# Meta-analysis of Robot-assisted *Versus* Laparoscopic Surgery for Rectal Cancer

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**Abstract.** Background/Aim: A meta-analysis was conducted to evaluate and compare the short- and long-term outcomes of robot-assisted (RAS) and conventional laparoscopic surgery (LAS) for rectal cancer. Materials and Methods: We searched MEDLINE for relevant papers published between 2010 and December 2017 by using specific search terms. We analyzed outcomes over short- and long-term periods. Results: We identified 23 papers reporting results that compared RAS for rectal cancer with LAS. Our metaanalysis included 4,348 patients with rectal cancer; 2,068 had undergone RAS, and 2,280 had undergone LAS. In the short- and long-term period, 27 and 7 outcome variables were examined, respectively. RAS for rectal cancer was significantly associated with a greater operative time and a lower conversion rate to open surgery in the short-term, and results in almost similar outcomes in the long-term, compared to LAS. Conclusion: RAS may be an acceptable surgical treatment option compared to LAS for rectal cancer.

Laparoscopy-assisted surgery (LAS) for colorectal cancer (CRC) was first described in 1991 (1) and has since been widely applied by surgeons to treat patients with CRC. Several randomized trials and meta-analyses described that LAS for colon cancer results in smaller surgical incisions, reducing intraoperative blood loss, shorter recovery and hospital stays, and similarity of morbidity rate in the short-

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Key Words: Rectal cancer, robot-assisted surgery, laparoscopic surgery, meta-analysis.

term, and is oncologically equivalent in the long-term, compared to open surgery (OS) (2, 3). The application of LAS for rectal cancer was controversial in the previous Council Conventional Medical Research Laparoscopic-Assisted Surgery In Colorectal Cancer (MRC CLASICC) trial (4). In 2013, the MRC CLASICC indicated that long-term results continue to support the use of LAS for both colonic and rectal cancer (5). In several randomized trials and our meta-analysis, LAS for rectal cancer is described to have the benefits of reducing intraoperative blood loss, earlier resumption of oral intake, and shorter duration of hospital stay in the short-term, and equivalent long-term outcomes, with comparison to OS (6, 7). However, LAS for rectal cancer has technical disadvantages such as inadequate two-dimensional view with a movable video camera, a limited range for maneuver of the long, straight and rigid laparoscopic instruments in the narrow pelvic cavity, and a reduction in tactile sense.

Robot-assisted surgery (RAS) for rectal cancer was introduced to compensate for these disadvantages of LAS. Several studies describe safety and feasibility of RAS for rectal cancer after RAS for CRC was first reported in 2002 (8). The advantages of RAS are a stable 3-dimensional view, an increased dexterity for maneuvering instruments with excellent ergonomics, and physiologic tremor filtering. RAS for rectal cancer may be of use to manipulate instruments in the narrow pelvic cavity.

The value of RAS for rectal cancer has remained controversial because the short- and long-term outcomes have not been clarified. To accurately evaluate the efficacy of RAS for rectal cancer, the short- and long-term outcomes of RAS for rectal cancer must be compared to those of LAS. However, there were few randomized controlled trials comparing RAS with LAS for rectal cancer. The methodological index for non-randomized studies (MINORS) is a valid instrument for assessing the methodological quality of non-randomized studies, especially for the purposes of

meta-analysis (9). Here, we conducted a meta-analysis of previously conducted non-randomized controlled trials (10-32). The outcomes of each of the surgical procedures were analyzed at short- and long-term periods.

#### **Materials and Methods**

Study designs. There were few randomized controlled trials comparing RAS versus LAS for rectal cancer. Non-randomized studies that compared the short- and long-term outcomes of RAS versus LAS for rectal cancer were considered for this meta-analysis.

Literature search. To identify papers relevant to our study, we searched the major medical databases – MEDLINE, EMBASE, Science Citation Index, and the Cochrane Controlled Trial Register—for studies published between 2010 and December 2017. The following search terms were used: "robotic", "robot-assisted", "laparoscopic", "laparoscopy-assisted", "surgery", "rectal cancer", and "colorectal cancer". Appropriate data from the studies were used for this meta-analysis. This meta-analysis was prepared in accordance with the Preferred Reporting Items for Systemic reviews and Meta-Analysis (PRISMA) statement (Figure 1) (33).

Inclusion criteria. To enter this meta-analysis, studies had to: [1] be written in English; [2] compare RAS with LAS for rectal cancer; and [3] report on at least one of the outcome measures mentioned below.

Exclusion criteria. Studies were excluded from this analysis if the outcomes of interest were not reported for the two surgical techniques.

Study quality. The MINORS was used to evaluate the methodological quality of the non-randomized studies. Two reviewers independently appraised the studies. Disagreements were resolved by discussion and consensus.

