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REVIEW ARTICLE

Robot-assisted hysterectomy for endometrial and cervical cancers: a systematic review

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Abstract Total and radical hysterectomies are the most common treatment strategies for early-stage endometrial and cervical cancers, respectively. Surgical modalities include open surgery, laparoscopy, and more recently, minimally invasive robot-assisted surgery. We searched several electronic databases for randomized controlled trials and observational studies with a comparison group, published between 2009 and 2014. Our outcomes of interest included both perioperative and morbidity outcomes. We included 35 observational studies in this review. We did not find any randomized controlled trials. The quality of evidence for all reported outcomes was very low. For women with endometrial cancer, we found that there was a reduction in estimated blood loss between the robot-assisted surgery compared to both laparoscopy and open surgery. There was a reduction in length of hospital stay between robot-assisted surgery and open surgery but not laparoscopy. There was no difference in total lymph node removal between the three modalities. There was no difference in the rate of overall complications between the robot-assisted technique and laparoscopy. For women with cervical cancer, there were no differences in estimated blood loss or removal of lymph nodes between robot-assisted and laparoscopic procedure. Compared to laparotomy, robot-assisted hysterectomy for cervical cancer showed an overall reduction in estimated blood loss. Although robot-assisted hysterectomy is clinically effective for the treatment of both endometrial and cervical cancers, methodologically rigorous studies are lacking to draw definitive conclusions.

Keywords Robot assisted · Laparoscopy · Laparotomy · Hysterectomy · Endometrial cancer · Cervical cancer · Systematic review · Effectiveness

Abbreviations

RCT	Randomized controlled trials
GRADE	Grading of recommendations assessment, development, and evaluation
USA	United States of America
MeSH	Medical subject headings
SD	Standard deviation
OP	Open
RB	Robotic
LP	Laparoscopic

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Introduction

Cervical cancer remains a significant cause of morbidity and mortality representing 7.5 % of all female cancer deaths worldwide [1]. Endometrial cancer is the fifth most common cancer among women, affecting over 300,000 women globally every year [2]. Management of women suffering from these cancers depends on the individual's general health condition, tumor stage, and comorbidities; however, surgical removal of the uterus or hysterectomy is generally the treatment of choice for early clinical stage disease [3]. Hysterectomy in gynecologic oncology has evolved from using invasive open abdominal technique also known as laparotomy to minimally invasive procedures that provide access to the reproductive system by small incisions otherwise known as laparoscopy. Laparoscopy in the management of endometrial cancer has been shown to provide clinical benefits including shorter length of hospitalization, decreased blood loss, and reduced post-operative complications [4, 5]. Despite evidence from randomized controlled trials showing clinical benefits with laparoscopy, prior to the introduction of robot- assisted technology, the majority of cases continued to be performed via open surgery. A recent analysis of Ontario women having undergone hysterectomy reveals that although there has been an increase in the use of laparoscopy over time, only 30 % of cases in 2011 were performed in this manner [6]. The low uptake of laparoscopy is likely due to a combination of factors including inadequate training and challenges in visual-special mechanics for surgeons. Counterintuitive hand movement, an unsteady two-dimensional visual field, restricted instrument motion, ergonomic difficulty, and tremor amplification result in many surgeons having difficulty performing laparoscopy, requiring additional training [7]. Robot-assisted surgery is a relatively new minimally invasive technology that has shown some theoretical advantages compared with other surgical techniques. These advantages include improved visualization through 3D imaging, greater precision, and more accurate control of instrumentation in addition to improved ergonomics for the surgeons [8]. Since the approval of Food and Drug Administration in 2005 for the use of robot-assisted gynecological surgery, this technology has been widely adapted in the United States for conducting hysterectomy for both benign and malignant indications [9]. This systematic review aims to update previously published systematic reviews and to identify the clinical effectiveness of robot-assisted hysterectomy compared with laparoscopic and/or open hysterectomy for women diagnosed with endometrial or cervical cancer.

Methods

We conducted and reported this systematic review according to the published guidelines using a pre-specified protocol [10, 11].

Eligibility criteria

We included any randomized controlled trials (RCTs) and cohort studies with comparison group that reported outcomes for women with endometrial or cervical cancer eligible for hysterectomy. We included studies that reported at least one clinical outcome of interest comparing robot-assisted hysterectomy with laparoscopic or open hysterectomy. Our primary outcomes of interest included morbidity factors such as number of complications and length of hospitalization, perioperative factors such as operation time, amount of blood loss, and number of conversions to laparotomy. Due to the numerous challenges with interpretation of lymph node counts in the management of women with endometrial cancer and cervical cancer, number of pelvic and para-aortic lymph nodes removed was considered a secondary outcome measure. We excluded animal or in vitro studies, conference abstracts, editorials, narrative reviews, case reports, cross sectional and case–control studies. We also excluded studies that reported outcomes in pregnant women, women undergoing emergent surgeries or women undergoing hysterectomy for benign conditions.

