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Review Article

Robot-assisted versus conventional laparoscopic surgery for endometrial cancer staging: A meta-analysis

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ABSTRACT

This meta-analysis broadly compared the safety and efficacy of robot-assisted laparoscopy (RAL) with that of conventional laparoscopy (CL) for endometrial cancer staging. The advantages of RAL were evaluated through the outcomes in terms of conversion rates, complications, length of operation, blood loss, number of lymph nodes harvested, and length of hospitalization. Three electronic databases (PubMed, MEDLINE, and Embase) were searched to identify eligible studies. We selected all retrospective studies documenting a comparison between RAL and CL for endometrial cancer staging between 2005 and 2015, and tallied with meta-analyses criteria. Only studies published in English were included in this analysis. The outcomes of the extracted data were pooled and estimated by the Review Manager version 5.1 software. Seventeen studies met the eligibility criteria. Among the 2105 patients reported, 912 underwent RAL and the other 1193 underwent CL for endometrial cancer staging. Compared with CL, RAL had lower conversion rates [risk ratio, 0.4; 95% confidence interval (CI), 0.25–0.64; $p = 0.0002$]. Its complications were also less than that of CL (risk ratio, 0.72; 95% CI, 0.56–0.94; $p = 0.02$). RAL was associated with significantly less intraoperative blood loss (weighted mean difference, -79.2 mL; 95% CI, from -103.43 to -54.97 ; $p < 0.00001$) and a shorter length of hospitalization (weighted mean difference, -0.37 days; 95% CI, from -0.57 to -0.17 ; $p = 0.0003$). We found no significant differences in the length of operation and number of lymph nodes harvested between the two groups. From our meta-analysis results, RAL is a safe and effective alternative to CL for endometrial cancer staging. Further studies are required to determine potential advantages or disadvantages of RAL.

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Introduction

Endometrial cancer is one of the most commonly seen gynecologic malignancies, with a highly increasing incidence in the developed world [1]. The primary treatment for endometrial cancer is total hysterectomy, bilateral salpingo-oophorectomy, and surgical staging [2]. Safe and effective surgery for endometrial cancer serves as a linchpin for both disease prognosis and improved life quality of the patients.

Over the past decade and a half, minimally invasive approaches have increasingly been adopted by gynecologic oncologists for the

treatment of endometrial cancer. Laparoscopic surgery is considered a preferred alternative to laparotomy because of less blood loss and blood transfusion, shorter hospitalization, and better cosmetic results [3,4]. However, the minimally invasive approach to treat endometrial cancer has been limited owing to two dimensioned visualization and strict requirement of skilled and experienced surgeons. In recent years, the use of a robotic surgical platform (Da Vinci Surgical System) has grown exponentially [5]. It offers numerous potential benefits, especially extensive suturing and less collateral damage, in endometrial cancer staging.

All the benefits of robot-assisted laparoscopic surgery (RAL) surmounted the limits of conventional laparoscopic surgery (CL) [6]. It was associated with a shorter hospital stay, a lower overall complication rate, and fewer blood transfusions. In addition, it has shortened the transition time of patients to normal social life and improved their quality of life as well. However, studies comparing RAL with CL in endometrial cancer staging are limited. The real

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benefits of robot-assisted laparoscopic endometrial cancer staging remained controversial.

The aim of this meta-analysis is to evaluate the efficacy and safety of RAL in endometrial cancer staging compared with CL.

Materials and methods

Search strategy

A systematic literature review was performed using electronic databases (PubMed, MEDLINE, and Embase). All English-language publications comparing RAL with CL for endometrial cancer staging from January 1, 2005 to April 25, 2015 have been identified. The following key words were used in the search: [(robot* or “robotic surgery” or “robotic staging”) and (“endometrial cancer” or “endometrial carcinoma”)]. Moreover, the “related articles” offered by databases were explored to broaden the search, and all abstracts, studies, and citations were reviewed.

Finally, a manual search for relevant studies was also carried out to identify studies for possible inclusion as a supplement.

Data extraction

The data were extracted by two researchers (Z.A. and H.R.) independently for each eligible study comparing RAL and CL. Any disagreements were resolved by a third reviewer (S.H.), until a consensus was reached.

