [16]. Analysis of long-term survival was performed by the combination of hazard ratios (HRs) and a 95% CI in the included studies; these were rarely reported and, if possible, were estimated using the method described by Parmar *et al.* [17]. The studies that reported the numbers at risk were combined with either the quoted survival rates or the values read from the enlarged plots of the Kaplan–Meier curves in order to produce estimates. When the numbers at risk were not quoted, constant censoring over the follow-up period was assumed during the estimate. The studies were weighted using an inverse variance approach, and a HR < 1 favoured RTME.

The significance level in all analyses was set at $P < 0.05$. Cumulative meta-analysis was conducted using STATA software (v.15, Stata Corp LP, College Station, Texas, USA).

Sensitivity analysis

Analyses of outcomes were performed using both random- and fixed-effects models to assess the impact of heterogeneity on the results. Publication bias was estimated using funnel plots on the outcomes in at least 15 studies [18]. A subgroup analysis of the studies in Western and Asian countries was performed, and these results were compared with the total sample. Cumulative meta-analysis was performed to detect the accumulation of evidence over time and examine whether any particular study had a specific influence on the results [19].

Definitions

Operative time was defined as the time elapsed from when the scalpel touched the skin until the last skin stitch was performed. Length of stay was defined as the number of days from the day of operation until discharge. Time to oral intake was defined as the time elapsed after the operation until the patient was able to eat soft food. Major morbidity included complications classified as Clavien–Dindo III and IV [20]. All variables were reported as described by the authors of each of the included studies. Overall survival and DFS were defined as the time from surgery to death from any cause and the time from surgery to any recurrence, respectively.

Results

Search strategy and included study characteristics

Twenty-five studies including 4805 patients were selected from a pool of 183 studies (Fig. 1). In these studies, 2413 (50.2%) and 2392 (49.8%) patients underwent RTME and LTME, respectively [8,21-44].

Twenty-one studies scored > 7 on the NOS and were therefore characterized as of high quality (Table 1).

Demographic characteristics

No significant differences in age and male gender between the two patient cohorts were observed. However, patients in the LTME cohort had a significantly lower BMI [MD = 0.22 (0.07, 0.36); $P = 0.005$] (Table 2).

Neoadjuvant treatment

A significantly higher number of patients underwent neoadjuvant therapy in the RTME than in the LTME cohort [$n = 1021/1974$ (52%) *vs* $n = 1021/1990$ (45%); OR = 1.47 (1.11, 1.93); $P = 0.006$] (Table 2).

Distance from the anal verge

Patients in the RTME cohort presented with tumours at a significantly smaller distance from the anal verge (about 0.97 cm) than those in the LTME cohort [MD = −0.97 (−1.57, −0.36); $P = 0.002$] (Table 2).

Operative time

Operative time was shorter by 50 min in the LTME cohort [MD = 50.35 (31.70, 70.69); $P < 0.001$] (Table 2).

Conversion to open surgery

Conversion to open surgery was significantly lower in the RTME cohort [RTME, 1.7%, $n = 29/1725$; LTME, 6.8%, $n = 113/1656$; OR = 0.26 (0.17, 0.38); $P < 0.001$] (Table 2, Fig. 2).

Statistically nonsignificant results

No significant differences were observed between the two groups in the following parameters: T3 and T4 tumours, previous surgery, blood loss, protective stoma,