Search strategy

We conducted a literature search with the help of a librarian. We searched the following databases from January 1, 2009 to June 24, 2014: Ovid MEDLINE, Ovid MEDLINE In-Process, and Other Non-Indexed Citations, Ovid Embase, and EBM Reviews. The search date was confined to last 5 years to provide an update to the previously published systematic reviews in this topic. The search strategy included a combination of keywords and MeSH terms and was adapted for each database to account for differences in indexing. We restricted our search to English language publications. We also searched reference lists and non-indexed journals for any additional relevant studies not identified through the search. See Online Appendix 1 for literature search strategy details.

Study selection and data abstraction

A reviewer (IN) independently screened titles and abstracts. We retrieved the full text for any article considered potentially relevant by the reviewer. Data were abstracted using a data collection form for studies considered eligible for inclusion. We abstracted the following data: (a) study characteristics such as year of publication, country where study was conducted, study design, sample size, year of study, and funding sources; (b) methodological characteristics such as definitions of population and outcomes studied, whether confounding variables were accounted for in the study, and whether the studies reported loss to follow-up; (c) patient characteristics including the number of women in each group, mean age, race, whether the control group was laparoscopy or open or both; (d) the outcomes and any adjusted measures of association. We contacted the authors of the studies included in the review for any missing data. We entered all data into Review Manager Version 5.2 [12]. We assessed the quality of the body of evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. The overall quality was determined to be high, moderate, low, or very low using a stepwise, structural methodology. Study design was the first consideration; the starting assumption was that randomized controlled trials (RCTs) are high quality, whereas observational studies start as low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, we considered three main factors that may raise the quality of evidence: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors [13–15].

Results

We screened and evaluated 1236 citations published between January 1, 2009 and June 24, 2014. We obtained 42 full text articles for further assessment. Figure 1 shows the flow diagram of studies identified, included, and excluded from the review. Thirty-five observational studies met the inclusion criteria, including 23 for endometrial cancer [16–36] and 12 for cervical cancer [37–48] (Table 1). List of studies not included in the review, detailed description of the intervention and comparator of each of the included study, study characteristics of included studies, the evidence GRADE profile, and the PRISMA checklist are presented in Online Appendices 2, 3, 4, 5, 6, and 7, respectively. Figures 2 and 3 show forest plots with

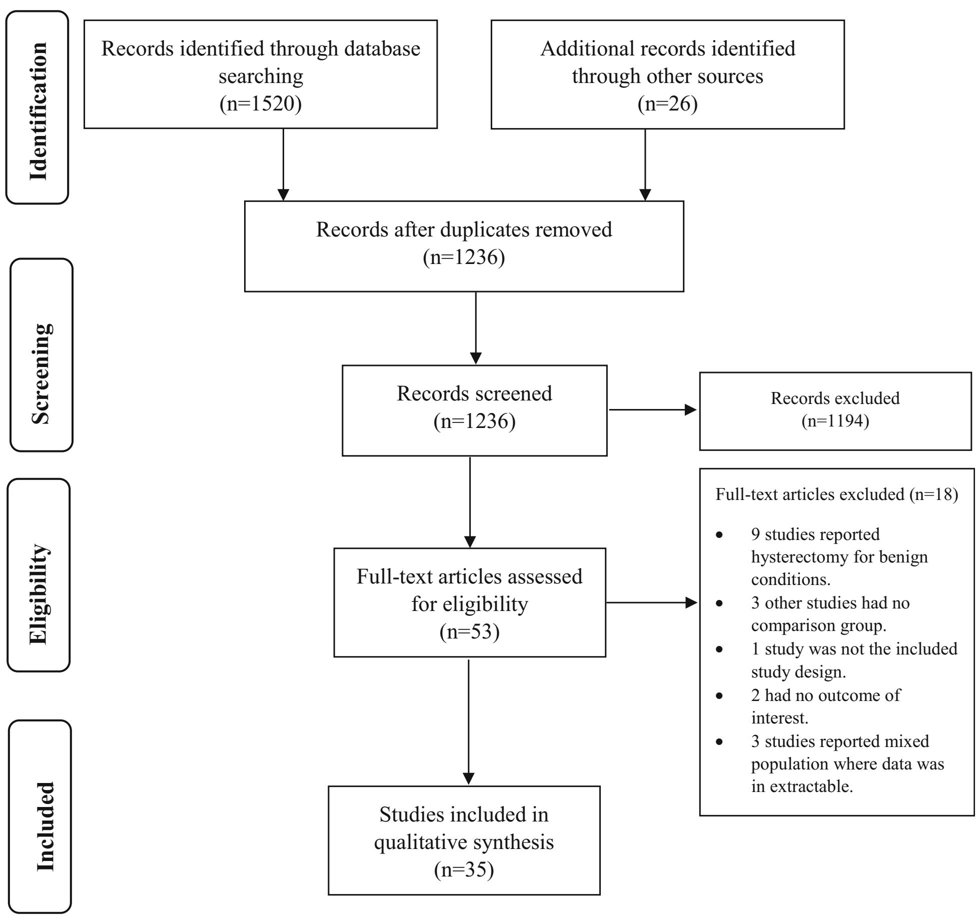


Fig. 1 Depicts the process by which study selection was performed in a stepwise pattern. The Prisma flow chart shows the study selection process including details on how the studies were identified, screened, and included in the review