The quality of each study was evaluated using the Newcastle–Ottawa Scale [7]. Seventeen studies were selected according to the criteria based on the following three items: patient selection, comparability of RAL and CL groups, and exposure. The quality of study grades was evaluated based on an ordinal star scoring scale. Higher scores represented higher quality of the study. One star for each numbered item within the selection and exposure categories in one study and a maximum of two stars for the comparability of the two groups have been formulated. The studies with six or more stars were considered to be of much higher quality.

Inclusion criteria

All the selected studies in the meta-analysis adhered to the following inclusion criteria: (1) comparison of outcomes of RAL with CL for endometrial cancer staging; (2) evaluation of length of operation, blood loss, operative complications, and length of hospital stay; (3) patient medical parameters (age, body mass index, history of abdominal surgery, pre-existing complication conditions, uterine weight, tumor stage, and tumor grade) in compared groups not being statistically different; and (4) patients not having received radiation therapy or chemotherapy preoperatively.

Exclusion criteria

The exclusion criteria for this meta-analysis were as follows: (1) research articles, such as letters, editorials, and expert opinions; (2) studies without original data, case reports, or studies lacking CL as a control group; (3) studies not providing clear outcomes or patient parameters; (4) studies including open hysterectomy or single-port laparoscopic surgery alone; and (5) reports only on RAL surgeries.

Statistical analysis

This meta-analysis was performed using Revman 5.3 (Review Manager version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark) for the five primary outcome parameters: length of operation, blood loss, conversion rates, number

of lymph nodes harvested, and length of hospitalization. The statistical package of the software was applied to analyze the risk ratios (RRs) for dichotomous variables and weighted mean differences (WMDs) for continuous variables. Heterogeneity was evaluated by F and I^2 . We considered heterogeneity to be present if the I^2 statistic was $> 50\%$, and the threshold of significance was considered at $p < 0.05$. The publication bias was evaluated by funnel plots.

Results

Study selection and study characteristics

The 17 studies [8–24] were selected from the search on RAL surgery for endometrial cancer staging (Figure 1). All included studies were retrospective and nonrandomized controlled comparison. The characteristics of these studies were summarized, and the quality of studies was assessed. A total of 2105 patients were identified: 912 in the RAL group and 1193 in the CL group. All studies involved RAL versus CL for endometrial cancer staging. The first author and year of publication, patient parameters (age, body mass index, tumor stage, tumor grade, and uterine weight), study design, and the quality assessment of studies are given in Table 1.

Synthesis of results

Ten studies reported the rates of conversion. The pooled estimate showed an RR of 0.4 (95% CI, 0.25–0.64) in favor of patients who received RAL. The I^2 was 0%, which suggested no heterogeneity in pooled studies (see Figure 2). The reason for conversion in RAL was exposure difficulty. However, other reasons, such as dense adhesions, vascular injury, and obscuring anatomy, induced conversion in CL to a greater extent.

Fourteen studies assessed the complications of the two surgical procedures. It showed fewer complications in the RAL group than in the CL group (RR, 0.72; 95% CI, 0.55–0.95; $p = 0.02$; see Figure 3). Even though a large number of studies reported fewer

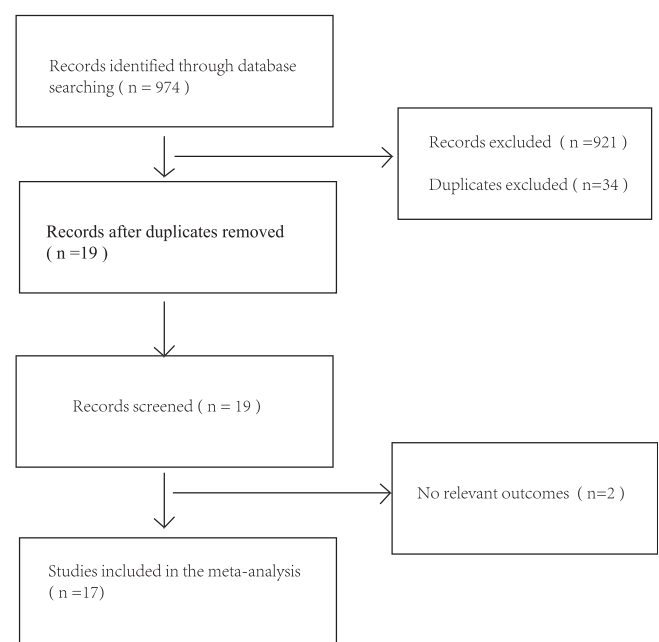


Figure 1. Flow diagram of studies identified in the meta-analysis.

