# Difference in surgical outcomes of rectal cancer by study design: meta-analyses of randomized clinical trials, case-matched studies, and cohort studies

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#### Abstract

**Background:** RCTs are considered the standard in surgical research, whereas case-matched studies and propensity score matching studies are conducted as an alternative option. Both study designs have been used to investigate the potential superiority of robotic surgery over laparoscopic surgery for rectal cancer. However, no conclusion has been reached regarding whether there are differences in findings according to study design. This study aimed to examine similarities and differences in findings relating to robotic surgery for rectal cancer by study design.

**Methods:** A comprehensive literature search was conducted using PubMed, Scopus, and Cochrane CENTRAL to identify RCTs, case-matched studies, and cohort studies that compared robotic *versus* laparoscopic surgery for rectal cancer. Primary outcomes were incidence of postoperative overall complications, incidence of anastomotic leakage, and postoperative mortality. Meta-analyses were performed for each study design using a random-effects model.

**Results:** Fifty-nine articles were identified and reviewed. No differences were observed in incidence of anastomotic leakage, mortality, rate of positive circumferential resection margins, conversion rate, and duration of operation by study design. With respect to the incidence of postoperative overall complications and duration of hospital stay, the superiority of robotic surgery was most evident in cohort studies (risk ratio (RR) 0.83, 95 per cent c.i. 0.74 to 0.92, P < 0.001; mean difference (MD) -1.11 (95 per cent c.i. -1.86 to -0.36) days, P = 0.004; respectively), and least evident in RCTs (RR 1.12, 0.91 to 1.38, P = 0.27; MD -0.28 (-1.44 to 0.88) days, P = 0.64; respectively).

**Conclusion:** Results of case-matched studies were often similar to those of RCTs in terms of outcomes of robotic surgery for rectal cancer. However, case-matched studies occasionally overestimated the effects of interventions compared with RCTs.

## Introduction

RCTs are currently considered the standard for studying treatment effects in surgical research<sup>1,2</sup>. However, RCTs require considerable resources such as time, resources, costs, and collaboration among various specialists to ensure patient security, standardization of interventions, and data correctness. Although blinding is an important design feature of RCTs, blinding of outcome assessors, as well as for patients and surgeons, is difficult to achieve in surgical research, making it difficult to conduct high-quality RCTs<sup>3,4</sup>. Moreover, it is often impossible to conduct surgical RCTs for various reasons, such as feasibility and ethics<sup>1</sup>. Thus, findings from high-quality RCTs are not always available in surgical research<sup>5</sup>.

Recently, matching methods such as propensity score matching have been adopted as alternative methods to randomization. A number of studies using matching methods have been published, and such studies are generally referred to as casematched studies<sup>1,6–8</sup>. However, only measurable confounding factors can be adjusted for in case-matched studies, and reports of such studies occasionally lack sufficient details of matching variables and patient characteristics  $^{9\matchar{-}12}.$ 

Both high- and low-quality RCTs and case-matched studies have been published. Apart from methodological differences between the two types of study, such as patient selection and adjustment for confounders, it remains unclear whether there are differences in results by study design<sup>2,13</sup>.

RCTs and case-matched studies have been conducted to examine the potential superiority of robotic surgery over laparoscopic surgery for rectal cancer, a topic of major interest among surgeons. However, no conclusion has been reached regarding whether differences exist by study design. On this basis, the present study aimed to examine similarities and differences in findings related to surgical outcomes for rectal cancer according to study design.

# Methods

Eligible studies were those comparing robotic *versus* laparoscopic surgery for rectal cancer. Studies of transanal surgery were

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excluded. RCTs, case-matched studies, and cohort studies were subjected to analysis. Both prospective and retrospective studies were included in non-RCT studies. No restrictions were placed regarding methods of randomization or matching.

A comprehensive literature search was conducted on 12 June 2019 using PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The following search terms were used: 'rectal cancer', 'surgery', 'robot', 'laparoscopy', and related terms (*Appendix S1*). Duplications were excluded by checking author names, year of publication, and study characteristics (such as study design, setting, and period). Two authors independently screened the extracted publications according to title and abstract, and then reviewed the full text of potentially eligible articles. Disagreement was resolved by discussion.

Data extracted included: study design and setting, number and characteristics of patients, type of surgery, and short-term surgical outcomes. The extracted data were checked for consistency, and discordance was resolved by discussion. For cohort studies, unadjusted data were extracted.

#### Outcome measures

Primary outcomes were: incidence of postoperative overall complications, incidence of anastomotic leakage, and mortality. Secondary outcomes were: duration of hospital stay, conversion rate, duration of operation, estimated blood loss, rate of positive circumferential resection margins, and quality of total mesorectal excision.

#### Statistical analysis

Data synthesis was performed using Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). A randomeffects model was used for all meta-analyses, as all types of rectal cancer surgery were included in the present review. An inverse-variance method was used for continuous variables, and the Mantel–Haenszel method for dichotomous variables. Mean difference (MD) with 95 per cent confidence interval was used for continuous variables when a single measure was included in the meta-analysis. Median (range) values were converted to mean(s.d.)<sup>14</sup>. Risk ratio (RR) with 95 per cent c.i. was used for dichotomous variables. When an outcome was rare, risk difference (RD) was used instead of RR. P < 0.050 (2-sided) was considered statistically significant.