Table 1 Summary of study characteristics

Author, year	Study location	Study design	Length of follow-up	LP/RB, n
Endometrial cancer				
Seamon, 2009 [30]	USA	Prospective with historic control	Not reported	56/92
Cardenas-Goicoechea, 2010 [17]	USA	Retrospective cohort	Not reported	173/102
Martino, 2011 [27]	USA	Retrospective cohort	Not reported	114/104
Boruta, 2011 [16]	USA	Retrospective cohort	Not reported	121/48
Lim, 2011 [26]	USA	Prospective with historic control	Not reported	122/122
Fagotti, 2012 [23]	USA, Italy	Retrospective cohort	Not reported	75/75
Leitao, 2012 [24]	USA	Prospective with historic control	Up to 30 days post-op	302/347
Escobar, 2012 [21]	USA	Retrospective cohort (matched)	Up to 30 days post-op	30/30
Turunen, 2013 [33]	Finland	Retrospective cohort	Not reported	150/67
Cardenas-Goicoechea, 2013 [18]	USA	Retrospective cohort	8 weeks after hospital discharge	245/187
Fagotti, 2013 [22]	Italy	Retrospective cohort (matched)	Up to 30 days post-op	38/19
Author, Year	**Study location**	**Study design**	**OP/RB**	**OP/RB**
Endometrial cancer				
Nevadunsky 2010 [35]	USA	Retrospective cohort	Not reported	43/66
Paley, 2011 [29]	USA	Retrospective cohort	6 weeks post-surgery	131/377
Goel, 2011 [50]	USA	Retrospective cohort	Not reported	38/59
Subramaniam, 2011 [31]	USA	Retrospective cohort	Not reported	104/73
Bernardini, 2012 [49]	Canada	Prospective with historic control	Not reported	41/45
Tang, 2012 [32]	USA	Retrospective cohort	Not reported	110/129
Elshawi, 2012 [20]	USA	Retrospective cohort	30 days following surgery	150/155
Mok, 2012 [28]	Singapore	Retrospective cohort	30 days following surgery	90/34
Author, Year	**Study location**	**Study design**	**LP/RB/OP**	**LP/RB/OP**
Endometrial cancer				
Lim, 2010 [25]	USA	Prospective with historic controls	Not reported	56/56/36
Coronado, 2012 [19]	Spain	Retrospective cohort	Not reported	84/71/192
Estape, 2012 [34]	USA	Prospective with historic control	5 years	104/102/78
Nevadunsky, 2012 [36]	USA	Retrospective cohort	Not reported	115/102/79
Author, Year	**Study location**	**Study design**	**Length of follow-up**	**LP/RB**
Cervical cancer				
Tinelli, 2011 [47]	USA	Retrospective cohort	Median (range) 46.5 (3–90)/24.5 (2–48) months	76/23
Chong, 2013 [38]	Korea	Prospective with historic controls	Not reported	50/50
Author, Year	**Study location**	**Study design**	**OP/RB**	**OP/RB**
Cervical cancer				
Maggioni, 2009 [42]	Italy	Prospective with historic controls	Not reported	40/40
Geisler, 2010 [39]	USA	Retrospective cohort	Not reported	30/15
Cantrell, 2010 [37]	USA	Retrospective cohort	Not reported	64/63
Nam, 2010 [43]	Korea	Prospective with historic controls	Mean of 15.3 months	32/32
Schreuder, 2010 [44]	Netherlands	Retrospective cohort	Not reported	14/13
Göçmen, 2010 [40]	Turkey	Prospective cohort	Not reported	7/8
Halliday, 2010 [41]	Canada	Prospective with historic controls	Not reported	24/16
Author, Year	**Study location**	**Study design**	**LP/RB/OP**	**LP/RB/OP**
Cervical cancer				
Sert, 2011 [45]	Norway	Prospective with historic controls	Mean (SD) 56.4 (14)/36 (14.4)/70.0 (21) months	7/35/26
Soliman, 2011 [46]	USA	Retrospective cohort	Not reported	31/34/30
Wright, 2012 [48]	USA	Retrospective cohort	Not reported	217/67/1610

RB robot-assisted surgery, *LP* laparoscopy, *OP* open surgery individual point estimates derived from the included studies comparing robot-assisted hysterectomy with laparoscopic hysterectomy and open hysterectomy, respectively. Figures 2 and 3 have data from individual studies included for endometrial and cervical cancer within each of the individual outcomes. Due to a high level of both clinical and statistical heterogeneity observed in the included studies, the pooled point estimates are not reported.