Table 1
Descriptive data for each study.

Author	Year	Design	Group	Sample size (n)	Age (y)	BMI (kg/m ²)	Uterine weight (g)	Tumor stage	Basic state	Matching	Scores
Bell et al [8]	2008	RCS	RAL	40	63.0 (10.1)	33.0 (8.5)	135.9 (72.8)	NR	1, 2, 8	a, b, c, d, e, f	*****
			CL	30	68.4 (11.9)	31.9 (9.8)	138.5 (75.5)	NR			
Bogges et al [9]	2008	RCS	RAL	103	61.9 (10.6)	32.9 (7.6)	NR	89/3/10/1	1, 2, 3	a, b, c, d, e, f	*****
			CL	81	62 (10.8)	29.0 (6.5)	NR	62/4/14/1			
Magrina et al [10]	2008	RCS	RAL	27	50.0 (15.6)	27.2 (5.9)	NR	6/2/1/0	1, 2, 3, 4, 5, 6	a, b, c, d, e, f	*****
			CL	31	54.9 (14.3)	26.8 (4.6)	NR	11/1/1/0			
Gehrig et al [11]	2008	RCS	RAL	49	53.7 (12)	39.5 (5.8)	NR	0/44/0/5	1, 2, 3, 4, 8	a, b, c, d, e, f	*****
			CL	32	58.6 (12)	38.8 (6.3)	NR	0/26/0/6			
Veijovich et al [12]	2008	RCS	RAL	25	59.5 (36–85)	27.6 (18.7–49.4)	106.5 (42–255)	NR	1, 2	a, b, c, d, f	****
			CL	4	54 (51–67)	24.6 (22–29)	76.3 (36–113)	NR			
Seamon et al [13]	2009	RCS	RAL	105	59 (8.9)	34.2 (9)	132 (64)	87/3/10	1, 2, 3, 4, 6, 8	a, c, d, e, f	*****
			CL	76	57 (11)	28.7 (6.9)	133 (60)	86/5/9			
CG et al [14]	2010	RCS	RAL	102	62 (8.7)	32.32 (8.13)	148 (111)	82/3/16/1	1, 2, 3, 4, 5, 6, 7, 8	a, b, c, d, e, f	*****
			CL	173	59.6 (9.75)	32.7 (9.5)	139 (89.8)	152/9/11/1			
Holtz et al [15]	2010	RCS	RAL	13	63.5 (11.3)	35.3 (10.7)	119 (54)	12/1/0/0	1, 2, 3, 4, 8	a, b, c, d, e, f	****
			CL	20	63.3 (11.2)	27.8 (7.1)	109 (54)	17/2/1/0			
Jung et al [16]	2010	RCS	RAL	28	52.89 (11.91)	23.38 (3.08)	123.7 (61.25)	24/1/3/0	1, 2, 3, 5, 6, 7, 8	a, b, c, d, e, f	*****
			CL	25	49.88 (10.75)	25.17 (5.11)	118.1 (45.0)	20/4/1/0			
Lim et al [17]	2010	RCS	RAL	56	62.5 (8.4)	30.4 (8.8)	NR	NR	1, 2, 8	a, b, c, d, e, f	****
			CL	56	61.4 (11.7)	28.2 (6.7)	NR	NR			
Shah et al [18]	2011	RCS	RAL	45	58.2 (7.57)	40.5 (11.0)	176.3 (45.5–905)	NR	1, 2, 3	a, b, c, e, f	****
			CL	118	69.9 (7.5)	29.8 (7.5)	134.4 (34–704)	NR			
Coronado et al [19]	2012	RCS	RAL	71	63.7 (10.2)	28.7 (4.7)	NR	57/4/9/1	1, 2, 3, 4, 5, 8	a, b, c, d, e, f	*****
			CL	84	65.9 (11.2)	27.2 (5.3)	NR	72/4/6/2			
Venkat et al [20]	2012	RCS	RAL	27	58.2 (31–85)	33.5 (20–54)	138.9 (65–402)	19/0/6/1	1, 2, 3, 4, 8	a, b, c, d, h	*****
			CL	27	60.2 (42–92)	32.5 (19–61)	132.8 (31–222)	18/1/5/1			
Escobar et al [21]	2012	RCS	RAL	30	59.7 (60)	31.2 (32.0)	NR	28/2/0/0	1, 2, 3, 4, 8	a, b, c, d, e, f	*****
			CL	30	60.9 (62.1)	28.7 (4.7)	NR	57/4/9/1			
Seror et al [22]	2014	RCS	RAL	40	66.27 (63.4–69.2)	24.95 (23.6–26.3)	NR	35/1/1/3	1, 2, 3, 6, 8	a, b, d, e, f	****
			CL	106	66.91 (64.6–69.2)	25.35 (24.4–26.3)	NR	76/10/18/1			
Turunen et al [23]	2013	RCS	RAL	67	65.4 (8.5)	28.2 (5.7)	NR	NR	1, 2	a, b, c, d, f	****
			CL	150	67.4 (10.6)	28.8 (5.9)	NR	NR			
Chiou et al [24]	2015	RCS	RAL	86	53.6 (11.1)	26.0 (5.2)	NR	72/2/12/0	1, 2, 3, 5	a, b, c, d, f	*****
			CL	150	51.4 (14.2)	25.6 (5.6)	NR	121/9/20/0			