Data extraction. Three researchers (H.O., S.N., and H.N.) extracted data from each article by using a structured sheet and entered the data into a database. We conducted meta-analyses for short- and long-term. For the short-term analysis, we collected data on the perioperative period, clinical course, postoperative complications, and pathological findings. For the perioperative period, we collected data on operation time, estimated blood loss, intraoperative transfusion, conversion rate to open surgery, perioperative mortality, the rate of the patients with lower rectal cancer and undergoing the neoadjuvant radiochemotherapy, and cost of surgery. Time to bowel movement and oral diet, duration of hospital stay were examined as the data of clinical course. For the postoperative complications, overall complications, postoperative bleeding, anastomotic leakage, interperitoneal abscess, wound infection, ileus, and deep venous thrombosis (DVT) were analyzed. Number of retrieved lymph nodes, length of circumferential resection margin (CRM), proximal margin (PM) and distal margin (DM), number of cases with inadequate CRM, DM and TME, tumor size of the specimen, and the distance from anal verge to the lower margin of tumor, were examined for the pathological data. For the long-term analysis, we used data on the rate of overall recurrence, local recurrence, distant recurrence, 3-

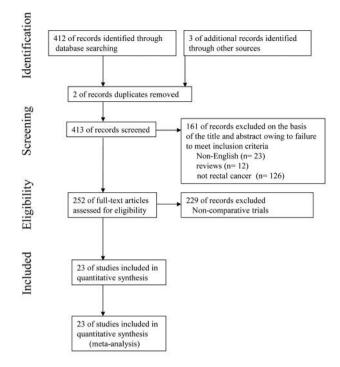


Figure 1. Flow diagram of this meta-analysis in accordance with PRISMA Statement.

year overall mortality and disease-free survival, urinary retention and erectile dysfunction.

Statistical analysis. Weighted mean differences (WMDs) and odds ratios were used for the analysis of continuous and dichotomous variables, respectively. Random effects models were used to identify heterogeneity between the studies, and the degree of heterogeneity was assessed using the  $\chi^2$  test. For the analysis of the conversion rate, the  $\chi^2$  test was used. The confidence interval (CI) was established at 95%, and *p*-values of less than 0.05 were considered to indicate statistical significance. For the computation of the CI, estimates of the mean and standard deviation were obtained using formulas proposed by Hozo *et al.* (34). Statistical analyses were performed using the Review Manager (RevMan) software, version 5.3, provided by the Cochrane Collaboration, Copenhagen, Denmark.

#### Results

Search results. The present meta-analysis met the PRISMA statement. Overall, 412 citations were retrieved from the search strategy. Three additional articles were identified by contacting clinical experts and searching bibliographies. Two studies were excluded because of duplicate reports. One hundred and sixty-one studies were removed from the 413 because they were not written in English, reported carcinomas of the other organs except the rectum, and were described in the form of review. Two hundred and twenty-nine studies were excluded on account of non-comparative trials.

We identified 23 trials that compared RAS with LAS for rectal cancer for this meta-analysis. The characteristics of each trial are presented in Table I. Our meta-analysis included 4348 patients with rectal cancer; of these, 2068 had undergone RAS, and 2280 had undergone LAS. Short- and long-term results are shown in Figure 2 and Figure 3, respectively. The study quality by using the MINORS was shown in Table II.

Short-term outcomes. The operative time for RAS was significantly greater, by 44.8 min, than that for LAS (weighed mean difference=44.80; 95%CI=28.44-61.15; p < 0.00001). No significant difference was found in the intraoperative estimated blood loss (Figure 2a), number of patients receiving intraoperative transfusion, the time to bowel movement, the time to oral diet, and the duration of hospital stay between RAS and LAS from the analysis. The occurrence rate of overall postoperative complications, postoperative bleeding, anastomotic leakage, interperitoneal abscess, wound infection, ileus, and DVT did not differ significantly between the two procedures (Figure 2b). Examining 3232 resections (1548 RAS and 1684 LAS), 0 and 3 perioperative mortality occurred among patients who underwent RAS and LAS, respectively. The cause of death in the 3 cases of LAS was 2, cardiovascular event, remaining 1 case was unknown.

No significant difference was found in number of retrieved lymph nodes, length of CRM, DM and PM, number of cases with inadequate CRM and DM, and number of patients with incomplete TME between RAS and LAS.

The rate of the patients undergoing the neoajuvant chemoradiotherapy and with lower rectal cancer was significantly higher in RAS than in LAS. The distance from anal verge to the lower margin of tumor was significantly shorter in RAS than in LAS (Figure 2c). No significant difference was found in the tumor size of the specimen between the 2 groups.

Conversion rate. The conversion rate from RAS to OS, and LAS to OS ranged from 0 to 9.1%, and 0 to 32% in the analysis of 23 studies (Table I). The conversion rate of RAS was significantly lower than that of LAS.

Cost of surgery. In an analysis of the cost of surgery, the cost of RAS was 1.26-1.61 times higher than that of LAS.

#### Long-term outcomes

Tumor recurrence. The rate of overall recurrence, metastatic recurrence, and local recurrence were not significant different between RAS and LAS (Figure 3a), from the analysis of 1932 resections (953 RAS and 979 LAS), 2261 resections (1130 RAS and 1131 LAS) and 2016 resections (1000 RAS and 1016 LAS), respectively.

Long-term mortality. We found no significant difference in 3-year overall survival rate and 3-year disease free survival rate between RAS and LAS in the analysis of 1241 resections (654 RAS and 587 LAS; Figure 3a) and 1193 resections (654 RAS and 539 LAS), respectively.

Long-term morbidity. Nine and 4 articles reported data on urinary and sexual dysfunction, respectively (Figure 3b).

Urinary dysfunction did not differ significantly between the 2 groups (Odds Ratio= 0.85; 95%CI=057-1.26; p=0.41). There was no significant difference in erectile dysfunction between robotic and laparoscopic groups (Odds Ratio=0.54; 95%CI=0.19-1.58; p=0.26).