Endometrial cancer

Among the 23 studies that examined outcomes in women with endometrial cancer, 11 studies compared robot assisted with laparoscopic hysterectomy [16–18, 21–24, 26, 27, 30, 33], 8 studies compared robot-assisted with open hysterectomy [20, 28, 29, 31, 32, 35, 49, 50], and 4 studies compared robot-assisted with laparoscopic and open hysterectomy [19, 25, 34, 36]. Of the 23 studies, 6 studies were prospective and had historic control group [24–26, 30, 34, 49] and 17 studies were retrospective cohort studies [16–23, 27–29, 31–33, 35, 36, 50]. Eighteen studies were from USA [16–18, 20, 21, 23–27, 29–32, 34–36, 50], followed by one study each from Italy [23], Finland [33], Canada [49], Spain [19], and Singapore [28]. The number of participants in the included studies ranged from 30 to 377. Length of follow-up ranged from 30 days to 5 years post-op. Length of follow-up was not reported for all the comparison groups.

Robot-assisted compared with laparoscopic hysterectomy for endometrial cancer

When compared with laparoscopic hysterectomy, robot-assisted hysterectomy was associated with lower mean volume of blood loss in all included studies (109 ± 83 vs. 187 ± 187) [17]; (89 ± 45 vs. 209 ± 92) [25]; (81 ± 46 vs. 207 ± 109) [26]; (99 ± 75 vs. 190 ± 120) [19]; (108 ± 94 vs. 194 ± 110) [34]; (110 ± 83 vs. 187 ± 169) [18] (Fig. 2a). Mean length of hospital stay was shown in two studies to be reduced with robot-assisted hysterectomy (1.6 ± 0.7 vs. 2.6 ± 0.9) [25]; (1.5 ± 0.9 vs. 3.2 ± 2.3) [26], while a trend in reduction of mean length of stay in favor of robot-assisted surgery was demonstrated in three other studies (1.8 ± 1.6 vs. 2.3 ± 2.2) [17]; (3.5 ± 3.6 vs. 4.6 ± 4) [19]; (2 ± 2 vs. 2.5 ± 2.1) [18] (Fig. 2b). Four studies demonstrated increase in the mean number of pelvic lymph nodes removed among the laparoscopy group (19 ± 8 vs. 24 ± 12) [25]; (13 ± 7 vs. 16 ± 9) [17]; (19 ± 9 vs. 25 ± 12) [26]; (13 ± 6 vs. 15 ± 8) [18], while two other studies showed no difference (16 ± 8 vs. 18 ± 8) [19]; (15 ± 8 vs. 16 ± 7) [33]. One of the included studies demonstrated more pelvic lymph nodes removed by robotic surgery (14 ± 7 vs. 12 ± 5) [27] (Fig. 2c). When looking at perioperative complication rates, we observed that the included studies did not show a difference between robot assisted and laparoscopic hysterectomy [22, 30, 33, 34]. However, intraoperative events were shown in two studies to be reduced with robot-assisted hysterectomy (0/56 vs. 7/56) [25]; (1/122 vs. 7/122) [26] (Fig. 2d).

Comparison of the mean length of operative time between robot assisted and laparoscopic hysterectomy was inconclusive, with shorter mean length of operative time favoring robot-assisted hysterectomy observed in four of the included studies (242 ± 53 vs. 287 ± 55) [30]; (163 ± 53 vs. 192 ± 56) [25]; (147 ± 48 vs. 187 ± 60) [26]; (189 ± 35 vs. 218 ± 54) [19]. In contrast, four other studies demonstrated shorter mean length of operative time with laparoscopic hysterectomy (237 ± 57 vs. 178 ± 59) [17]; (109 ± 38 vs. 218 ± 54) [34]; (210 ± 66 vs. 120 ± 41) [33]; (218 ± 59 vs. 161 ± 59) [18] (Fig. 2e).

Of the six studies comparing the mean number of para-aortic lymph nodes removed by robot-assisted and laparoscopic hysterectomy, two studies demonstrated more para-aortic nodes removed by laparoscopic surgery (13 ± 8 vs. 21 ± 12) [25]; (6 ± 8 vs. 18 ± 10) [26], while the results of one study showed more nodes removed in the robot-assisted surgery (9 ± 6 vs. 7 ± 6) [17]. The other three studies demonstrated no difference between the two procedures (Fig. 2f). When comparing the mean number of total lymph nodes removed, one study demonstrated more nodes removed by laparoscopy compared with robot-assisted hysterectomy (25 ± 13 vs. 43 ± 18) [26], while the rest of the included studies showed no difference between the two procedures (Fig. 2g).

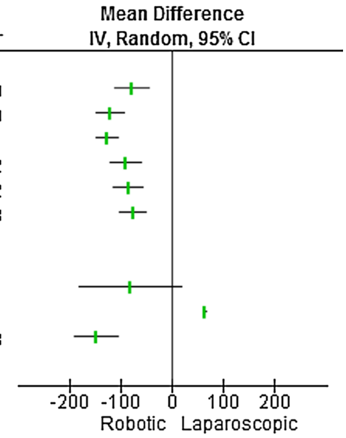
Two of the 11 included studies demonstrated a reduction in conversion to open surgery with robot-assisted surgery compared to laparoscopy (13/05 vs. 20/76) [30]; (1/187 vs. 10/245) [18], while the rest of the studies showed no statistical difference (Fig. 2h).