RAL = robot assisted laparoscopic group; CL = conventional laparoscopic group; NR = no reported; RCS = retrospective comparative. Scores: *a = length of operation; b = length of hospitalization; BMI = body mass index; c = blood loss; CL = conventional laparoscopy; d = number of lymph nodes harvested; df = degrees of freedom; e = conversion rates; f = complications; NR = not reported; RAL = robot-assisted laparoscopy; RCS = retrospective comparative scores; 1 = age; 2 = tumor stage; 4 = tumor grade; 5 = tumor type; 6 = operation history; 7 = medication history; 8 = same surgeon or same group component.

complications in the RAL group, no statistical significance existed between the two groups. In the meta-analysis, the results favored the patients of the RAL group.

Fourteen studies showed significantly less blood loss in RAL than in CL (WMD, −79.2 mL; 95% CI, from −103.43 to −54.97; $p < 0.00001$; see Figure 4).

Sixteen studies examined the length of hospital stay in both RAL and CL groups. The mean difference of −0.37 days (from −0.57 to −0.17; $p = 0.0003$) shows that the patients in the RAL group recovered more quickly with relatively high quality of life. The I^2 was 87%, which indicated high statistical heterogeneity in the studies (see Figure 5).

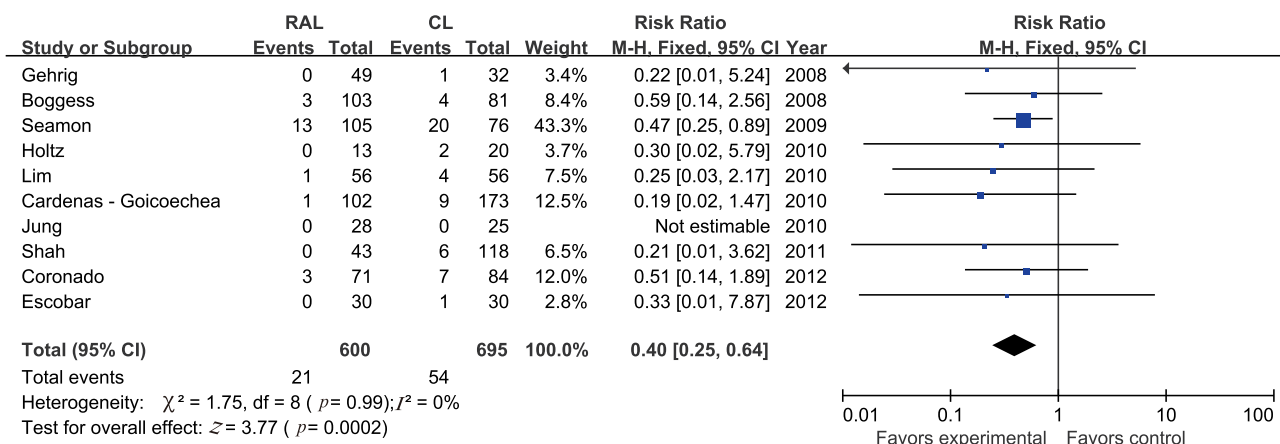


Figure 2. Forest plot for conversion rates comparing RAL with CL. CI = confidence interval; CL = conventional laparoscopy; df = degrees of freedom; RAL = robot-assisted laparoscopy.