Heterogeneity. In the short-term period, significant heterogeneity was found between studies with respect to operative time, estimated blood loss, rate of the patients with lower rectal cancer and undergoing the neoadjuvant radiography, cost of surgery, time to bowel movement, time to oral diet, duration of hospital stay, number of retrieved lymphnodes, length of PM and DM, the distance from anal verge to the lower margin of tumor. There was no significant heterogeneity in number of the patients receiving intraoperative transfusion, conversion rate to open surgery, perioperative mortality, overall complications, postoperative bleeding, anastomotic leakage, interperitoneal abscess, wound infection, ileus, DVT, length of CRM, number of cases with inadequate CRM, DM and TME, and tumor size of the specimen. In the long-term period, we found no significant heterogeneity in all the types of recurrence, survival rate, and rate of dysfunction between studies.

#### **Discussion**

The short- and long-term outcomes of RAS and LAS for rectal cancer were compared in this meta-analysis. While there have been few randomized trials comparing RAS to LAS for rectal cancer, several non-randomized trials have been reported (10-32).

In the short-term period, this analysis of pooled data revealed that RAS for rectal cancer was associated with a significantly longer operative time, by 44.8 min. Although most surgeons are suspected to be already skilled to LAS, they may be in learning curve because RAS is a new procedure. Another reason may be that the set-up time for RAS is longer than that of LAS. Significant heterogeneity of the operation time between studies may be depend on the difference of points on learning curve of the surgeons, surgical procedures, tumor condition, and the factors of patients which are obesity, adhesion, and so on. The learning curve of LAS and RAS for colorectal cancer is described to be from 30 to 70 cases, and from 20 to 40 cases, respectively (29). The operation time for RAS will be expected to decrease in future, as surgeons experience RAS.

Table I. Characteristics of all the trials.

	Year	Ref.	Style of study		mber of tients		Convers to OS (or HAI	}	for nversion		eration ethod		erative ment	Follow-up period		
				RAS	LAS	RAS	LAS	RAS	LAS	RAS	LAS	RAS	LAS	entire	RAS	LAS
1 Bianchi PP et al.	2010	10	pro- spective	25	25	0 (0%)	1 (4%)	-	ischemia of the left colon	AR (72%)	AR (76%)	CRT (52%) APR (28%)	CRT (40%) APR (24%)	10M (mean)	U	U
2 Popescu et al.	2010	11	retro- spective	38	84	2 (5.2%)	9 (10.5%)	Adhesion, bleeding tumor condition		AR (79%) APR (21%)	AR (60%) APR (40%)	U	U	U	13M (median	27.5M) (median)
3 Park JS et al.	2011	12	pro- spective	52	123	0 (0%)	0 (0%)	-	-	AR APR	AR APR	CRT (23.1%)	CRT (10.2%)	U	U	U
4 Kwak JM <i>et al</i> .	2011	13	retro- spective	59	59	0 (0%)	2 (3.4%)	-	Difficulty in pelvic dissection	AR (91.5%) ISR (8.5%) APR (0%)	AR (88.1%) ISR (10.2%) APR (1.7%)	CRT (13.6%)	CRT	U	17M (median	13M ) (median)
5 Baek SJ et al. *	2012	14	retro- spective		150	U	U	U	U	AR (69.4%) ISR (23.4%) APR (7.1%)	AR (86.7%) ISR (9.3%) APR (2.7%) IPAA (1.3%)	CRT (22.7%)	CRT (8%)	U	U	U
6 Saklani AP et al.	2013	15	retro- spective	74	64	1 (1.4%)	4 (6.3%)	Early experience	Early experience	ISR (4.1%) CAA (31.1%) APR	AR (71.9%) ISR (1.6%) CAA (21.9%) APR (4.7%)	U	U	30.1± 9.9M (mean)	U	U
7 Baek SJ et al. **	2013	16	retro- spective	47	37	1 (2.1%)	6 (16.2%)	U	U	(2.7%) AR (87.2%) ISR (12.8%)	(4.7%) AR (89.2%) ISR (10.8%)	CRT (42.6%)	CRT (32.4%)	31.5M (median		U
8 Kang J et al.	2013	17	pro- spective		165		3 (1.8%)	U	U	SPP (99.4%)	(10.8%) SPP (95.8%) Hartmann (0.6%) APR (3.6%)		CRT (21.8%)	22.4M (median		U
9 Fernandez et al.	2013	18	retro- spective		59	1 (8%)	10 (17%)	U	U	AR (39%) APR (62%)	(3.5%) AR (75%) APR (25%)	CRT (77%)	CRT (54%)	U	U	U
10 D'Annibale A et al.	2013	19	retro- spective	50	50	0 (0%)	6 (12%)	-	U	AR (100%)	AR (100%)	CRT (68%)	CRT (56%)	U	U	U
11 Park SY et al.	2013	20	retro- spective	40	40	0 (0%)	0 (0%)	-	-	ISR (100%)	ISR (100%)	CRT (80%)	CRT (50%)	U	U	U
12 Kim YS et al.	2016	21	retro- spective	33	66	2 (6.1%)	0	Invasion to ureter ischemia of the left colon	-	AR (93.9%)	AR (92.4%) Hartmann (1.5%) APR (6.1%)	CRT (100%)	CRT (100%)	U	U	U