Robot-assisted compared with laparotomy (open hysterectomy) for endometrial cancer

When robot-assisted hysterectomy was compared with laparotomy, all of the eight included studies showed significant reduction in the mean estimated blood loss in robot-assisted procedure (89 ± 45 vs. 266 ± 145) [25]; (232 ± 48 vs. 308 ± 34) [50]; (96 ± 109 vs. 409 ± 290) [31]; (119 ± 45 vs. 185 ± 304) [20]; (108 ± 94 vs. 412 ± 312) [34]; (111 ± 25 vs. 250 ± 84) [28]; (99 ± 75 vs. 232 ± 10) [19]; (160 ± 150 vs. 292 ± 226) [32] (Fig. 3a). All eight included studies also demonstrated a reduction in the mean length of hospital stay, favouring robot-assisted hysterectomy (1.6 ± 0.7 vs. 4.9 ± 1.9) [25]; (2.73 ± 1.84 vs. 5.07 ± 2.54) [31]; (1.28 ± 0.87 vs. 3.26 ± 0.64) [50]; (1.5 ± 2 vs. 4 ± 3) [20]; (3.5 ± 3.4 vs.

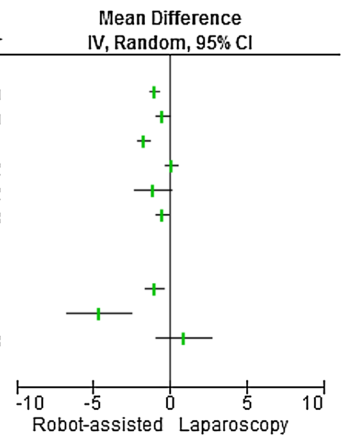
(a) Estimated Blood Loss

Study or Subgroup	Robotic Mean	Robotic SD	Robotic Total	Laparoscopic Mean	Laparoscopic SD	Laparoscopic Total	Mean Difference IV, Random, 95% CI	Year
1.7.1 Mean blood loss: endometrial cancer								
Cardenas-Goicoechea, 2010	109	83	102	187	187	173	-78.00 [-110.19, -45.81]	2010
Lim, 2010	89	45	56	209	92	56	-120.00 [-146.82, -93.18]	2010
Lim, 2011	81	46	122	207	109	122	-126.00 [-146.99, -105.01]	2011
Coronado, 2012	99	75	71	190	120	84	-91.00 [-122.03, -59.97]	2012
Estape, 2012	108	94	102	194	110	104	-86.00 [-113.92, -58.08]	2012
Cardenas-Goicoechea, 2013	110	83	187	187	169	245	-77.00 [-101.28, -52.72]	2013
1.7.2 Mean blood loss: cervical cancer								
Sert, 2011	82	74	35	164	131	7	-82.00 [-182.09, 18.09]	2011
Tinelli, 2011	157	7	23	95	5	76	62.00 [58.93, 65.07]	2011
Chong, 2013	55	32	50	202	148	50	-147.00 [-188.97, -105.03]	2013



(b) Length of Hospital Stay in Days

Study or Subgroup	Robot-assisted Mean	Robot-assisted SD	Robot-assisted Total	Laparoscopy Mean	Laparoscopy SD	Laparoscopy Total	Mean Difference IV, Random, 95% CI	Year
1.2.1 Length of hospital stay in days for endometrial cancer								
Lim, 2010	1.6	0.7	56	2.6	0.9	56	-1.00 [-1.30, -0.70]	2010
Cardenas-Goicoechea, 2010	1.8	1.6	102	2.3	2.2	173	-0.50 [-0.95, -0.05]	2010
Lim, 2011	1.5	0.9	122	3.2	2.3	122	-1.70 [-2.14, -1.26]	2011
Estape, 2012	1.9	1.5	102	1.8	1.1	104	0.10 [-0.26, 0.46]	2012
Coronado, 2012	3.5	3.4	71	4.6	4	84	-1.10 [-2.26, 0.06]	2012
Cardenas-Goicoechea, 2013	2	2	187	2.5	2.1	245	-0.50 [-0.89, -0.11]	2013
1.2.2 Length of hospital stay in days for cervical cancer								
Tinelli, 2011	3	1	23	4	2	76	-1.00 [-1.61, -0.39]	2011
Sert, 2011	3.8	0.9	35	8.4	2.8	7	-4.60 [-6.70, -2.50]	2011
Chong, 2013	9.6	5.6	50	8.7	3.1	50	0.90 [-0.87, 2.67]	2013