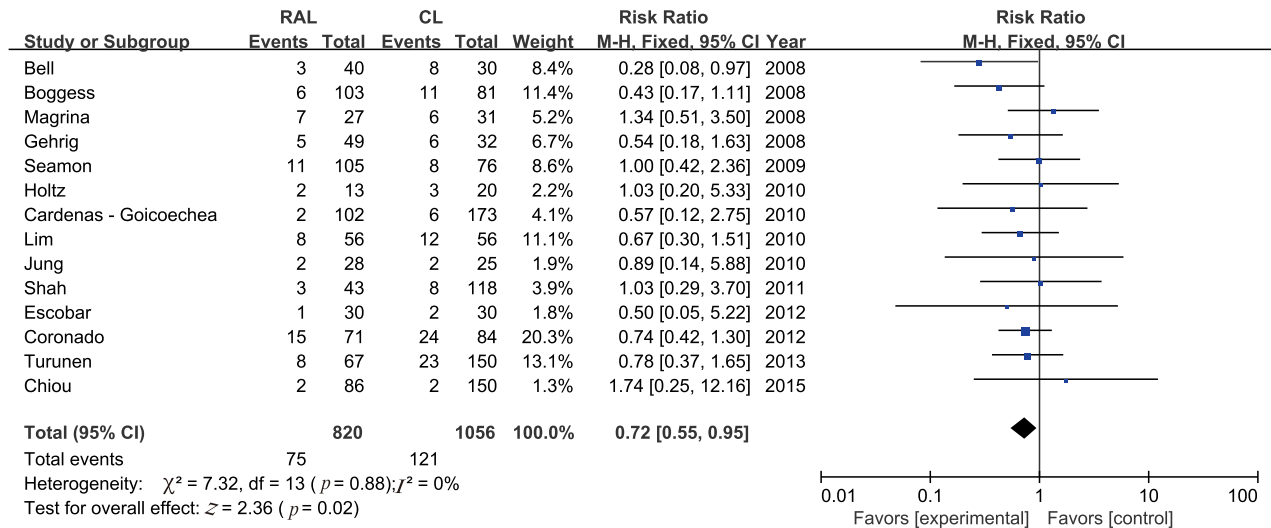


Figure 3. Forest plot for complications comparing RAL with CL. CI = confidence interval; CL = conventional laparoscopy; df = degrees of freedom; RAL = robot-assisted laparoscopy.

With regard to the length of operation, all 17 studies indicated no significant difference between RAL and CL (WMD, 13.28 minutes; 95% CI, from −6.66 to 33.22; $p = 0.19$; see Figure 6).

The total lymph nodes harvested were not clearly indicated in five studies. Therefore, the results of the remaining 12 studies were pooled. The analysis of pooled results showed no statistical significance (WMD, 0.86; 95% CI, from −2.24 to 3.96; $p = 0.59$; see Figure 7).

Publication bias

A funnel plot for studies comparing the conversion rates of surgical technique was set up to assess the publication bias. Effect estimates with corresponding CIs showed that no study was outside the limit of the 95% CI, which indicated a minimal publication bias in the literature review (see Figure 8). However, further studies should be included so that the funnel plot could precisely reflect the possible publication bias.

Discussion

Surgical staging for endometrial cancer is considered the standard of care [8], which provides patients with a better chance for cure. However, different surgical approaches could affect intra- and postoperative outcomes and then directly influence the quality of life of patients. RAL is a burgeoning technology that has improved some of the inherent limitations of CL, such as two-dimensional visualization and strict requirements for surgeons with skills and experience. Our results in this meta-analysis showed that the robotic surgical platform might offer outstanding advantages in endometrial cancer staging. It could not only lower major complications, conversion rate, and blood loss, but also reduce hospital stay. Nonetheless, there were significant differences between RAL and CL in terms of the length of operation and number of lymph nodes harvested.