# **Results**

The literature search yielded 1091 articles in total. Among these, 426 duplicates were removed, and the remaining 665 articles were screened for eligibility based on title and abstract. After screening, 67 articles were subjected to full-text review, and 59 articles that met the inclusion criteria were included in the present review (Fig. 1)<sup>15–73</sup>. Reviewed studies included seven RCTs, 13 case-matched studies, and 39 cohort studies; two were conducted internationally, and 57 were reported from 17 countries. All case-matched studies were retrospective. Among the 13 case-matched studies, propensity score matching was used in seven, and manual matching in one; no matching method was described in five. Variables used for matching included patient age, sex, comorbidity, tumour location and stage, and surgical procedure. Among cohort studies, one was prospective and 38 were retrospective (Table 1).

#### Incidence of postoperative overall complications

Forty-five studies involving a total of 8390 patients (6 RCTs, 895 patients; 9 case-matched studies, 2582 patients; 30 cohort studies, 4913 patients) reported on the incidence of overall complications and were included in a meta-analysis stratified by study design. The incidence of overall complications did not differ significantly between robotic and laparoscopic surgery in RCTs (RR 1.12, 95 per cent c.i. 0.91 to 1.38; P = 0.27) and case-matched studies (RR 1.01, 0.89 to 1.15; P = 0.88). In cohort studies, however, robotic surgery was associated with a significantly lower incidence of overall postoperative complications compared with laparoscopic surgery (RR 0.83, 0.74 to 0.92; P < 0.001) (Table 2 and Fig. 2).

## Incidence of anastomotic leakage

Fifty-three studies involving a total of 8372 patients (6 RCTs, 784 patients; 12 case-matched studies, 2222 patients; 35 cohort studies, 5366 patients) that reported on the incidence of anastomotic leakage were included in a meta-analysis stratified by study design. The incidence of anastomotic leakage did not differ significantly between robotic and laparoscopic surgery in RCTs (RR 0.97, 95 per cent c.i. 0.67 to 1.39; P = 0.86), case-matched studies (RR: 0.97, 0.74 to 1.29; P = 0.85), and cohort studies (RR0.94, 0.74 to 1.18; P = 0.57) (*Table 2* and Fig. S1).

#### Mortality

Forty-two studies involving a total of 7839 patients (6 RCTs, 904 patients; 10 case-matched studies, 1910 patients; 26 cohort studies, 5025 patients) that reported on mortality were included in a meta-analysis stratified by study design. Mortality did not differ significantly between robotic and laparoscopic surgery in RCTs (RD –0.00, 95 per cent c.i. –0.01 to 0.01; P=0.99), case-matched studies (RD –0.00, –0.01 to 0.00; P=0.38), and cohort studies (RD –0.00, –0.00 to 0.00; P=0.45) (Table 2 and Fig. S2).

## Duration of hospital stay

Thirty-nine studies involving a total of 7651 patients (6 RCTs, 781 patients; 8 case-matched studies, 1904 patients; 25 cohort studies, 4966 patients) that reported on duration of hospital stay were included in a meta-analysis stratified by study design. Duration of hospital stay did not differ significantly between robotic and laparoscopic surgery in RCTs (MD –0.28 (95 per cent c.i. –1.44 to 0.88) days; P = 0.64) and case-matched studies (MD –0.59 (–1.18 to 0.00) days; P = 0.05). In cohort studies, however, robotic surgery was associated with a significantly shorter hospital stay than laparoscopic surgery (MD –1.11 (–1.86 to –0.36) days; P = 0.004) (Table 2 and Fig. 3).

## **Conversion** rate

Fifty-three studies involving a total of 9813 patients (6 RCTs, 803 patients; 11 case-matched studies, 2976 patients; 36 cohort studies, 6034 patients) that reported on conversion rate were included in a meta-analysis stratified by study design. Conversion rate did not differ significantly between robotic and laparoscopic surgery in RCTs (RR 0.42, 95 per cent c.i. 0.17 to 1.03; P = 0.06). On the other hand, robotic surgery was associated with a significantly lower conversion rate than laparoscopic surgery in case-matched studies (RR 0.40, 0.31 to 0.51; P < 0.001) and cohort studies (RR 0.34, 0.24 to 0.49; P < 0.001) (Table 2 and Fig. S3).

#### Duration of operation

Forty-two studies involving a total of 7792 patients (six RCTs, 803 patients; seven case-matched studies, 1644 patients; 29 cohort



Fig. 1 Flow diagram showing selection of studies for review

CENTRAL, Central Register of Controlled Trials.

studies, 5345 patients) that reported on duration of operation were included in a meta-analysis stratified by study design. Duration of operation did not differ significantly between robotic and laparoscopic surgery in RCTs (MD 33.53 (95 per cent c.i. –3.25 to 70.31) min; P = 0.07). However, robotic surgery was associated with a significantly longer operating time than laparoscopic surgery in case-matched studies (MD 83.41 (54.37 to 112.45) min; P < 0.001) and cohort studies (MD 44.70 (32.40 to 57.00) min; P < 0.001) (*Table 2* and *Fig. S4*).

#### Estimated blood loss

Twenty-nine studies involving a total of 5783 patients (3 RCTs, 250 patients; 5 case-matched studies, 1095 patients; 21 cohort studies, 4438 patients) that reported on estimated blood loss were included in a meta-analysis stratified by study design. Estimated blood loss did not differ significantly between robotic and laparoscopic surgery in RCTs (MD 36.09 (95 per cent c.i. -136.41 to 208.59) ml; P = 0.68), case-matched studies (MD -16.23 (-69.27 to 36.82) ml; P = 0.55) and cohort studies (MD -13.49 (-29.11 to 2.14) ml; P = 0.09) (Table 2 and Fig. S5).