(c) Mean Number of Pelvic Lymph Nodes Removed

Study or Subgroup	Robot-assisted Mean	Robot-assisted SD	Robot-assisted Total	Laparoscopy Mean	Laparoscopy SD	Laparoscopy Total	Mean Difference IV, Random, 95% CI	Year
1.3.1 Number of pelvic lymph nodes: endometrial cancer								
Lim, 2010	19	8	56	24	12	56	-5.00 [-8.78, -1.22]	2010
Cardenas-Goicoechea, 2010	13	7	102	16	9	173	-3.00 [-4.91, -1.09]	2010
Lim, 2011	19	9	122	25	12	122	-6.00 [-8.66, -3.34]	2011
Martino, 2011	14	7	101	12	5	114	2.00 [0.35, 3.65]	2011
Coronado, 2012	16	8	71	18	8	84	-2.00 [-4.53, 0.53]	2012
Cardenas-Goicoechea, 2013	13	6	180	15	8	230	-2.00 [-3.36, -0.64]	2013
Turunen, 2013	15	8	67	16	7	150	-1.00 [-3.22, 1.22]	2013
1.3.2 Number of pelvic lymph nodes: cervical cancer								
Tinelli, 2011	25	5	23	27	5	76	-2.00 [-4.33, 0.33]	2011
Sert, 2011	20	7	35	15.4	8	7	4.60 [-1.76, 10.96]	2011

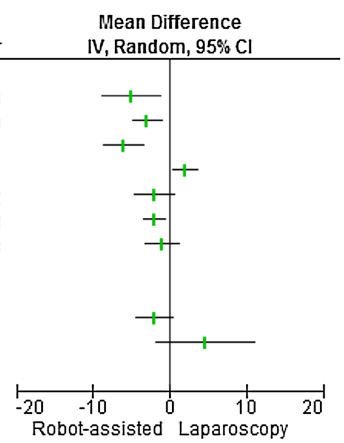
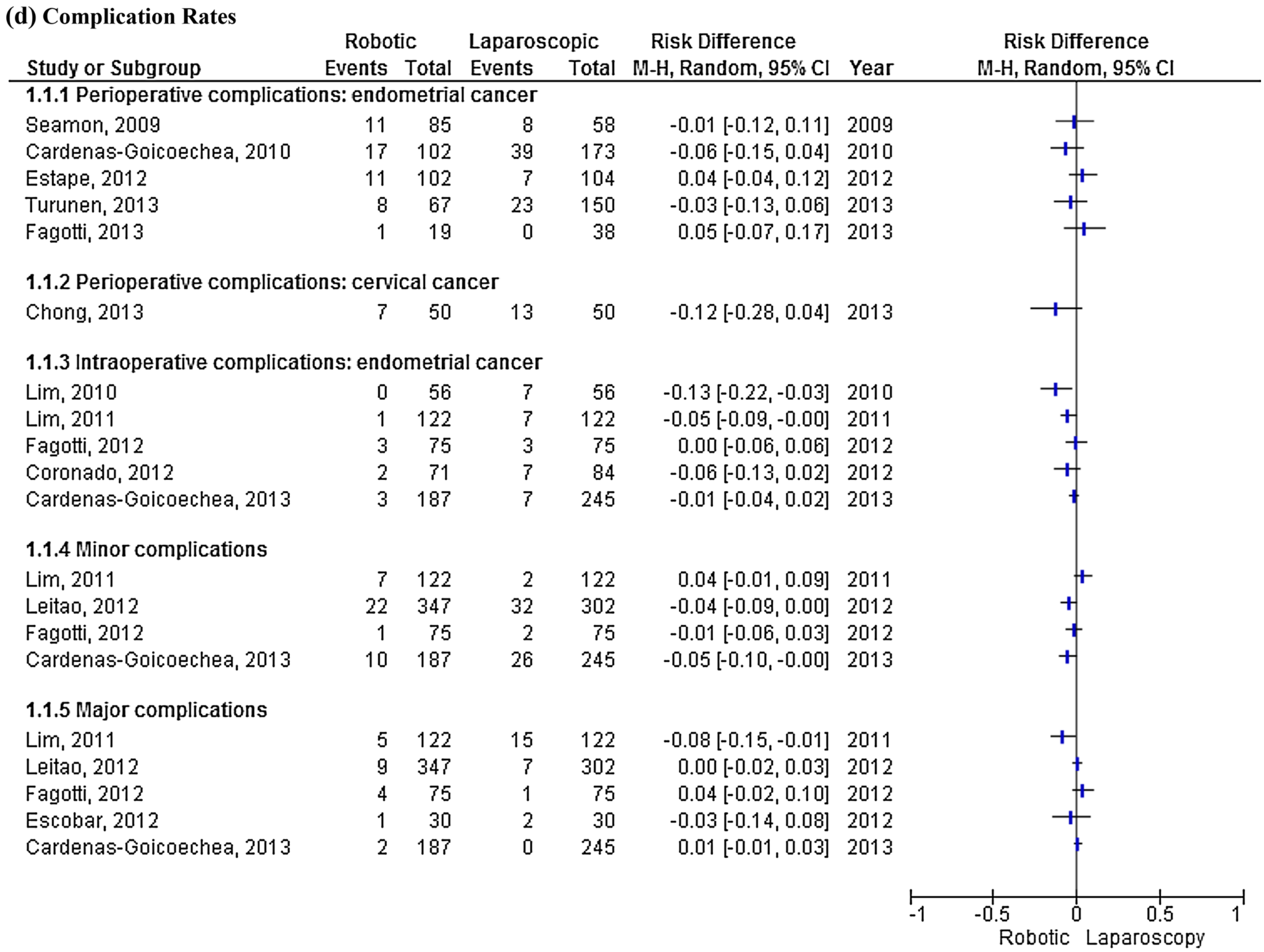