Most of the studies reported that perioperative outcomes of RAL compared with CL embraced fewer operative complications, lower

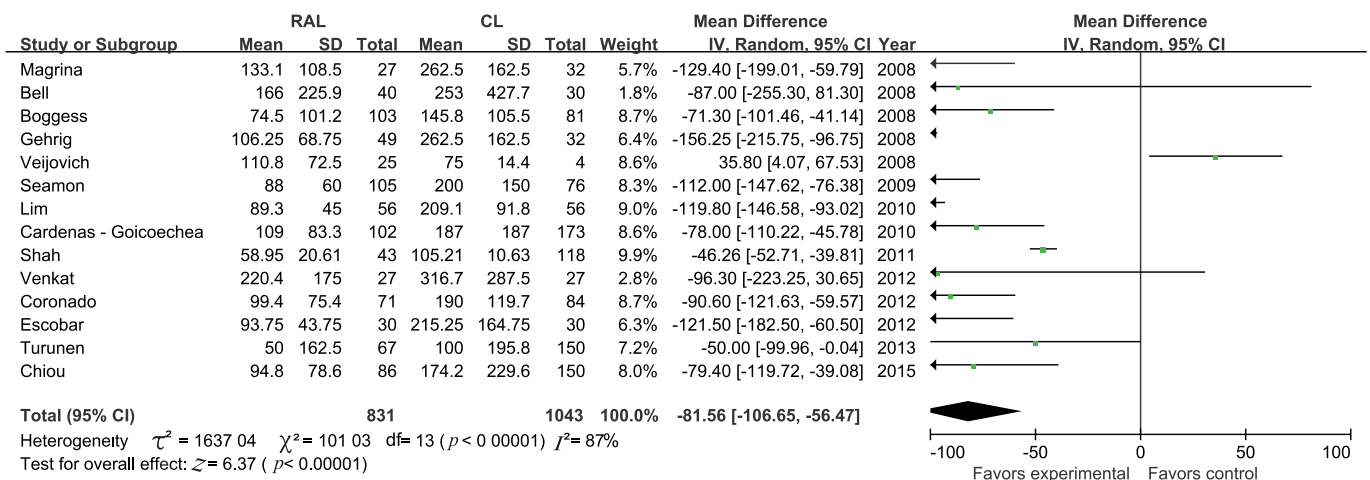


Figure 4. Forest plot for blood loss comparing RAL with CL. CI = confidence interval; CL = conventional laparoscopy; df = degrees of freedom; RAL = robot-assisted laparoscopy.

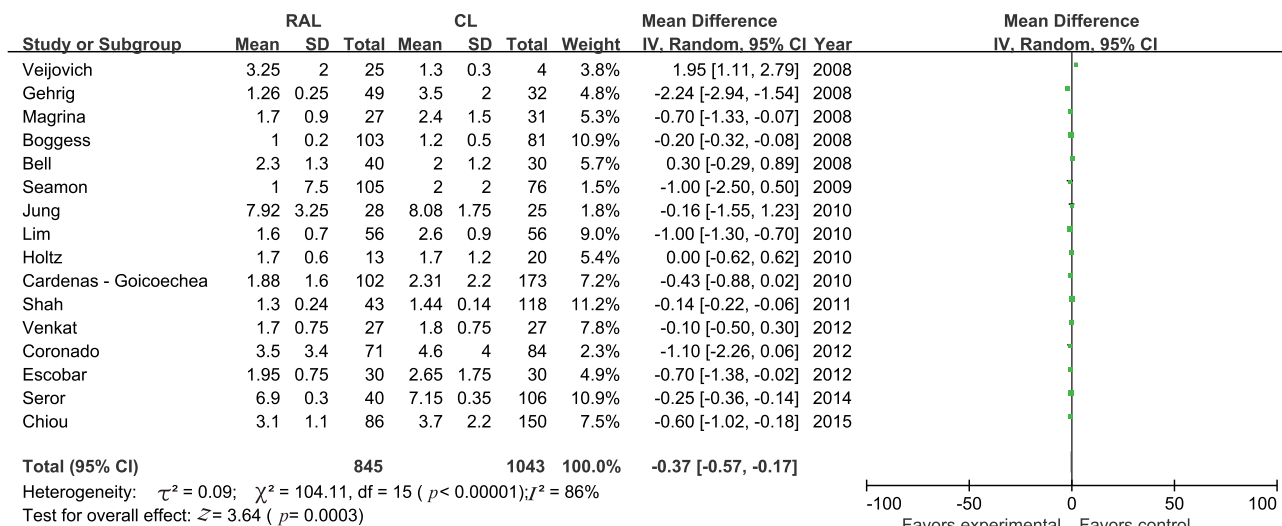


Figure 5. Forest plot for the length of hospitalization comparing RAL with CL. CI = confidence interval; CL = conventional laparoscopy; df = degrees of freedom; RAL = robot-assisted laparoscopy; SD = standard deviation.