## Rate of positive circumferential resection margins

Forty-two studies involving a total of 8255 patients (3 RCTs, 664 patients; 10 case-matched studies, 2046 patients; 29 cohort studies, 5545 patients) that reported on the rate of positive circumferential resection margins were included in a meta-analysis

stratified by study design. The rate of positive circumferential resection margins did not differ significantly between robotic and laparoscopic surgery in RCTs (RR 0.88, 95 per cent c.i. 0.46 to 1.69; P = 0.70), case-matched studies (RR 1.05, 0.70 to 1.57; P = 0.81) and cohort studies (RR 0.84, 0.63 to 1.12; P = 0.23) (*Table 2* and Fig. S6).

## Quality of total mesorectal excision

Fifteen studies involving a total of 1585 patients (4 RCTs, 686 patients; 2 case-matched studies, 133 patients; 9 cohort studies, 1585 patients) that reported on the quality of total mesorectal excision were included in a meta-analysis stratified by study design. The quality of total mesorectal excision did not differ significantly between robotic and laparoscopic surgery in RCTs (RR 1.08, 95 per cent c.i. 0.95 to 1.23; P=0.22) and casematched studies (RR 1.34, 0.74 to 2.42; P=0.33). In cohort studies, however, robotic surgery was associated with a significantly higher quality of total mesorectal excision than laparoscopic surgery (RR 1.14, 1.01 to 1.28; P=0.03) (Table 2 and Fig. S7).

# Discussion

The present systematic review and meta-analyses revealed that, among 59 studies that compared robotic *versus* laparoscopic surgery for rectal cancer, similarities and differences in findings