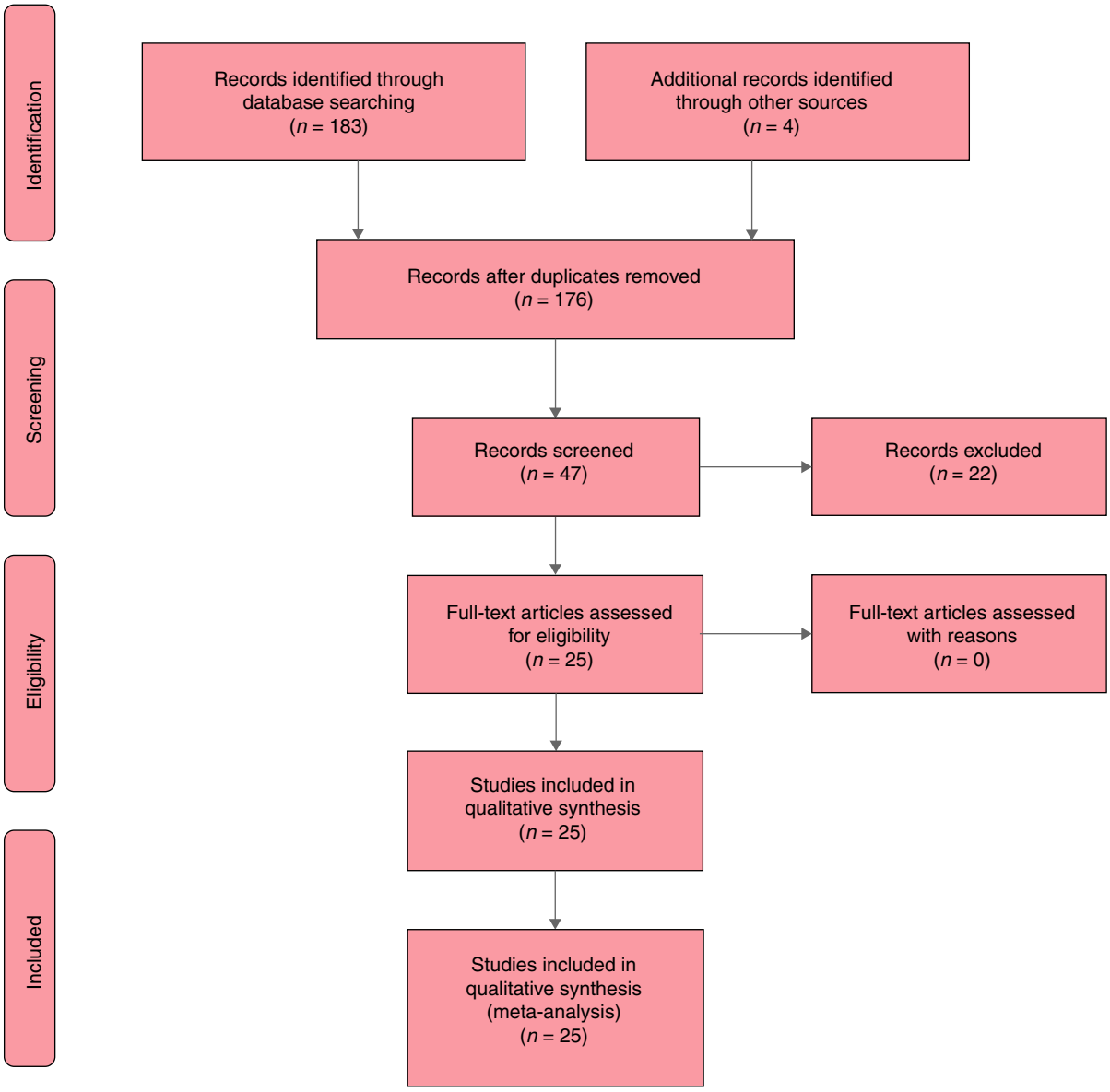

Figure 1 Flow diagram showing the different steps of the search strategy.

major morbidity, time to soft diet, number of lymph nodes harvested, distal resection margin, CRM, positive CRM, length of stay, readmission, local recurrence, overall survival and 3-year DFS (Table 2).

Sensitivity analysis and cumulative meta-analysis

Significant differences were observed between the studies conducted in Western and Asian countries in the following parameters: BMI, neoadjuvant treatment and distance from the anal verge. Parameters such as operative time and conversion to open have shown significantly different results between the two groups, but showed no differences among different geographical regions (Table 2).

No differences in the results between fixed- and random-effects models were observed. The findings of the cumulative meta-analysis indicated that no particular study influenced the results (Figure S1 in the online Supporting Information). The investigation of publication bias demonstrated a lack of studies in favour of the laparoscopic approach (Fig. 3).

Subgroup analysis of the RCTs

Subgroup analysis of the RCTs did not find any significant differences in the outcomes of interest among

Table 1 Study characteristics and Newcastle–Ottawa scale (NOS) evaluation.