Table I. Continued

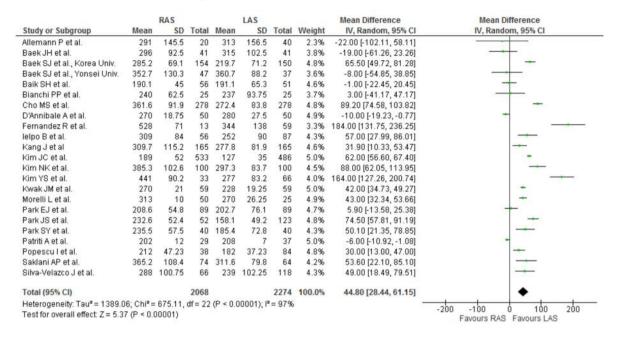
Table I. Continued

	Year	Ref.	Style of study		mber of tients		Conversi to OS (or HAL		Reasons for onversion		eration ethod		erative tment	F	Follow-up period	)
				RAS	LAS	RAS	LAS	RAS	LAS	RAS	LAS	RAS	LAS	entire	RAS	LAS
13 Cho MS et al.	2015	22	retro- spective			1 (0.4%)	2 (0.7%)	Bowel perfo- ration	Severe tumor adhesion major vessel bleeding	AR (80.9%) CAA (19.1%)	AR (84.5%) CAA (15.5%)	CRT (65.5%)	CRT (65.1%)	15.3M	51.0± 13.1M (mean)	51.0± 13.1M (mean)
14 Baik SH et al.	2009	23	pro- spective	56	57	0 (0%)	6 (10.5%)	-	Severe hemorrhage severe narrow pelvic cavity	AR e (100%)	AR (100%)	CRT (8.9%)	CRT (12.3%)	14.3M (median		U
15 Patriti A et al.	2009	24	pro- spective	29	37	0 (0%)	7 (18.9%)	-	U	AR (65.5%) APR (17.2%) ISR (17.2%)	AR (86.4%) APR (8.1%) ISR (5.4%)	CRT (24.1%)	CRT (5.4%)	U	29.2M (mean)	18.7M (mean)
16 Kim NK et al.	2010	25	retro- spective		100	2 (2%)	3 (3%)	U	U	Sphincter	Sphincter preserving surgery (99%)		CRT (46%)	U	U	U
17 Baek JH et al.	2011	26	pro- spective	41	41	3 (7.3%)	9 (22%)	Obesity with narrow pelvis Adhesion	Adhesion to adjacent organ Instrument too short Obesity with narrow pelvis	AR (80.5%) CAA (4.9%) APR	AR (80.5%) CAA (4.9%) APR (14.6%)	CRT (80.5%)	CRT (43.9%)	U	U	U
18 Ielpo B et al.	2014	27	retro- spective	56	87	2 (3.6%)	10 (11.5%)	U	difficult mesorectal dissection border tumoral invasion	AR (71.4%) APR (26.7%) CAA (1.8%)	AR (75.8%) APR (23%) CAA (1.1%)	CRT (80.5%)	CRT (82.1%)	U	U	U
19 Kim JC et al.	2016	28	retro- spective			1 (0.2%)	25 (5.1%)	U	Advanced cancer difficult mobilization	AR (95.1%) APR	AR (97.9%) APR (2.1%)	CRT (32.3%)	CRT (12.6%)	U	U	U
20 Park EJ et al.	2014	29	retro- spective	89	89	0 (0%)	5 (5.6%)	-	U	AR (100%)	AR (100%)	U	U	U	U	U
21 Morelli L et al.	2016	30	retro- spective		25	1 (2%)	8 (32%)	Visceral obesity	Visceral obesity	AR (64%) ISR (22%) APR (14%)	AR (84) ISR (8%) APR (8%)	CRT (46%)	CRT (36%)	U	U	U
22 Silva- Velazco et al.	2016	31	retro- spective		118		18 (15.4%)	U	U	AR (65.2%) APR (33.3%)	AR (77.1%) APR (21.2%)	CRT (51.5%)	CRT (49.2%)	U	U	U
23 Allemann P	2016		pro- spectively	20 y	40	1 (5%)	8 (20%)	Obesity	Obesity	AR (75%) ISR (15%) APR (10%)	AR (62.5%) ISR (22.5%) APR (15%)	CRT (65%)	CRT (60%)	7.0M	31.8± 17.1M (mean)	U

<sup>-:</sup> Not stated; U: unknown; M: month; Y: year; CRT: chemoradiation; AR: anterior resection; ISR: intersphncteric resection; APR: abdominoperitoneal resection; CAA: coloanal anastomosis; IPAA: ileal pouch-anal anastomosis; SPP: sphincter-preserving procedure. \*Korea University, Anam Hospital; \*\*Yonsei University Health System. Ref.: Reference.



### Operative time (minutes)



## Intraoperative estimated blood loss (ml)

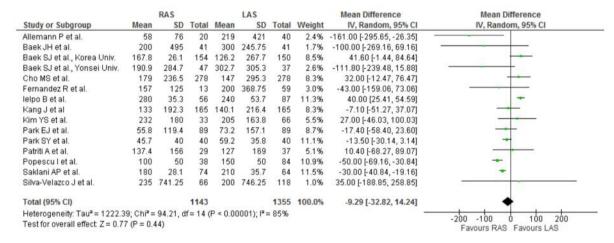


Figure 2. Continued

No significant difference was found in intraoperative blood loss and number of patients receiving intraoperative transfusion. The reason for significant heterogeneity of the intraoperative blood loss may be almost similar to that of the operation time.