#### **Table 1 Patient characteristics**

Reference	Setti	ng	Study interval	Study type	Surgical	No. of patients	
	Country	Institution			procedures	Robotic	Laparoscopic
RCTs							
Baik et al <sup>15</sup>	Korea	Single	Apr 2006 to Feb 2007	Prospective	IAR	18	18
Debakev et al <sup>16</sup>	Fount	Single	April 2015 to Feb 2017	Prospective	AR LAR APR	21	24
lavne et al <sup>17</sup>	International	Multiple	Ian 2011 to Sent 2014	Prospective	AR LAR APR	236	230
Kim et al <sup>18</sup>	Korea	Single	Feb 2012 to Mar 2015	Prospective	IAR HO APR	230 66	73
Patriti et al <sup>19</sup>	Italy	Single	Mar 2004 to Oct 2008	Prospective	DME TME ADR CAA	29	37
Toletrup et al <sup>20</sup>	Denmark	Single	Nov 2012 to Apri 2014	Prospective	DME TME ADD ISD	25	26
Wang at al <sup>21</sup>	China	Single	Nov 2012 to April 2014	Prospective		71	20 66
Case-matched studies	Giiiia	Siligie	1100 2010 to Sept 2015	riospective	LAR, 110	/1	00
Ackormon at al 22	TIC A	Multiple	Ian 2012 to Dec 2014	Potrocpoctivo	۸D	E00	E 2 2
Allomann at al 23	Switzorland	Single	May 2012 to Dec 2014	Retrospective	TAR ADD ICD	222	10
Anemann et al <sup>24</sup>	Voron	Single	May 2012 to Jali 2014	Retrospective	LAR, APR, ISR	20	40
Baek et al. $Che et al.$	Korea	Single	Apr 2003 to Mar 2009	Retrospective	LAR, CAA, APR	41	41
Cho et al.	когеа	Single	Jan 2007 to Jun 2011	Retrospective	LAR, CAA	2/8	278
$K_{1}$ et al.	Korea	Single	Mar 2010 to Jan 2012	Retrospective	LAR, HO, APR	33	66
Kim et al. <sup>27</sup>	Korea	Single	Apr 2007 to Mar 2014	Retrospective	AR, LAR, ISR, APR	224	224
Kim et al. <sup>28</sup>	Korea	Single	2009–2013	Retrospective	lar, caa, apr	130	130
Koh et al. <sup>29</sup>	Singapore	Single	Aug 2008 to Aug 2011	Retrospective	LAR, APR	19	19
Panteleimonitis et al. <sup>30</sup>	International	Multiple	2006–2012	Retrospective	AR, LAR, HO, APR	63	61
Park et al. <sup>31</sup>	Korea	Single	Dec 2005 to Jun 2009	Retrospective	lar, caa, apr	41	82
Park et al. <sup>32</sup>	Korea	Single	Feb 2009 to Dec 2010	Retrospective	LAR, ISR, APR	32	32
Park et al. <sup>33</sup>	Korea	Multiple	Jan 2008 to May 2011	Retrospective	ISR	106	106
Sugoor et al. <sup>34</sup>	India	Single	Jun 2013 to Dec 2017	Retrospective	AR, LAR, ISR, TPE	84	84
Cohort studies		0		-			
Ahmed et al. <sup>35</sup>	UK	Single	May 2013 to Nov2015	Retrospective	AR, APR, HO, TPC	99	88
Aselmann et al. <sup>36</sup>	Germany	Single	Jan 2011 to Dec 2016	Retrospective	LAR	44	41
Baek et al. <sup>37</sup>	Korea	Single	Jan 2007 to Dec 2010	Retrospective	LAR, CAA	47	37
Baik et al <sup>38</sup>	Korea	Single	Apr 2006 to Sep 2007	Prospective	LAR	56	57
Bedirli et al <sup>39</sup>	Turkev	Single	Ian 2013 to Jun 2015	Retrospective	LAR	35	28
Bianchi et al <sup>40</sup>	Italy	Single	Mar 2008 to Jun 2009	Retrospective	AR APR	25	25
Bo et al <sup>41</sup>	China	Single	Mar 2010 to Jun 2016	Retrospective	AR LAR ISR APR HO	556	1139
Crolla et al $\frac{42}{}$	Netherlands	Single	2005_2015	Retrospective	$I A R H \cap A P R$	168	184
D'Appibalo et al $\frac{43}{43}$	Itoly	Single	2003-2013	Retrospective	TME	100	104
Ergupor et al 44	Turkov	Single	Eab 2009 to Jup 2011	Retrospective		20	27
Eiguilei et al.	Тигкеу	Single	Feb 2008 to Juli 2011	Retrospective	LAR THE DME	2/	3/