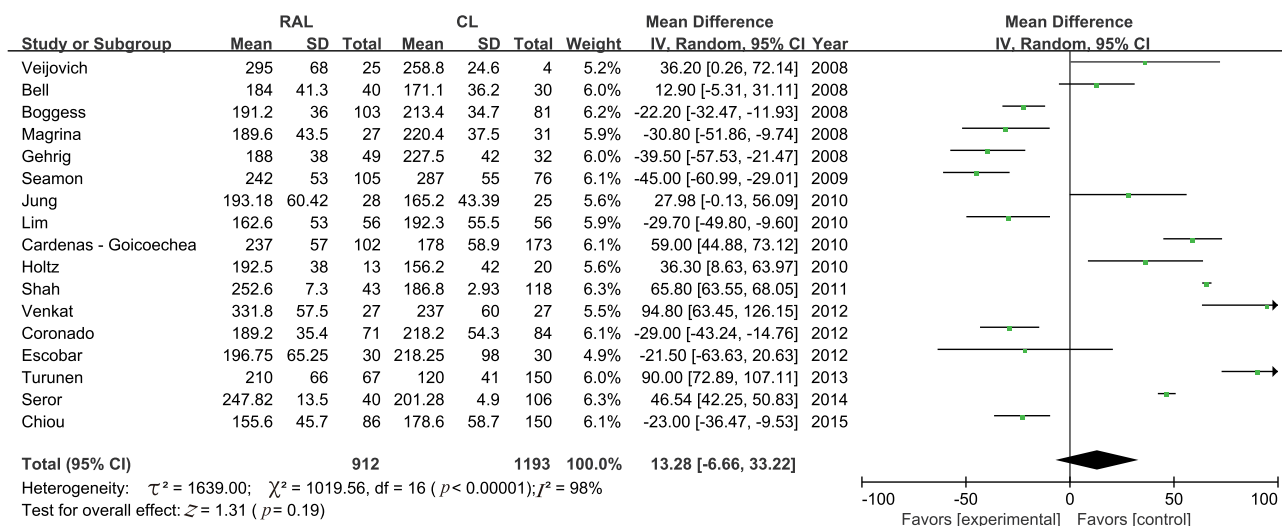


Figure 6. Forest plot for the length of operation comparing RAL with CL. CI = confidence interval; CL = conventional laparoscopy; df = degrees of freedom; RAL = robot-assisted laparoscopy; SD = standard deviation.

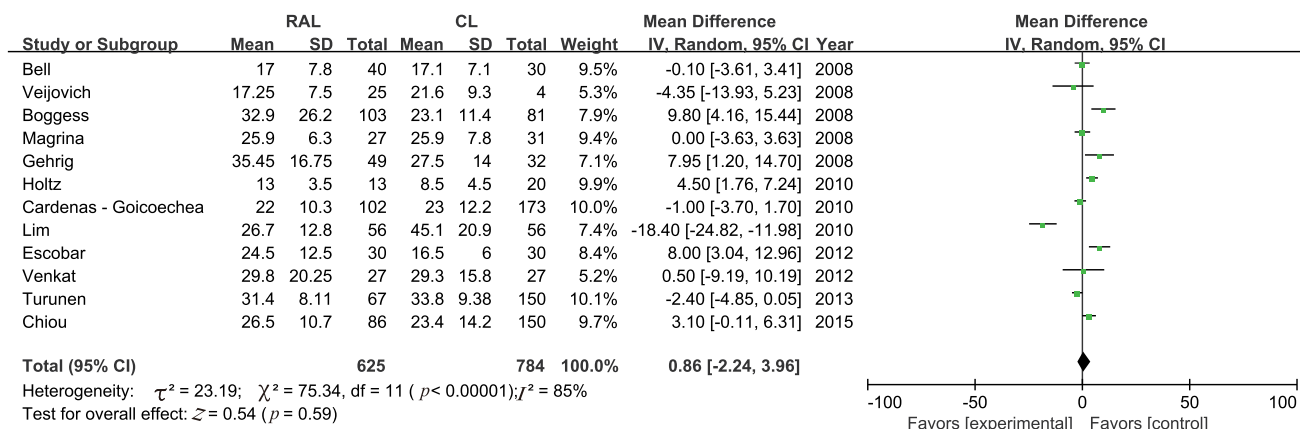


Figure 7. Forest plot for the number of lymph nodes harvested, comparing RAL with CL. CI = confidence interval; CL = conventional laparoscopy; df = degrees of freedom; RAL = robot-assisted laparoscopy.