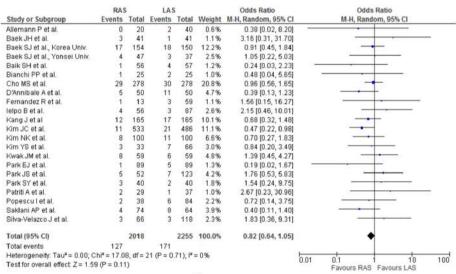
Higher rate of the patients undergoing the neoajuvant chemoradiotherapy in the RAS group may indicate more patients with locally advanced rectal tumor in RAS, comparing to LAS. Tumor location was lower in RAS than in LAS, however, the conversion rate of RAS was significantly lower than that of LAS. The reason may be that the surgeons for RAS are able to safely accomplish surgery, using ergonomic instruments and three-dimensional view, in the narrow and enclosed pelvic cavity, while controlling intraoperative bleeding. This may contribute to the longer operation time of RAS. Choi GS *et al.* described that 3-dimensional images and free articulation of EndoWrist instruments allow pinpoint bleeding control and make performing intracorporeal suture easy (35). We previously



### Overall complications

	RAS		LAS	5		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	om, 95% CI
Allemann P et al.	8	20	14	40	2.7%	1.24 [0.41, 3.74]		
Baek JH et al.	9	41	11	41	3.1%	0.77 [0.28, 2.11]	-	
Baek SJ et al., Korea Univ.	50	154	41	150	8.7%	1.28 [0.78, 2.09]		•
Baek SJ et al., Yonsei Univ.	9	47	10	37	3.1%	0.64 [0.23, 1.79]	-	_
Baik SH et al.	6	56	11	57	2.8%	0.50 [0.17, 1.47]		_
Bianchi PP et al.	4	25	5	25	1.7%	0.76 [0.18, 3.25]		
Cho MS et al.	72	278	66	278	11.1%	1.12 [0.76, 1.65]	-	_
D'Annibale A et al.	5	50	11	50	2.5%	0.39 [0.13, 1.23]		-
elpo B et al.	15	56	20	87	4.8%	1.23 [0.57, 2.66]	_	-
<ang al<="" et="" j="" td=""><td>34</td><td>165</td><td>46</td><td>165</td><td>8.4%</td><td>0.67 [0.40, 1.12]</td><td>-</td><td></td></ang>	34	165	46	165	8.4%	0.67 [0.40, 1.12]	-	
(im JC et al.	65	533	63	486	11.5%	0.93 [0.64, 1.35]		_
Gm NK et al.	20	100	27	100	6.1%	0.68 [0.35, 1.31]		_
Gm YS et al.	15	33	26	66	4.2%	1.28 [0.55, 2.98]	_	-
<wak al.<="" et="" jm="" p=""></wak>	19	59	14	59	4.5%	1.53 [0.68, 3.44]		
Park EJ et al.	9	89	23	89	4.3%	0.32 [0.14, 0.75]		
Park JS et al.	10	52	15	123	4.0%	1.71 [0.71, 4.12]	-	
Park SY et al.	6	40	5	40	2.1%	1.24 [0.34, 4.43]	-	
Patriti A et al.	7	29	12	37	2.7%	0.66 [0.22, 1.98]		
Popescu l et al.	6	38	13	84	2.9%	1.02 [0.36, 2.94]	· ·	
Saklani AP et al.	15	74	3	64	2.1%	5.17 [1.42, 18.78]		
Silva-Velazco J et al.	26	66	52	118	6.7%	0.82 [0.45, 1.52]	-	_
Total (95% CI)		2005		2196	100.0%	0.93 [0.77, 1.14]	•	•00
Total events	410		488					
Heterogeneity: Tau² = 0.05; C Test for overall effect: Z = 0.6			20 (P = 0	12);  2	= 27%		0.05 0.2 1 Favours RAS	5 2 Favours LAS