Esemendez et al 46	TUIKey	Single	Dec 2014 to Aug 2017	Retrospective		100	/0
Fernandez et al.	USA	Single	2002-2012	Retrospective	LAR, APK	13	59
Feroci et al.	Italy	Multiple	Jan 2008 to Dec 2014	Retrospective	I ME	53	58
Gorgun et al. <sup>10</sup>	USA	Single	Jan 2011 to Jun 2014	Retrospective	AR, APR, CAA	29	27
Huang et al.	Taiwan	Single	Jan 2012 to Apr 2015	Retrospective	LAR, ISR	40	38
lelpo et al.	Spain	Single	Oct 2010 to Jul 2013	Retrospective	LAR, APR	56	8/
Ielpo et al. <sup>31</sup>	Spain	Single	Oct 2010 to Mar 2017	Retrospective	LAR, APR, CAA	86	112
Kamali et al. <sup>52</sup>	UK	Single	Jul 2014 to Sep 2016	Retrospective	AR	18	18
Kamali et al. <sup>53</sup>	UK	Single	Feb 2015 to Aug 2016	Retrospective	APR	11	11
Kim et al. <sup>54</sup>	Korea	Single	Jun 2009 to Nov 2009	Retrospective	SSP, HO	30	39
Kim et al. <sup>55</sup>	Korea	Single	May 2006 to Dec 2014	Retrospective	LAR, ISR, APR	50	35
Kuo et al. <sup>56</sup>	Taiwan	Single	Nov 2009 to Jul 2013	Retrospective	ISR	36	28
Law et al. <sup>57</sup>	China	Single	Jan 2008 to Jun 2015	Retrospective	lar, ho, apr	220	171
Levic et al. <sup>58</sup>	Denmark	Multiple	2010–2012	Retrospective	lar, ho, apr	56	36
Lim et al. <sup>59</sup>	Korea	Single	Jan 2006 to Dec 2010	Retrospective	LAR, ISR, CAA, APR	74	64
Liu et al. <sup>60</sup>	China	Single	Jul 2015 to Oct 2017	Retrospective	AR, APR	80	116
Megevand et al. <sup>61</sup>	Italy	Single	Jan 2011 to Dec 2015	Retrospective	AR, HO, APR	35	35
Panteleimonitis et al. <sup>62</sup>	UK	Single	Dec 2006 to Sep 2014	Retrospective	AR. HO. APR	48	78
Park et al. <sup>63</sup>	Korea	Single	Mar 2008 to Jul 2011	Retrospective	ISR	40	40
Park et al <sup>64</sup>	Korea	Single	Apr 2006 to Aug 2011	Retrospective	LAR	133	84
Pigazzi et al 65	USA	Single	Sep 2004 to Oct 2005	Retrospective	LAR	6	6
Popescu et al 66	Romania	Single	1995-2010	Retrospective	AR APR	38	84
Saklani et al 67	Korea	Single	Ian 2006 to Dec 2010	Retrospective	IAR CAA ICR ADR	74	64
Sprin et al 68	Turkey	Single	Jan 2000 to Dec 2010	Retrospective	I AR ISR	/ <del>1</del> 14	65
Schin et al $69$	Voron	Single	Jan 2005 to Dec 2015	Retrospective	ICD	24	60
$T_{\text{am}} = t_{\text{al}} \frac{70}{70}$	NOIES	Single	Jail 2011 to Dec 2014	Retrospective		24 21	00
I dIII EL UI. Vomographist -171	USA	Single	Appr 2010 to Appr 2015	Retrospective	AR, LAR, ISK, APK, IPC	202	21
r amagucni et al.	Japan	Single	Apr 2010 to Apr 2015	Retrospective	lak, isk, hu, apk	203	239
100 et al	кorea	Single	Sep 2006 to Aug 2008	ketrospective	ISK	44	26
r oon et al.	коrea	Single	Jun 2006 to Dec 2010	ketrospective	AK, LAK	1/	LΟ

LAR, low anterior resection; AR, anterior resection; APR, abdominoperineal resection; HO, Hartmann's operation; PME, partial mesorectal excision; TME, total mesorectal excision; CAA, coloanal anastomosis; ISR, intersphincteric resection; TPE, total pelvic excision; TPC, total proctocolectomy; SSP, sphincter-saving procedure.

were observed by study design, particularly between RCTs and case-matched studies. Among the nine outcomes assessed, two (estimated blood loss and quality of total mesorectal excision)

were difficult to compare by meta-analyses, as the number of included studies was small and the 95 per cent confidence intervals were wide.