Author, study, country, year	No. of patients RTME/LTME	Age (years) RTME/LTME	BMI (kg/m^2) RTME/LTME	Gender (male) RTME/LTME	NOS (max. = 9)
Baik, RCT, Korea, 2008 [21]	18/18	57.3 ± 6.3/62 ± 9 *P* = 0.08	22.8 ± 1.8/24 ± 2.5 *P* = 0.12	14/14 *P* = 1.00	7
Patriti, Italy, 2009 [22]	29/37	68 ± 10/69 ± 10 *P* > 0.05	24 ± 6.2/25.4 ± 6.44 *P* > 0.05	11/12 *P* > 0.05	7
Bianchi, Italy, 2010 [23]	25/25	69 ± 12.5/62±.75 *P* = 0.8	24.5 ± 3.18/26.5 ± 4.22 *P* = 0.06	18/17 *P* = 0.8	8
Baek JH, USA, 2011 [24]	41/41	63.6 ± 11.5/63.7 ± 11.5 *P* = 0.95	25.7 ± 4.22/26.7 ± 5.88 *P* = 1.00	25/25 *P* = 1.00	8
Park, Korea, 2011 [25]	52/123	57.3 ± 12.3/65.1 ± 10.3 *P* <.001	23.7 ± 2.4/23.6 ± 3.3 *P* = 0.37	28/70 *P* = 0.69	6
Kim JY, Korea, 2012 [26]	30/39	54.1 ± 8.5/56 ± 11 *P* = 0.28	24.4 ± 2.4/24.01 ± 2.19 *P* = 0.52	12/19 *P* = 0.47	6
Baek SJ, Korea, 2012 [27]	154/150	59.1 ± 12.2/62.3 ± 10.9 *P* = 0.82	23.4 ± 3.1/23.1 ± 3 *P* = 0.75	105/109 *P* = 0.62	8
D'Annibale, Italy, 2013 [28]	50/50	66 ± 12.1/65.7 ± 11.6 *P* = 0.88	NR	30/30 *P* = 1.0	6
Kang, Korea, 2013 [29]	165/165	61.2 ± 11.4/60.4 ± 11.8 *P* = 0.28	23.1 ± 2.8/23.2 ± 3.1 *P* = 0.72	104/97 *P* = 0.33	7
Barnajian, USA, 2014 [30]	20/20	62 ± 9.5/63 ± 11.25 *P* = 0.62	22 ± 3.25/22 ± 3.25 *P* = 1.0	12/12 *P* = 1.0	7
Ramji, Canada, 2016 [31]	26/27	62.1 ± 9.1/63.7 ± 11.2 *P* = 0.06	27.8 ± 5.5/27.6 ± 5.5 *P* = 0.96	19/19 *P* = 0.52	8
Cho, Korea, 2015 [32]	278/278	57.4 ± 11.6/58.3 ± 10.4 *P* < 0.001	23.5 ± 2.9/23.7 ± 3.3 *P* = 0.52	182/184 *P* = 1.00	7
Law, Hong Kong/China, 2017 [33]	220/171	65 ± 14/67 ± 18 *P* = 0.46	24.9 ± 0.1/24.6 ± 0.1 *P* = 0.99	148/97 *P* = 0.035	7
Shiomi (1), Japan, 2016 [34]	127/109	65 ± 14/68 ± 15 *P* = 0.07	23.7 ± 5.4/22.8 ± 5.52 *P* = 0.07	93/65 *P* = 0.04	7
Shiomi (2), Japan, 2016 [34]	52/30	65 ± 10/67.5 ± 8.5 *P* = 0.17	25.4 ± 4.6/26.6 ± 3.42 *P* = 0.38	45/24 *P* = 0.53	7
Bedirli, Turkey, 2016 [35]	35/28	64.7 ± 8.5/60.4 ± 7.1 *P* = NS	24.7 ± 3.9/23.2 ± 3.2 *P* = ns	24/19 *P* = ns	6
Feroci, Italy, 2016 [36]	53/58	66 ± 11.8/66 ± 11 *P* = 0.60	24.6 ± 3.25/24.6 ± 4.5 *P* = 0.51	27/42 *P* = 0.03	7
Lim, Korea, 2017 [37]	74/64	65.1 ± 12.4/65.8 ± 11.1 *P* = 0.09	23.4 ± 2.9/22.7 ± 2.9 *P* = 0.73	50/50 *P* = 0.44	8
Valverde, France, 2017 [38]	65/65	67 ± 11/65 ± 10 *P* = 0.45	25 ± 4/25 ± 5 *P* = 0.68	42/45 *P* = 0.57	8
Jayne, RCT, UK, 2017 [8]	237/234	64.4 ± 11/65.5 ± 11.9 *P* = 0.30	≥ 30 54 55	161/159 *P* = 1.00	9
Esen, Turkey, 2018 [39]	100/78	59 ± 11/56 ± 13 *P* = 0.11	59 ± 11/56 ± 13 *P* = 0.68	60/51 *P* = 0.57	7
Aselmann, Germany, 2018 [40]	44/41	61.1 ± 11.54/65.1 ± 12 *P* > 0.05	25 ± 3.8/25.7 ± 4 *P* > 0.05	26/24 *P* > 0.05	8