### Anastomotic leakage

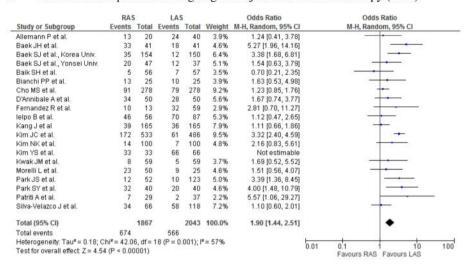


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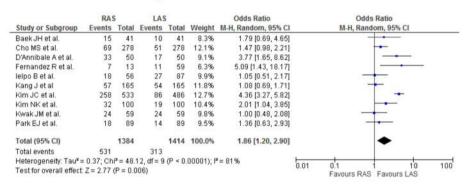
Study or Subgroup	RAS Events	Total	LAS Events	Total	Weight	Odds Ratio M-H, Random, 95% CI			Ratio om, 95% CI	
Allemann P et al.	Events				-			M-H, Kallu	OIII, 95% CI	
	1	20	0	40	0.9%	6.23 [0.24, 160.03]		54	August 100	
Baek JH et al.	3	41	2	41	2.7%	1.54 [0.24, 9.73]				
Baek SJ et al., Korea Univ.	19	154	/	150	11.2%	2.88 [1.17, 7.06]				
Baek SJ et al., Yonsei Univ.	1	47	2	37	1.5%	0.38 [0.03, 4.37]				
Baik SH et al.	1	56	3	57	1.7%	0.33 [0.03, 3.25]		-		
Cho MS et al.	16	278	9	278	13.0%	1.83 [0.79, 4.20]		100		
lelpo B et al.	4	56	6	87	5.2%	1.04 [0.28, 3.86]		-		
Kang Jetal	6	165	9	165	8.1%	0.65 [0.23, 1.88]			-	
Kim JC et al.	17	533	16	486	18.7%	0.97 [0.48, 1.94]		-	_	
Kim NK et al.	3	100	2	100	2.8%	1.52 [0.25, 9.27]		-		
Kwak JM et al.	5	59	6	59	5.8%	0.82 [0.24, 2.84]		-	<del></del>	
Morelli L et al.	4	50	3	25	3.6%	0.64 [0.13, 3.10]			_	
Park EJ et al.	2	89	3	89	2.7%	0.66 [0.11, 4.04]				
Park JS et al.	1	52	1	123	1.2%	2.39 [0.15, 38.99]		-		30
Patriti A et al.	2	29	1	37	1.5%	2.67 [0.23, 30.96]		9	-	
Popescu I et al.	1	38	0	84	0.9%	6.76 [0.27, 169,81]		-		_
Saklani AP et al.	2	74	3	64	2.7%	0.56 [0.09, 3.49]		-	_	
Silva-Velazco J et al.	14	66	21	118	15.8%	1.24 [0.58, 2.65]		_	•	
Total (95% CI)		1907		2040	100.0%	1.20 [0.89, 1.62]			•	
Total events	102		94						190	
Heterogeneity: Tau <sup>2</sup> = 0.00; 0	hi <sup>2</sup> = 13.3	2. df=	17 (P = 0	71); [2:	= 0%		t	-1-	1	
Test for overall effect: Z = 1.2							0.005	0.1 Favours RAS	1 10 Favours LAS	200

Figure 2. Continued

#### C Number of the patients undergoing neoadjuvant chemoradiotherapy (CRT)



#### Number of patients with lower rectal cancer



#### Length from anal verge to the lower margin of tumor (cm)

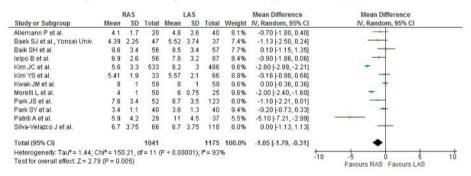


Figure 2. Continued

conducted a meta-analysis, by 12 randomized controlled trials, to evaluate and compare the short- and long-term outcomes of LAS and OS for the treatment of patients with rectal cancer (16). The operative time for OS was significantly shorter, by 40.96 min, than that for LAS. The intraoperative blood loss in OS were significantly more than that in LAS. There were no

significant differences in time to bowel movement, time to oral diet and duration of hospital stay. Significant heterogeneity was found in all of them. Differences in the clinical approach at different institutions may have caused the heterogeneity in time to bowel movement, time to oral diet and the duration of hospital stay.

#### Conversion rate to open surgery RAS Odds Ratio LAS ents Total M-H, Random, 95% CI M-H, Random, 95% Cl Park SY et al. n 40 n 40 Not estimable Park JS et al. 52 0 123 Not estimable Blanchi PP et al. 0 25 25 0.32 (0.01 8.25) 33 0 66 2.0% Kim YS et al. 10.56 [0.49, 226, 44] Kwak IM et al. 59 89 59 2.0% 0.19 [0.01, 4.11] 89 Park EJ et al. 2.2% 0.09 (0.00, 1.58) 29 50 37 Patriti A et al. 0.07 [0.00, 1.26] D'Annibale A et al 6 50 2.2% 0.07 [0.00, 1.24] Cho MS et al. 278 278 0.50 [0.04, 5.53] Kang J et al 166 165 3.6% 0.33 (0.03.3.20) Saklani AP et al. 64 3.8% 0.21 [0.02, 1.89] 4.0% Baek SJ et al., Yonsei Univ. 47 37 40 0.11 [0.01, 0.98] Allemann P et al. 20 4.0% 0.21 [0.02, 1.82] 13 59 4.0% Fernandez R et al 533 486 Kim JC et al. 25 4.6% 0.03 (0.00, 0.26) Kim NK et al. 100 100 Popescu Let al 38 84 7.4% 0.46 (0.10, 2.25) lelpo B et al 56 Baek JH et al. 41 41 9.7% 0.28 (0.07, 1.13) 56 57 Baik SH et al 10.4% 0.24 [0.06, 0.90] Silva-Velazco J et al 66 18 118 19.5% 0.56 [0.21, 1.48] Total (95% CI) 1864 2105 100.0% 0.30 (0.19, 0.46) Total events 27 139 Heterogeneity: Tau\* = 0.00; Chi\* = 16.89, df = 18 (P = 0.53); F = 0%

#### Figure 2. Meta-analysis of the short-term outcomes for rectal cancer. a) The operative time for RAS was significantly greater than that for LAS (p<0.00001; upper part). No significant difference was found in the intraoperative estimated blood loss (p=0.44; lower part). b) The occurrence rate of overall complications did not differ significantly between RAS and LAS (upper part). The occurrence rate of anastomotic leakage did not differ significantly between the two procedures (middle part). The occurence rate of ileus did not differ significantly between the two procedures (lower part). c) The rate of the patients undergoing the neoadjuvant chemoradiotherapy was significantly higher in RAS than in LAS (first part). The rate of the patients with lower rectal cancer was significantly higher in RAS than in LAS (second part). The distance from anal verge to the lower margin of tumor was significantly shorter in RAS than in LAS (third part). The conversion rate of RAS was significantly lower than that of LAS (fourth part).