Table 2 Summary of meta-analyses by study design

	Measure	RCTs			Case-ma	tched studie	ŝ	Cohort st	udies	
		No. of	No. of	Point	No. of	No. of	Point	No. of	No. of	Point
		studies	patients	estimate	studies	patients	estimate	studies	patients	estimate
Primary outcomes										
Postoperative overall complications	RR	9	895	1.12 (0.91,1.38)	б	2582	1.01 (0.89, 1.15)	30	4913	0.83 (0.74, 0.92)
Anastomotic leakage	RR	9	784	0.97 (0.67, 1.39)	12	2222	0.97 (0.74, 1.29)	35	5366	0.94 (0.74, 1.18)
Mortality	RD	9	904	-0.00 (-0.01, 0.01)	10	1910	-0.00 (-0.01, 0.00)	26	5025	-0.00 (-0.00, 0.00)
Secondary outcomes										
Duration of hospital stay (days)	MD	9	781	-0.28 (-1.44, 0.88)	8	1904	-0.59 (-1.18, 0.00)	25	4966	-1.11 (-1.86, -0.36)
Conversion rate	RR	9	803	0.42 (0.17, 1.03)	11	2976	0.40 (0.31, 0.51)	36	6034	0.34 (0.24, 0.49)
Duration of operation (min)	MD	9	803	33.53 (-3.25, 70.31)	7	1644	83.41 (54.37, 112.45)	29	5345	44.70 (32.40, 57.00)
Estimated blood loss (ml)	MD	Ś	250	36.09 (-136.41, 208.59)	Ŀ	1095	-16.23 (-69.27, 36.82)	21	4438	-13.49 (-29.11, 2.14)
Positive circumferential resection margins	RR	Ś	664	0.88 (0.46, 1.69)	10	2046	1.05 (0.70, 1.57)	29	5545	0.84 (0.63, 1.12)
Quality of total mesorectal excision	RR	4	686	1.08 (0.95,1.23)	2	133	1.34 (0.74 , 2.42)	6	1585	1.14 (1.05, 1.23)
Values in parentheses are 95 per cent confidence inte	ervals. RR, risk	t ratio; RD, ri	sk difference;	MD, mean difference.						

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With respect to the incidence of anastomotic leakage, mortality, and rate of positive circumferential resection margins, metaanalyses for each study design revealed no significant differences between robotic and laparoscopic surgery, suggesting that findings related to these outcomes did not differ by study design. On the other hand, meta-analyses of case-matched studies and cohort studies, but not RCTs, revealed significant differences between robotic and laparoscopic surgery with respect to conversion rate and duration of operation. However, the number of included patients was lower for RCTs than for casematched studies and cohort studies, and 95 per cent confidence intervals were also wider, suggesting that the statistical power might have been lower. Given the wide range of 95 per cent confidence intervals and lower statistical power, the difference between the three study designs in terms of conversion rate and operating time in the meta-analysis could be considered minimal.

The incidence of postoperative overall complications (primary outcome) and duration of hospital stay (secondary outcome) did not differ significantly between robotic surgery and laparoscopic surgery in RCTs and case-matched studies, whereas significant differences were observed in cohort studies. In-depth analyses of the distribution of 95 per cent confidence across study designs showed that outcomes from case-matched studies fell between those of RCTs and cohort studies in meta-analyses. Specifically, superiority of robotic surgery was most evident in cohort studies, least evident in RCTs, and intermediate (between cohort studies and RCTs) in case-matched studies. These differences by study design might reflect the degree of adjustment for confounding factors between study designs. All confounding factors including measurable and unmeasurable factors could be adjusted for in RCTs, whereas confounding factors in cohort studies were not controlled for in the present meta-analyses because the data were unadjusted.

In this review, the results of meta-analyses did not show differences in most of the outcomes assessed. This is consistent with a previous report<sup>2</sup> that results of RCTs were similar to those of case-matched studies in cardiac surgery. On the other hand, other authors<sup>13</sup> reported that case-matched studies tended to overestimate the efficacy of interventions compared with RCTs in patients with acute coronary syndrome. In the present review, the incidence of postoperative overall complications differed by study design, whereas that of anastomotic leakage did not. Postoperative overall complications include anastomotic leakage and so the rates are higher for postoperative overall complications than for anastomotic leakage. Because the statistical power was greater for postoperative overall complications than for anastomotic leakage, the difference in power might have had some influence. Moreover, although anastomotic leakage can be assessed objectively, other complications such as surgical-site infection and ileus are often influenced by subjective judgements. Duration of hospital stay can also be influenced by subjective judgements because the timing of discharge may depend on surgeon preference. In addition, experimental and comparator interventions are usually performed during the same interval in RCTs, whereas historical comparators are sometimes used in cohort studies. Duration of hospital stay tends to shorten as time progresses owing to the introduction of newer and more effective treatment modalities. In this regard, robotic surgery is a newer technique than laparoscopic surgery. Thus, hospital stay after robotic surgery might be shorter in RCTs than in cohort studies. Clinicians should