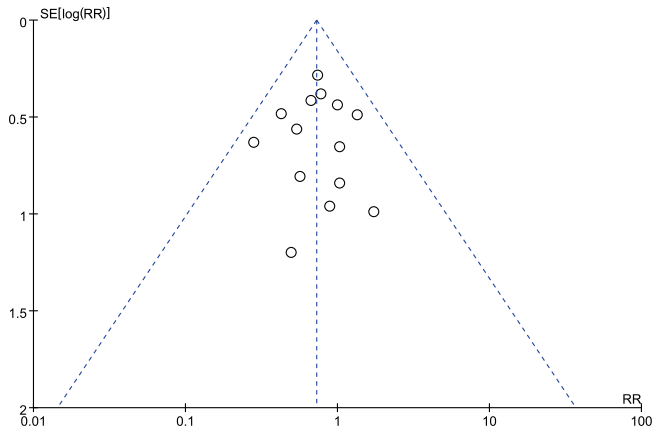


Figure 8. Funnel plot for assessing publication bias. RR = risk ratio; SE = standard error.

conversion rates, and less blood loss [25,26]. These advantages of RAL might be attributed to the following factors: (1) the robotic device allowed better detection of large and small vessels; (2) improved hemostasis and clear identification of small vessels contributed to lower rates of blood transfusion in RAL; (3) RAL might provide prominent advantages for endometrial cancer patients with obesity and other complex conditions, such as previous abdominal surgery with severe adhesion, by lowering the conversion rates [27–29]; and (4) robotic surgery has drastically decreased the musculoskeletal fatigue over time in surgeons and perhaps improves overall productivity and longevity of practice [12].

In this meta-analysis, there were only slight differences in the hospital stay between the two groups, but the majority of studies were in favor of RAL. Robotic procedures allowed patients to mobilize earlier and shorten their hospitalization [30].

Pelvic node dissection is suggested to have a therapeutic benefit for endometrial cancer staging in selected cases. Two studies reported that the robotic instruments allowed better exposure and reduced the technical challenges of surgical procedures [31,32]. RAL offered easier and more comprehensive lymphadenectomy, which surmounted the technical limitations of CL and improved the staging surgery process for endometrial cancer. However, the numbers of lymph nodes harvested were not statistically different between the two groups in this meta-analysis.

Our analysis of the pooled data of 17 studies did not show significant differences in the length of operation between the RAL and CL groups. Among the studies we examined, some [8,16,18] reported the operative time to be prolonged but in a reasonable frame in RAL. The difference in the length of operation could be attributed to multiple variables: room setup time, time for draping and docking the robot, and skin-to-skin procedure time. Meanwhile, the learning curve for RAL was also a critical factor, which might exert a confounding effect on this matter.

The length of operation, blood loss, length of stay, and lymph nodes harvested showed significant heterogeneity in the studies we analyzed. This heterogeneity might be explained by the differences in many factors among surgeries reported in these studies, such as surgeons' skills, surgical approaches, learning curves of the robot operating system, and the extent of lymph node dissection.

The limitations of this meta-analysis should be taken into account while interpreting the results. First, most data were derived from retrospective nonrandomized comparisons. Even though a majority of surgical procedures were well designed, some shortcomings in their methodology still existed. Smaller sample size and

low level of clinical evidence might lead to a certain bias in the study. Second, we still could not eliminate the differences in patients, as well as the skills and experience of surgeons, between the two groups. It is well known that these factors affect the outcomes of endometrial cancer staging. Third, this meta-analysis provided a short-term outcome to expound the value of robotic assistance, which might influence the comprehensive evaluation of the measured markers. Based on that, further studies on long-term outcomes should be performed, which will be helpful to find potential advantages and disadvantages of RAL.

In conclusion, this meta-analysis has shown more benefits of RAL for patients with endometrial cancer staging in comparison with CL. However, multicenter, prospective, randomized controlled studies should be performed to delineate the differences between RAL and CL. These approaches can ultimately help determine whether RAL is a safe and effective alternative to CL for endometrial cancer staging surgery.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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