Fig. 2 Depicts a forest plot with different study estimates for the included studies comparing robotic hysterectomy with laparoscopic hysterectomy; **a** shows the outcome of mean-estimated blood loss among women who underwent hysterectomy for cervical and endometrial cancer separately, **b** shows the outcome of mean number of hospital stay in days post-op for both the cervical and endometrial cancer cohort, **c** shows the outcome of mean pelvic lymph nodes removed, **d** shows complication rates including perioperative for both endometrial and cervical cancer, intraoperative for endometrial cancer (as data were not available for cervical cancer from the included studies), minor and major complications for women who underwent hysterectomy for endometrial and cervical cancer, **e** shows the mean operative time for both endometrial and cervical cancer, **f** shows mean number of para-aortic lymph nodes removed in both the cohorts, **g** shows the number of total lymph nodes removed among the endometrial cancer cohort, **h** shows the mean number of conversions from laparoscopy and robotic hysterectomy to open hysterectomy



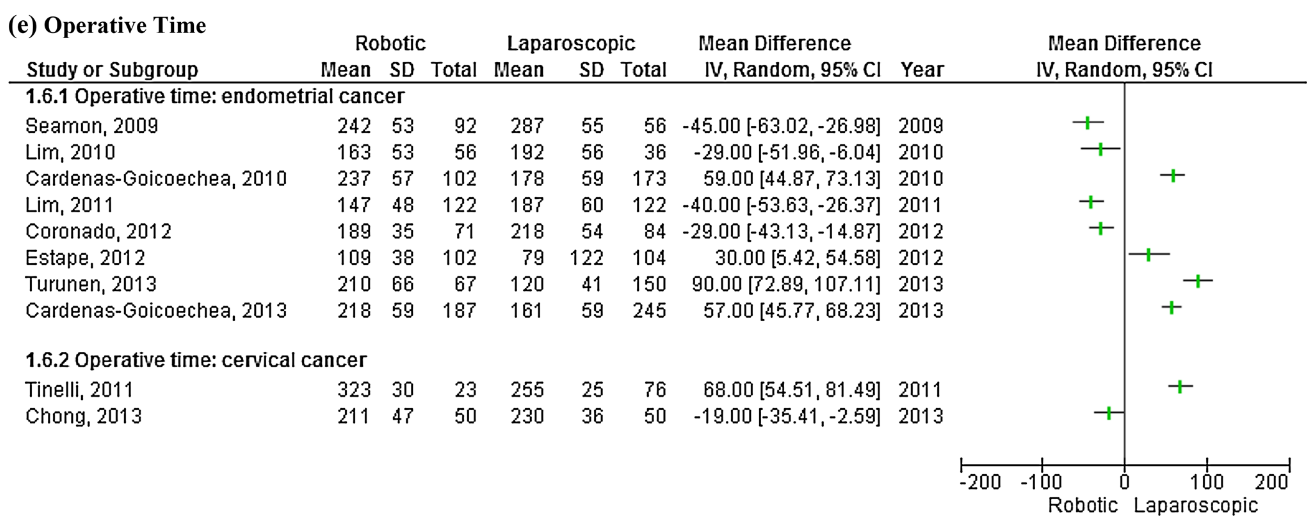
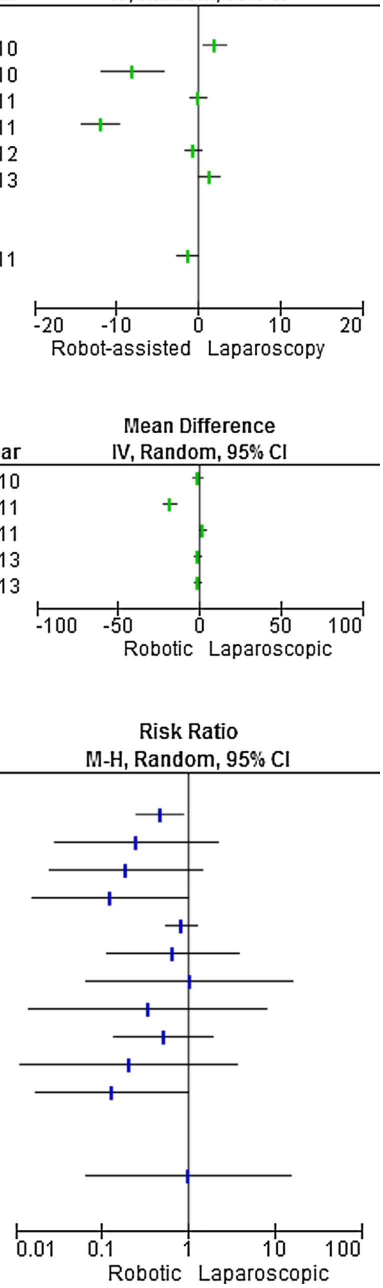


Fig. 2 continued

8.1 ± 4.8) [19]; (1.9 ± 1.5 vs. 4.1 ± 2.3) [34]; (1.5 ± 1 vs. 4.1 ± 2.2) [32]; (2.06 ± 1.1 vs. 6.02 ± 4.53) [28] (Fig. 3b). Two of the three included studies reported increase in the number of pelvic lymph nodes removed in the open hysterectomy group (19 ± 8 vs. 31 ± 14) [25]; (15 ± 6.3 vs. 25.6 ± 12.9) [28] (Fig. 3c).