Referance         Robotic         Laparoscopic         Weight (%)         Risk ratio         Risk ratio           LCT         Baik et al. <sup>15</sup> 4 of 18         1 of 18         0.2         4.00 (0.49, 32.39)           Jayne et al. <sup>17</sup> 78 of 236         73 of 230         8.0         1.04 (0.80, 1.35)           Kim et al. <sup>18</sup> 23 of 66         17 of 73         2.3         1.50 (0.88, 2.55)           Patritt et al. <sup>19</sup> 9 of 29         7 of 37         0.9         1.64 (0.89, 3.86)           Tolstrup et al. <sup>170</sup> 10 of 25         10 of 26         1.4         1.04 (0.53, 2.06)           Wang et al. <sup>121</sup> 8 of 71         10 of 26         0.9         0.74 (0.31, 1.77)           Stubtolal         132 of 445         118 of 450         13.5         1.12 (0.91, 1.38)           Heterogeneity: t <sup>2</sup> = 0.00; $\chi^2 = 4.53$ , 5.df, $P = 0.48$ ; t <sup>2</sup> = 0%         Test tor overall effect: Z = 1.10, $P = 0.27$ Case-matched study         Ackerman et al. <sup>23</sup> 8 of 20         1.4 of 40         1.4         1.14 (0.58, 2.26)           Cho et al. <sup>25</sup> 72 of 278         6.6 of 278         6.8         1.09 (0.82, 1.46)         Test or overall effect: Z = 1.00; $P = 0.87$ Kim et al. <sup>26</sup> 3 of 19         7 of 19         0.5	
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Park et al. <sup>33</sup> 20 of 106       32 of 106       2.6       0.63 (0.38, 1.02)         Sugoor et al. <sup>34</sup> 18 of 84       16 of 84       1.8       1.13 (0.62, 2.05)         Subtotal       328 of 1244       359 of 1338       33.2       1.01 (0.89, 1.15)         Heterogeneity: $r^2 = 0.00; \chi^2 = 7.30, 8 d.f, P = 0.50; l^2 = 0\%$ Test for overall effect: $Z = 1.15, P = 0.88$ Cohort study         Back et al. <sup>37</sup> 9 of 47       10 of 37       1.1       0.71 (0.32, 1.56)         Baik et al. <sup>38</sup> 6 of 56       11 of 57       0.8       0.56 (0.22, 1.40)         Bianchi et al. <sup>40</sup> 4 of 25       6 of 25       0.5       0.67 (0.21, 2.08)         Bo et al. <sup>41</sup> 83 of 556       195 of 1139       9.4       0.87 (0.69, 1.10)         Annibale et al. <sup>43</sup> 5 of 50       11 of 50       0.7       0.45 (0.17, 1.21)         Erguner et al. <sup>44</sup> 3 of 27       8 of 37       0.4       0.51 (0.15, 1.76)         Esen et al. <sup>45</sup> 23 of 100       19 of 78       2.3       0.94 (0.56, 1.61)         Feroci et al. <sup>47</sup> 17 of 53       26 of 58       2.7       0.72 (0.44, 1.16)         Gorgun et al. <sup>49</sup> 6 of 40       7 of 38       0.7       0.81 (0.30, 2.20)	
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Huang et $al.^{49}$ 6 of 40       7 of 38       0.7       0.81 (0.30, 2.20)         lelpo et $al.^{50}$ 15 of 56       20 of 87       1.9       1.17 (0.65, 2.08)         lelpo et $al.^{51}$ 20 of 86       25 of 112       2.4       1.04 (0.62, 1.75)         Kamali et $al.^{52}$ 1 of 18       0.1       1.00 (0.07, 14.79)         Kamali et $al.^{53}$ 5 of 11       4 of 11       0.6       1.25 (0.45, 3.45)         Kim et $al.^{55}$ 14 of 50       12 of 35       1.6       0.82 (0.43, 1.55)         Kuo et $al.^{56}$ 9 of 36       9 of 28       1.1       0.78 (0.36, 1.70)	
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Kamali et al. <sup>52</sup> 1 of 18       1 of 18       0.1       1.00 (0.07, 14.79)         Kamali et al. <sup>53</sup> 5 of 11       4 of 11       0.6       1.25 (0.45, 3.45)         Kim et al. <sup>55</sup> 14 of 50       12 of 35       1.6       0.82 (0.43, 1.55)         Kuo et al. <sup>56</sup> 9 of 36       9 of 28       1.1       0.78 (0.36, 1.70)	
Kamali et al. <sup>55</sup> 5 of 11       4 of 11       0.6       1.25 (0.45, 3.45)         Kim et al. <sup>55</sup> 14 of 50       12 of 35       1.6       0.82 (0.43, 1.55)         Kuo et al. <sup>56</sup> 9 of 36       9 of 28       1.1       0.78 (0.36, 1.70)	-
Kim et al. <sup>33</sup> 14 of 50       12 of 35       1.6       0.82 (0.43, 1.55)         Kuo et al. <sup>56</sup> 9 of 36       9 of 28       1.1       0.78 (0.36, 1.70)	
Kuo <i>et al.</i> 9 of 36 9 of 28 1.1 0.78 (0.36, 1.70)	
Law et al." 42 of 220 38 of 1/1 4.0 $0.86 (0.38, 1.27)$	
Levic <i>et al.</i> $12 \text{ of } 56 = 10 \text{ of } 36 = 1.2 \text{ of } 71 \text{ (0.37, 1.60)}$	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	<b>→</b>
Park et $a^{(6)}$ 6 of 40 5 of 40 0.5 2.17 (0.01, 9.27)	ŕ
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	<b>→</b>
$Poperci at a = \begin{cases} -66 & -6 & -638 & 13 & -684 & 0.8 & -102 & 0.42 & 248 \\ -66 & -66$	
Sakalari <i>et al</i> <sup>67</sup> 15 of 74 13 of 64 1.5 $100(51.194)$	
Serie $t = d^{68}$ 2 of 14 16 of 65 0.4 0.58 (0.15, 1.57)	
Shin $eta^{69}$ 5 of 34 21 of 60 0.9 0.42 (0.17 1.01)	
Tam et al. <sup>70</sup> 9 of 21 7 of 21 1.1 1.29 (0.59.2.81)	
Yamaguchi <i>et al.</i> <sup>71</sup> 18 of 203 54 of 239 2.5 0.39 (0.24, 0.65)	
Yoo <i>et al.</i> <sup>72</sup> 17 of 44 7 of 26 1.2 1.44 (0.69, 2.99)	
Yoon <i>et al.</i> <sup>73</sup> 3 of 17 7 of 61 0.4 1.54 (0.44, 5.32)	
Subtotal 395 of 2090 603 of 2823 53.3 0.83 (0.74, 0.92)	
Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2 = 25.34$ , 29 d.f, $P = 0.66$ ; $I^2 = 0\%$ Test for overall effect: $Z = 3.53$ , $P < 0.001$	
Total 855 of 3779 1080 of 4611 100 0 0 92 (0 85 1 00)	
Hotorogonoity: $z^2 = 0.00$ : $z^2 = 46$ E6. 44 df $B = 0.27$ : $l^2 = 69/$	
Test for overall effect: $Z = 1.99$ , $P = 0.05$ Test for subgroup differences: $x^2 = 9.47$ , $2 df$ , $P = 0.009$ ; $l^2 = 78.9\%$ Test for subgroup differences: $x^2 = 9.47$ , $2 df$ , $P = 0.009$ ; $l^2 = 78.9\%$	