Table 1 (Continued).

Author, study, country, year	No. of patients RTME/LTME	Age (years) RTME/LTME	BMI (kg/m^2) RTME/LTME	Gender (male) RTME/LTME	NOS (max. = 9)
Rouanet, France, 2018 [41]	200/200	> 60, 122–122 $P = 1.00$	> 30 28–27 $P = 0.93$	131/136 $P = 0.59$	8
Crolla, The Netherlands, 2018 [42]	168/184	67 ± 9.64/68 ± 10.7 $P = 0.94$	26.4 ± 3.86/ 25.8 ± 3.90 $P = 0.91$	113/103 $P = 0.30$	7
Sugoor, India, 2018 [43]	84/84	48.7 ± 15/49.2 ± 15 $P = 0.82$	23.8 ± 6/22.9 ± 3 $P = 0.54$	76/69 $P = 0.62$	7
Kim MJ, RCT, Korea, 2018 [44]	66/73	60.4 ± 9.7/59.7 ± 11.7 $P = 0.69$	24.1 ± 3.3/23.6 ± 3 $P = 0.33$	51/58 $P = 0.42$	8
Pooled estimates	2413 (50.2%)/ 2392 (49.8%) Total = 4805	MD = –0.85 (–1.85, 0.16), $P = 0.10$	MD = 0.22 (0.07, 0.36), $P = 0.005$	OR = 1.04 (0.92, 1.18), $P = 0.49$	HQ = 21 studies

HQ, high quality; LTME, laparoscopic total mesorectal excision; NS, nonsignificant; RCT, randomized controlled trial; RTME, robotic total mesorectal excision.

RTME and LTME, which is in contrast to the significant differences observed in the sample of retrospective studies in the meta-analysis. In particular, there was no evidence of significant differences in the conversion to open rate of the RTME cohort (6%; 20/320 patients) compared with the LTME cohort (9%; 30/319 patients), only nonsignificant differences with 0% heterogeneity [OR = 0.63 (0.35, 1.13), $P = 0.12$, $I^2 = 0\%$]. The major morbidity rate demonstrated nonsignificant differences between the RTME (28%; 84/303 patients) and LTME cohorts (25%; 77/303 patients) [OR = 1.10 (0.76, 1.59), $P = 0.62$, $I^2 = 0\%$]. The lymph node harvest rate showed nonsignificant differences between RTME and LTME cohorts [MD = 0.94 (0.76, 1.59), $P = 0.62$, $I^2 = 0\%$]. Positive CRM rates demonstrated nonsignificant differences between the RTME (5%; 17/319) and LTME cohorts (7%; 21/315 patients) [OR = 0.79 (0.41, 1.53), $P = 0.48$, $I^2 = 0\%$] (Tables 2 and 3, Fig. 2).

Discussion

The RTME cohort included patients with a higher BMI, tumours located closer to the anal verge and a higher proportion of patients needing neoadjuvant therapy. Significantly fewer RTME procedures were converted to open surgery when compared with LTME. However, the operative time in the LTME cohort was significantly shorter (by 50 min) than in the RTME cohort when the docking time of the robot was counted in the RTME operative time. If one assumes the docking time of the robot is as previously reported (30 min), when this time is subtracted there is no significant difference between the two techniques [45].