0.005

Favours RAS Favours LAS

There was no significant difference in overall postoperative complications or in specific complications, such as anastomotic leakage, interperitoneal abscess, wound infection, ileus, postoperative bleeding or DVT between RAS and LAS. There were no cases and three cases of perioperative mortality in RAS and in LAS, respectively. Two cases in LAS were died because of cardiovascular complications, and cause of death of the remaining 1 case is unknown.

Test for overall effect: 7 = 5.48 (P < 0.00001)

In resected specimen, no significant difference was found in number of retrieved lymph nodes, length of CRM, DM and PM, number of cases with inadequate CRM and DM, and number of patients with incomplete TME, between RAS and LAS. The quality of RAS may be almost similar to that of LAS. All of the above-mentioned observations suggest that the safety and feasibility of RAS for rectal cancer is not inferior to that of LAS.

In the long-term period, we found that the rates of overall recurrence, metastatic recurrence and local recurrence are not significantly different between RAS and LAS. We found no significant difference in 3-year overall survival and 3-year disease free survival. These findings suggest that RAS is comparable to LAS with respect to long-term oncologic results and, therefore, may be an optional surgical treatment for rectal cancer.

Eight and 4 articles reported data on urinary and sexual dysfunction, respectively.

In the long-term quality of life, urinary dysfunction did not differ significantly between the 2 groups (Odds Ratio=0.74; 95%CI=0.45-1.20; p=0.22). There was no significant difference in male erectile dysfunction between RAS and LAS groups. In the previous literature, no significant difference of urinary and sexual dysfunction was found between LAS and OS (6).

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There are several limitations in this study. First, all of the 23 articles are non-randomized clinical trials, which may bias to estimating the results. Second, there is a problem regarding the variation of surgical procedures. Yet, most procedures were anterior resection of the rectum, the type of operation - e.g., intersphincteric resection or abdominal peritoneal resection - varied depending on tumor location or condition. Third, twenty of the 23 articles reported the preoperative chemoradiation for rectal cancer. The influence of preoperative chemoradiation to selection for the surgical procedures or prognosis could not be discussed. Fourth, as RAS is a relatively recent procedure, duration of following up patients is not adequate. 3-year over survival and diseasefree interval were reported and estimated in this study. Data for 5-year follow-up may be requested.

In conclusion, although there are several limitations, this meta-analysis showed that RAS for rectal cancer result in almost similar outcomes in the short-term except for a longer operation and a lower conversion rate, but is not inferior in

Table II. The revised and validated version of MINORS.

					Additional criteria in the case of comparative study								
	A clearly stated aim	Inclusion of con- secutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	assessment of the study	Follow-up period appropriate to the aim of the study	follow-up less than	Pro- spective calculation of the study size	An adequate control group	Contempo- rary groups	equi-	Adequate statistical analyses	
1 Bianchi PP et al.	2	2	1	2	0	1	2	0	2	2	2	2	18
2 Popescu et al.	2	2	0	2	0	1	2	0	2	2	2	2	17
3 Park JS et al.	2	2	1	2	0	0	2	0	2	2	2	2	17
4 Kwak JM et al.	2	2	1	2	0	1	2	0	2	2	2	2	18
5 Baek SJ et al.	2	2	0	2	0	0	2	0	2	2	2	2	16
6 Saklani AP et al.	2	2	1	2	0	1	2	0	2	2	2	2	18
7 Baek SJ et al.	2	2	0	2	0	1	2	0	2	2	2	2	17
8 Kang J et al.	2	2	1	2	1 ***	1	2	0	2	2	2	2	19
9 Fernandez et al.	2	2	0	2	0	0	2	0	2	2	2	2	16
10 D'Annibale A et al.	2	2	1	2	0	0	2	0	2	2	2	2	17
11 Park SY et al.	2	2	0	2	0	0	2	0	2	2	2	2	16
12 Kim YS et al.	2	2	1	2	0	0	2	0	2	2	2	2	17
13 Cho MS et al.	2	2	0	2	1 ***	2	2	0	2	2	2	2	19
14 Baik SH et al.	2	2	2	2	1	1	2	1	2	2	2	2	21
15 Patriti A et al.	2	2	2	2	1	1	2	1	2	2	2	2	21
16 Kim NK et al.	2	2	0	2	0	0	2	0	2	2	2	2	16
17 Baek JH et al.	2	2	1	2	0	0	2	0	2	2	2	2	17
18 Ielpo B et al.	2	2	0	2	0	0	2	0	2	2	2	2	16
19 Kim JC et al.	2	2	0	2	0	1	2	0	2	2	2	2	18
20 Park EJ et al.	2	2	0	2	0	0	2	0	2	2	2	2	16
21 Morelli L et al.	2	2	0	2	0	0	2	0	2	2	2	2	16
22 Silva-Velazco et al.	2	2	0	2	0	0	2	0	2	2	2	2	16
23 Allemann P et al.	2	2	1	2	0	1	2	0	2	2	2	2	18

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies. \*\*\*\*Case-matched analysis.