## Fig. 2 Results of meta-analysis stratified by study design: incidence of postoperative overall complications

A Mantel-Haenszel random-effects model was used for statistical analysis. Mean differences are shown with 95 per cent confidence intervals.

	Robot	ic	Laparoso	opic			
Referance	Stay (days)*	Total	Stay (days)*	Total	Weight	t (%) Risk ratio	Risk ratio
RCT							
Baik <i>et al.</i> <sup>15</sup>	6.9(1.3)	18	87.7(1.3)	18	4.4	-1.80 (-2.65, -0.95)	
Debakev et al. <sup>16</sup>	5.5(3.8)	21	4.3(2.9	24	2.9	1.20 (-0.80, 3.20)	
Javne <i>et al</i> <sup>17</sup>	8(5.9)	223	8 2(6)	221	4 1	-0.20 (-1.31, 0.91)	
Kim <i>et al</i> <sup>18</sup>	10 3(3 4)	66	10 8(7 4)	73	3.0	-0.50 (-2.39, 1.39)	
Patriti et al <sup>19</sup>	11 9(7 5)	29	9 6(6 9)	37	1.5	2 30 (-1 22 5 82)	
Tolstrup et al 20	8 9(5 6)	25	9 5(7 7)	26	14	-0.60 (-4.28, 3.08)	
Subtotal	0.0(0.0)	382	0.0(1.1)	399	17.2	-0.28 (-1.44, 0.88)	
Heterogeneity: $\tau^2$ =	$1 13^{\circ} \gamma^2 = 13$	39.5 0	$f P = 0.02 \cdot l^2$	= 63%		( ) )	
Test for overall effe	ct: $Z = 0.47 P$	= 0.64	, / = 0.02, /	= 00 /0			
	on <u> </u>	0.0.					
Case-matched study	/						
Cho et al.25	10.4(5.6)	278	10.7(6.6)	278	4.2	-0.30 (-1.32, 0.72)	
Kim et al.26	10.9(6.2)	33	13.1(12.8)	66	1.4	-2.20 (-5.94, 1.54)	
Kim et al.27	13.5(14.1)	224	13.8(10.9)	224	2.5	-0.30 (-2.63, 2.03)	
Kim <i>et al.</i> <sup>28</sup>	9(6.6)	130	10.7(14.2)	130	2.1	-1.70 (-4.39, 0.99)	
Koh <i>et al.</i> <sup>29</sup>	9.8(5.2)	19	11(7.5)	19	1.2	-1.20 (-5.30, 2.90)	· · · · · · · · · · · · · · · · · · ·
Park <i>et al.</i> <sup>31</sup>	99(4.2)	41	9.4(2.9)	82	3.6	0.50 (-0.93, 1.93)	
Park <i>et al.</i> <sup>33</sup>	9.9(3.9)	106	11.7(8.8)	106	3.1	-1.80 (-3.63, 0.03)	
Sugoor <i>et al.</i> <sup>34</sup>	7.2(3.4)	84	8.1(4.7)	84	3.9	-0.90 (-2.14, 0.34)	
Subtotal		915	_	989	21.9		$\bullet$
Heterogeneity: $\tau^2$ =	$= 0.00; \chi^2 = 5.9$	97, 7 d.i	f, <i>P</i> = 0.54; <i>I</i> <sup>2</sup> =	= 0%			
Test for overall effe	ct: Z = 1.95, P	= 0.05					
Cohort study							
Boik at al 38	57(11)	56	7 6(2)	57	4.4	100/272 107	
Dalk <i>et al.</i> <sup>39</sup>	5.7(1.1)	25	7.0(3)	20	4.4	-1.90(-2.73, -1.07)	
Bionobi ot al 40	(3.1(3.7))	30	4.0(2.0)	20	3.4	1.00 (-1.11, 2.11)	
Bo of al 41	0(3.3)	20 556	9(4.9)	1120	2.0	-1.00(-3.32, 1.32)	
Crolla at $al^{42}$	20.2(20.5)	169	20 2(22 1)	194	4.0	10.00(-0.03, 1.03)	<b></b>
	20.3(20.3)	27	7 5 (2 8)	37	2.5	-10.00(-13.36, -4.42)	
Erguner <i>et al</i> .	7(4)	100	0(4)	79	2.5	2.00(3.18, 0.82)	
Eeroci et al 47	8(4.2)	53	18 5(15 1)	58	1.0	-2.00(-3.10, -0.02) -10.50(-14.55, -6.45)	←
Gorgun <i>et al</i> <sup>48</sup>	6 4 (4 2)	20	8 4 (4 4)	27	2.6	-2 00 (-4 26 0 26)	
Huppa at $al^{49}$	120(7.7)	40	11 7(6 7)	20	2.0	-2.00(-4.20, 0.20)	
I lobo of al 50	12(10.5)	40 56	10(2.6)	97	2.0	3 00 (0 15 5 85)	
Kamali <i>et al</i> <sup>52</sup>	8(4.8)	18	10 5 (9 4)	18	0.0	-2 50 (-7 38 2 38)	
Kamali <i>et al</i> <sup>53</sup>	10(7.3)	11	12 5(9 4)	11	0.5	-2 50 (-9 53 4 53)	· · · · · · · · · · · · · · · · · · ·
Kim et al <sup>55</sup>	10 2(8 1)	50	14 3(21 7)	35	0.0	_4 10 (_11 63 3 43)	· · · · · · · · · · · · · · · · · · ·
$L_{aw} et al^{57}$	19 5(19 5)	220	24 3(25 6)	171	1.0	_4 80 (_9 42 _0 18)	·
Levic et al $58$	30(30.5)	56	17(15)	36	0.3	13 00 (3 63 22 37)	<b>→</b>
Liu et al $^{60}$	11 2(5 8)	80	14 7(6 9)	116	3.1	-350(-529, -171)	
Park et al 63	10.6(4.2)	40	11 3(3 6)	40	3.2	-0.70(-2.41, 1.01)	
Park et al 64	5 9(14 4)	133	6 5(2 7)	84	47	-0.60(-1.22, 0.02)	
Popescu et al 66	5 1(4 5)	38	8 4(3 5)	84	3.4	-0.30 (-1.91, 1.31)	
Sakalani <i>et al</i> <sup>67</sup>	8(3.8)	74	9 2(4 3)	64	37	-1 20 (-2 56, 0 16)	
Shin et al 67	10 3(3 4)	34	10 3(3 4)	60	3.4	-0.20(-1.80, 1.40)	
Yamaguchi et al 71	7 3(2 3)	203	9 3(9 7)	239	3.8	-2.00(-3.27, -0.73)	
Yoo et al <sup>72</sup>	114(56)	44	11(6.3)	26	1.9	0.40(-2.53, 3.33)	
Yoon et al <sup>73</sup>	13.6(9.5)	17	12,9(6)	61	0.9	0.70 (-4 06 5 46)	
Subtotal	(0.0)	2163	0(0)	2803	60.9	-1.11 (-1.860.36)	$\bullet$
Heterogeneity: $\tau^2$ =	$= 2.02; \gamma^2 = 10$	6.18.2	4  d.f. P = 0.000	001: I <sup>2</sup>	= 77%		-
Test for overall effe	ct: Z = 2.90. P	= 0.004	4	,			
Total		2400		4101	100.0		
		3400		+191	100.0	-0.07 (-1.38, -0.35)	▼
Heterogeneity: $\tau^2$ =	$1.37; \chi^2 = 12$	5.83, 3	8 d.f, $P = 0.000$	)01; <i>l</i> <sup>2</sup>	= 70%		
lest for overall effe	ct: $Z = 3.31, P$	< 0.00	1	0			Favours robotic Favours lanaroscopic
Test for subgroup d	lifferences: $\gamma^2$	= 1.78,	2 d.f, P = 0.04	$1; I^2 =$	0%		

#### Fig. 3 Results of meta-analysis stratified by study design: duration of hospital stay

An inverse-variance random-effects model was used for statistical analysis. Mean differences are shown with 95 per cent confidence intervals. \*Values are mean(s.d.).

interpret findings related to these outcomes with caution, and consider the study design when doing so.

The strength of the present review is the large number of studies examined. In total, 59 studies were reviewed, compared with 5–23 in previous systematic reviews<sup>74</sup>. Moreover, previous studies that focused on differences by study design often investigated a single outcome for each comparison<sup>5,75</sup>, whereas nine outcomes for a single comparison (robotic *versus* laparoscopic surgery) were investigated here to highlight differences in surgical outcomes. However, this study also has some limitations. The numbers of studies and patients differed among the three types of study, and tended to be lower in RCTs. The present review included only published data and did not consider the quality of each study.

Finally, the results of case-matched studies were often similar to those of RCTs with respect to objective outcomes of robotic surgery for rectal cancer. However, case-matched studies potentially overestimated the effect of interventions compared with RCTs in terms of subjective outcomes.

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# **Supplementary material**

Supplementary material is available at BJS Open online.

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