The Robotic *vs* Laparoscopic Resection for Rectal Cancer (ROLARR) trial, considered a high-quality RCT, demonstrated the impact of 'difficult patients' on the statistical significance of the results [8]. The definition of 'difficult patients' was based on the following four criteria: BMI ≥ 30 kg/m^2, coloanal anastomosis, intertuberous distance < 10 cm and mesorectal fat area > 20.7 cm^2 [41,46,47]. Bulky and low tumours were also identified in the international transanal TME registry as risk factors for poor outcomes [48].

The present study demonstrated an inverse selection bias as the 'difficult patients' were selected to undergo RTME. However, parameters such as postoperative complications, oncological adequacy and efficiency were equivalent. In addition, the conversion rate to open was significantly lower in the RTME cohort compared with the LTME cohort.

The subgroup analysis of results from studies conducted in Western and Asian countries demonstrated differences in terms of BMI, neoadjuvant therapy and distance from the anal verge. In both regions, patients with a higher BMI were included in the RTME cohort. Asian studies reported a higher number of statistically significant results than Western studies. However, the World Health Organization for the Western Pacific region defines obesity in this region as a BMI > 25 kg/m^2 as opposed to > 30 in Western countries, although the percentage of visceral fat volume in Asians is 3–5% higher than that in Caucasians for the same BMI [49,50].

Table 2 Outcomes of interest.

Outcome of interest	No. of studies, no. of patients (%; events/total)	Statistical method, estimated effect, 95% CI	*P*-value	I^2 (%)
Age [8,20–43]	25, 4405	MD = −85 (−1.85, 0.16)	0.10	48
BMI [8,20–26,28–43]	24, 3973	MD = 0.22 (0.07, 0.36)	0.005	9
Male gender [8,20–43]	26, 4805 (67%; 1607/413) (65%; 1557/2392)	OR = 1.04 (0.92, 1.18)	0.49	12
Neoplasms T3, T4 [8,20–25,27–33,36,38–40,42]	19, 3964 (50%; 922/1848) (52%; 940/1805)	OR = 0.96 (0.79, 1.16)	0.65	39
Neoadjuvant [8,20–32,34,35,37–40,42,43]	21, 3964 (52%; 1021/1974) (45%; 1021/1990)	OR = 1.47 (1.11, 1.93)	0.006	68
Distance from anal verge [20,21,23,24,29–32,36,39]	11, 1955	MD = −0.97 (−1.57, −0.36)	0.002	77
Previous surgery [8,20,21,23,24,31–33,36,38,43]	13, 2609 (34%; 456/1329) (38%; 486/1280)	OR = 0.83 (0.69, 1.00)	0.05	10
Operative time [8,21–24,26–43]	26, 4734	MD = 50.35 (31.70, 70.69)	<.001	97
Blood loss [8,21,23,26,28–34,40,42,43]	16, 3210	MD = 10.48 (−15.50, 36.46)	0.43	84
Conversion to open [20,22,23,27–33,36–38,40–43]	17, 3381 (1.7%; 29/1725) (6.8%; 113/1656)	OR = 0.26 (0.17, 0.38)	< 0.001	0
Protective stoma [8,22–24,28,29,32,34,36–41,43]	15, 3132 (59%; 928/1561) (55%; 859/1571)	OR = 1.18 (0.88, 1.59)	0.26	56
Major morbidity [8,22–24,26–35,37,39,41,43]	20, 3806 (15%; 284/1922) (14%; 265/1884)	OR = 1.03 (0.86, 1.25)	0.72	0
Time to soft diet [23,24,26–29,31,33-35,43]	11, 2107	MD = −0.22 (−0.92, 0.49)	0.55	95
Lymph nodes harvested [8,20-24,27-39,41-43]	23, 4028	MD = 0.86 (−0.21, 1.94)	0.12	82
DRM [20-24,27-32,35,36,40,43]	15, 2667	MD = −0.04 (−0.27, 0.18)	0.70	64
CRM [24,29,39,43]	4, 442	MD = 0.50 (−4.74, 5.73)	0.85	97
Positive CRM [8,20-24,28,31-43]	20, 4123 (4%; 91/2107) (5.5%; 111/2016)	OR = 0.78 (0.59, 1.04)	0.09	0
LOS [8,20-24,26–35,37,38,40–43]	23, 4509	MD = −0.58 (−1.24, 0.09)	0.09	68
Readmission [28–30,39]	4, 508 (6%; 15/255) (5%; 13/253)	Peto OR = 1.17 (0.54, 2.56)	0.69	0
Local recurrence [21,31,35,36,39]	5, 956 (2%; 10/478) (4%; 17/478)	OR = 0.59 (0.27, 1.28)	0.18	0
Overall survival [31,32,35,36,39,40]	6, 1681	HR = 1.03 (0.80, 1.32)	0.83	0
3-year DFS [21,28,31,35,36,39]	6, 1315	HR = 0.94 (0.72, 1.23)	0.65	7
Subgroup analysis Western *vs* Asian				
BMI Western	11, 1286	MD = 0.19 (−0.25, 0.62)	0.40	2
BMI Asian	13, 2687	MD = 0.22 (0.06, 0.38)	0.007	25
Neoadjuvant Western	12, 1766 (55%; 490/890) (49%; 428/876)	OR = 1.55 (1.04, 2.30)	0.03	69
Neoadjuvant Asian	9, 2198 (49%; 531/1084) (43%; 476/1114)	OR = 1.40 (0.93, 2.11)	0.11	71