	RAS	S	LAS	5		<b>Odds Ratio</b>	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Allemann P et al.	0	20	1	40	0.6%	0.64 [0.03, 16.48]	
Cho MS et al.	49	278	53	278	33.2%	0.91 [0.59, 1.40]	<b>-</b>
Kim JC et al.	108	533	83	486	61.1%	1.23 [0.90, 1.69]	1
Kwak JM et al.	3	55	3	54	2.3%	0.98 [0.19, 5.09]	
Patriti A et al.	0	29	4	37	0.7%	0.13 [0.01, 2.44]	·
Popescu I et al.	2	38	5	84	2.2%	0.88 [0.16, 4.74]	i —
Total (95% CI)		953		979	100.0%	1.08 [0.84, 1.38]	ı •
Total events	162		149				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Ch	i² = 3.5	0, df = 5 (	P = 0.6	2); $I^2 = 09$	6	1005 04 40 20
Test for overall effect	Z = 0.60	(P = 0.5)	55)				0.005 0.1 1 10 20i

### 3-year overall survival

	RAS	S	LAS	5		Odds Ratio	Odds Ra	tio
Study or Subgroup	Events To		Events	ts Total	Weight	M-H, Random, 95% CI	M-H, Random	, 95% CI
Baek SJ et al., Yonsei Univ.	40	47	34	37	10.6%	0.50 [0.12, 2.10]		
Kim JC et al.	504	533	459	486	74.4%	1.02 [0.60, 1.75]	-	-
Saklani AP et al.	67	74	59	64	15.0%	0.81 [0.24, 2.69]	-	_
Total (95% CI)		654		587	100.0%	0.92 [0.58, 1.46]	•	
Total events	611		552					
Heterogeneity: Tau <sup>2</sup> = 0.00; C	$hi^2 = 0.87$	df = 2	(P = 0.65)	$();   ^2 = 0$	1%		205 00	± ±
Test for overall effect; Z = 0.3	7 (P = 0.7)	1)					0.05 0.2 1 Favours RAS Fa	5 20 avours LAS

### **b** Number of cases suffering from urinary dysfunction

	RAS	S	LAS			Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
Allemann P et al.	1	20	2	40	2.6%	1.00 [0.09, 11.74]				
Cho MS et al.	2	278	12	278	6.7%	0.16 [0.04, 0.72]				
Fernandez R et al.	5	13	18	59	9.7%	1.42 [0.41, 4.96]				
Kim JC et al.	29	533	29	486	44.8%	0.91 [0.53, 1.54]	·			
Kim NK et al.	4	100	9	100	10.2%	0.42 [0.13, 1.42]	<del></del>			
Morelli L et al.	4	50	1	25	3.1%	2.09 [0.22, 19.73]				
Park JS et al.	0	52	2	123	1.7%	0.46 [0.02, 9.81]				
Patriti A et al.	1	29	1	37	2.0%	1.29 [0.08, 21.47]	· · ·			
Silva-Velazco J et al.	10	66	15	118	19.3%	1.23 [0.52, 2.91]	<del></del>			
Total (95% CI)		1141		1266	100.0%	0.85 [0.57, 1.26]	•			
Total events	56		89							
Heterogeneity: Tau2 =	0.02; Chi <sup>2</sup>	= 8.36	, df = 8 (F	P = 0.40	); I= 4%		100	400		
Test for overall effect:	Z= 0.83 (I	P = 0.4	1)				0.01 0.1 1 10 Favours RAS Favours LAS	100		

### Number of cases suffering from erectile dysfunction

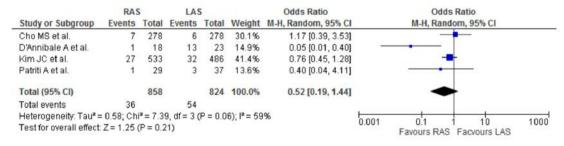


Figure 3. Meta-analysis of long-term outcomes for rectal cancer. a) The rate of overall recurrence was not significantly different between RAS and LAS (upper part). We found no significant difference in 3-year overall survival rate between RAS and LAS (lower part). b) Urinary dysfunction did not differ significantly between the 2 groups (upper part). There was no significant difference in erectile dysfunction between robotic and laparoscopic groups (lower part).

the long-term oncologic outcomes, compared to LAS. Therefore, RAS may be an acceptable optional treatment to LAS for rectal cancer.

If possible, some prospective randomized trials comparing RAS to LAS for rectal cancer should be performed in the near future.

#### **Conflicts of Interest**

Drs Hiroshi Ohtani, Kiyoshi Maeda, Shinya Nomura, Osamu Shinto, Yoko Mizuyama, Hiroji Nakagawa, Hisashi Nagahara, Masatsune Shibutani, Tatsunari Fukuoka, Ryosuke Amano, Kosei Hirakawa and Masaichi Ohira have no conflicts of interest or financial ties to disclose. All Authors meet the International Committee of Medical Journal Editors authorship criteria.

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