Table 2 (Continued).

Outcome of interest	No. of studies, no. of patients (%; events/total)	Statistical method, estimated effect, 95% CI	*P*-value	I^2 (%)
Distance from anal verge Western	5, 355	MD = −1.26 (−2.80, 0.27)	0.11	83
Distance from anal verge Asian	6, 1600	MD = −0.99 (−1.58, −0.39)	0.001	70
Operative time Western	13, 2114	MD = 46.95 (22.59, 71.31)	0.002	97
Operative time Asian	12, 2582	MD = 57.19 (33.07, 81.32)	< 0.001	92
Conversion to open Western	12, 2021 (3%; 32/1012) (10%; 104/1009)	OR = 0.30 (0.20, 0.44)	< 0.001	28
Conversion to open Asian	8, 1994 (1%; 10/1032) (2.5%; 24/962)	OR = 0.44 (0.22, 0.85)	0.02	0

Red highlighted favours robotic total mesorectal excision (RTME) and green highlighted favours laparoscopic total mesorectal excision (LTME).

BMI, body mass index; CI, confidence interval; CRM, circumferential resection margins; DFS, disease-free survival; DRM, distal resection margin; I^2, heterogeneity; LOS, length of stay; MD, mean difference; OR, odds ratio.

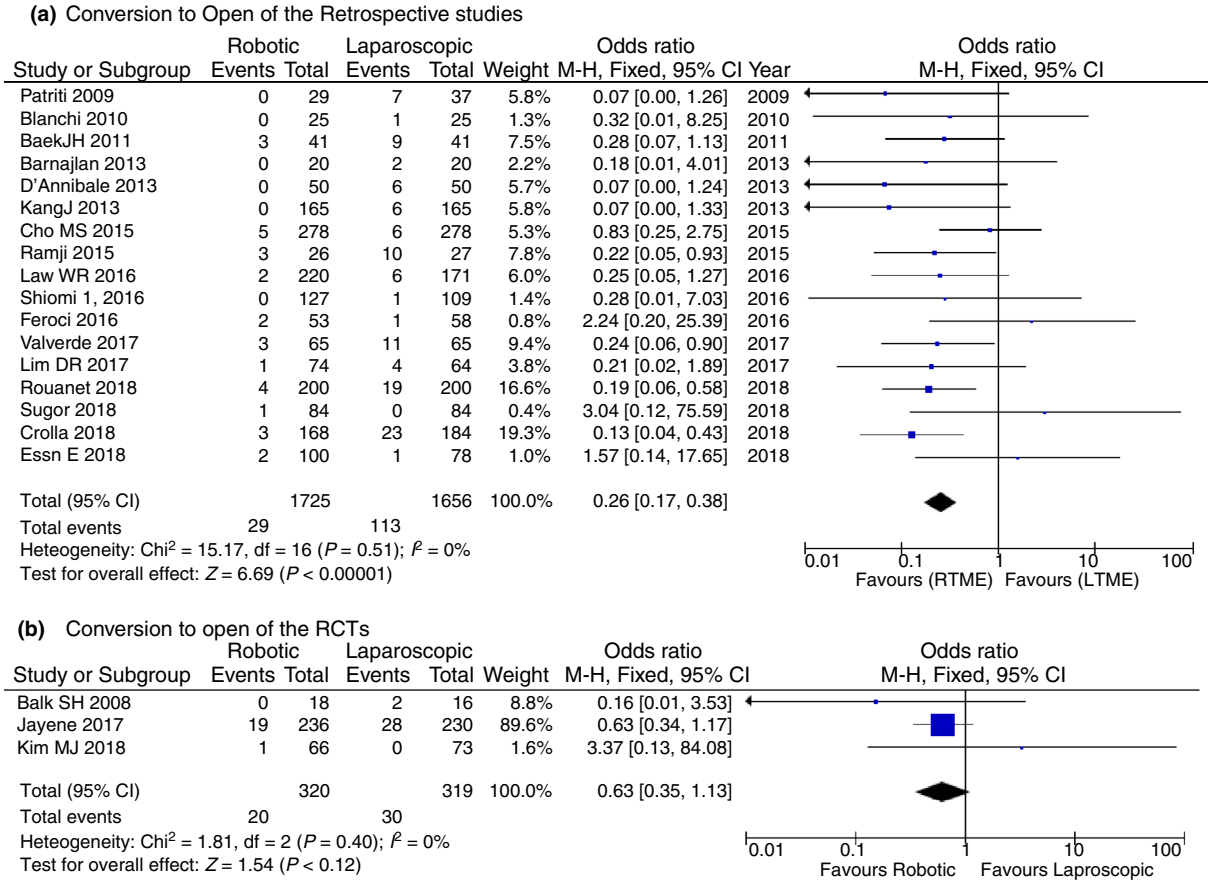

Figure 2 Forest plot illustrating conversion to open surgery: (a) retrospective studies and (b) RCTs.

Neoadjuvant therapy incorporated into multimodality treatment aims to downstage T3 and T4 tumours in order to achieve lower recurrence rates and possibly increase sphincter-preserving operations. However, TME may be technically more difficult because of postradiation tissue oedema and fibrosis

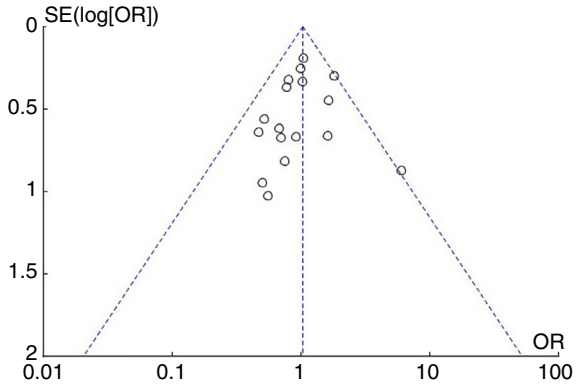

Figure 3 Funnel plot for publication bias.

that can cause difficulty with dissection of the planes [51].

More patients had neoadjuvant therapy in the RTME cohort. However, the outcomes were statistically significantly different only in the Western studies. Interestingly, lower tumours (in terms of the distance from the anal verge), were included in the RTME cohort in both Asian and Western studies. However, only the Asian studies exhibited statistically significant results between RTME and LTME. All the studies reported significantly lower conversion rates to open surgery in the RTME group.

Cumulative meta-analysis did not identify any study that had a particular influence on the results and no turning points on the accumulation of evidence over time.

The present study and all previous meta-analyses reveal that the main advantage of the robotic procedure is the significantly lower conversion rate to open surgery [9]. However, subgroup analysis of the RCTs did not demonstrate any significant differences in demographics, perioperative and postoperative variables, and the parameter of conversion to open that was highlighted as the principal advantage of the robotic procedure by all the previous retrospective studies and meta-analyses. The present meta-analysis of the RCTs demonstrates nonsignificant differences in contrast to previous studies, and may influence future practice (Fig. 2, Tables 2 and 3).

The RCTs produced this new evidence because they were of higher methodological quality than the retrospective studies. All of them met the Cochrane criteria of methodological quality, which include random sequence generation, allocation concealment and blinding of participants and personnel. Therefore, having lower rates of selection, detection, attrition and reporting bias produced better outcomes and evidence than the retrospective studies. Of note, the majority of the RCTs results produced 0% heterogeneity.

Limitations

There are limitations to this study. Three of the studies analysed were RCTs [8,21,44], and two had a low risk

Table 3 Subgroup analysis of the outcomes of interest of the RCTs.

Outcome of interest	No. of studies and no. of patients (%; events/total)	Statistical method, estimated effect, 95% CI	*P*-value	I^2 (%)
Age [8,21,44]	3, 646	MD = −1.18 (−3.46, 1.10)	0.31	31
Male gender [8,21,44]	3, 646 (70%; 226/321) (70%; 225/325)	OR = 1.06 (0.76, 1.49)	0.72	0
Neoplasms T3, T4 [8,21,44]	3, 642 (42%; 135/321) (42%; 133/321)	OR = 0.98 (0.69, 1.38)	0.89	0
Neoadjuvant [8,44]	2, 3964 (53%; 162/303) (52%; 160/310)	OR = 1.11 (0.80, 1.54)	0.52	0
Previous surgery [8,21,44]	3, 642 (24%; 78/321) (30%; 95/321)	OR = 0.76 (0.54,1.09)	0.13	0
Operative time [8,21,44]	3, 646	MD = 54.39 (−0.08, 108,86)	0.05	94
Conversion to open [8,21,44]	3, 639 (6%; 20/320) (9%; 30/319)	OR = 0.63 (0.35, 1.13)	0.12	0
Major morbidity [8,44]	2, 606	OR = 1.10 (0.76, 1.59)	0.62	0
Lymph nodes [8,21,44]	3, 646	MD = 0.94 (−1.95, 3.82)	0.52	44
Positive CRM [8,21,44]	3, 646 (5%; 17/319) (7%; 21/315)	OR = 0.79 (0.41, 1.53)	0.48	0
Length of stay	3, 646	MD = −1.00 (−2.13, 0.13)	0.08	63

CI, confidence interval; CRM, circumferential resection margins; I^2, heterogeneity; MD, mean difference; OR, odds ratio.

of bias [8,44]. Other studies were retrospective from single centres, with variable follow-up. National and institutional characteristics may have influenced our results. Local recurrence, overall survival and DFS were only reported in six studies [22,29,32,36-37,40]. Some studies may have been underpowered. Another potential source of bias was the heterogeneous sample size in the majority of studies with more upper rectal cancers included, which are technically easier to resect than mid- and low-rectal tumours. Currently, a European prospective controlled trial, Rectal Surgical Evaluation Trial (RESET), is being performed with the aim of assessing open, laparoscopic, robotic and transanal TME for mid- and low-rectal cancers in high-risk patients [52].

Conclusion

The present study demonstrates contrasting differences between the main meta-analysis and the subgroup analysis of the RCTs. The results of the ongoing RESET trial will further clarify the topic by negating or challenging the results of the present study.

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Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

PG (study concept and design; acquisition of data; analysis and interpretation of data; drafting the manuscript; statistical analysis); AS (acquisition of data; analysis and interpretation of data; drafting the manuscript); JW (acquisition of data; analysis and interpretation of data; drafting the manuscript); NA (acquisition of data; analysis and interpretation of data; drafting the manuscript); CC (acquisition of data; analysis and interpretation of data; drafting the manuscript); SDS (acquisition of data; analysis and interpretation of data; drafting the manuscript, study supervision).

Ethical approval

This study does not contain any studies with human participants or animals performed by any of the authors.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. (A) Conventional meta-analysis of the overall complications. (B) Cumulative meta-analysis of the overall complications.