When comparing the perioperative complication rates between robot-assisted and open hysterectomy, two out of two



(f) Mean Number of Para-Aortic Lymph Nodes Removed

Study or Subgroup	Robot-assisted Mean	SD	Total	Laparoscopy Mean	SD	Total	Mean Difference IV, Random, 95% CI	Year
1.4.1 Number of para-aortic lymph nodes: endometrial cancer								
Cardenas-Goicoechea, 2010	9	6	102	7	6	173	2.00 [0.53, 3.47]	2010
Lim, 2010	13	8	56	21	12	56	-8.00 [-11.78, -4.22]	2010
Martino, 2011	5	4	104	5	4	114	0.00 [-1.06, 1.06]	2011
Lim, 2011	6	8	122	18	10	122	-12.00 [-14.27, -9.73]	2011
Coronado, 2012	5.8	2.1	71	6.4	4	84	-0.60 [-1.59, 0.39]	2012
Cardenas-Goicoechea, 2013	8.9	5.4	136	7.6	5.8	169	1.30 [0.04, 2.56]	2013
1.4.2 Number of para-aortic lymph nodes: cervical cancer								
Tinelli, 2011	10.2	2.8	23	11.5	1.8	76	-1.30 [-2.51, -0.09]	2011

(g) Total Mean Number of Lymph Nodes Removed

Study or Subgroup	Robotic Mean	SD	Total	Laparoscopic Mean	SD	Total	Mean Difference IV, Random, 95% CI	Year
Cardenas-Goicoechea, 2010	22	10	102	23	12	173	-1.00 [-3.64, 1.64]	2010
Lim, 2011	25	13	122	43	18	122	-18.00 [-21.94, -14.06]	2011
Martino, 2011	19	10	101	17	7	114	2.00 [-0.34, 4.34]	2011
Cardenas-Goicoechea, 2013	18.9	10.4	187	20	12	245	-1.10 [-3.22, 1.02]	2013
Turunen, 2013	16.5	8.5	67	17.4	7.2	150	-0.90 [-3.24, 1.44]	2013

(h) Conversion to Open

Study or Subgroup	Robotic Events	Total	Laparoscopic Events	Total	Risk Ratio M-H, Random, 95% CI	Year
1.8.1 Conversion to open hysterectomy: endometrial cancer						
Seamon, 2009	13	105	20	76	0.47 [0.25, 0.89]	2009
Lim, 2010	1	56	4	56	0.25 [0.03, 2.17]	2010
Cardenas-Goicoechea, 2010	1	102	9	173	0.19 [0.02, 1.47]	2010
Lim, 2011	1	122	8	122	0.13 [0.02, 0.98]	2011
Leitao, 2012	37	347	39	302	0.83 [0.54, 1.26]	2012
Fagotti, 2012	2	75	3	75	0.67 [0.11, 3.88]	2012
Estape, 2012	1	102	1	104	1.02 [0.06, 16.08]	2012
Escobar, 2012	0	30	1	30	0.33 [0.01, 7.87]	2012
Coronado, 2012	3	71	7	84	0.51 [0.14, 1.89]	2012
Turunen, 2013	0	67	5	150	0.20 [0.01, 3.60]	2013
Cardenas-Goicoechea, 2013	1	187	10	245	0.13 [0.02, 1.01]	2013
1.8.2 Conversion to open hysterectomy: cervical cancer						
Chong, 2013	1	50	1	50	1.00 [0.06, 15.55]	2013

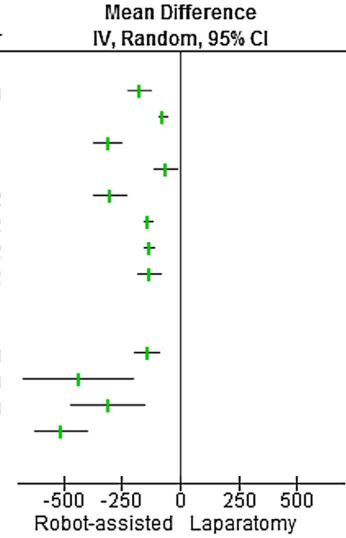
Fig. 2 continued

included studies demonstrated a better outcome with robot-assisted procedure (2/66 vs. 10/43) [35]; (11/102 vs. 20/78) [34], while no difference in intraoperative complications was demonstrated between the two procedures. Among studies comparing the minor and major complications in robot-assisted and open hysterectomy, all but one showed no significant difference (Fig. 3d). Mean length of operative time was consistently longer for the robot-assisted group across the eight included studies, with one study demonstrating a shorter mean time of operation with robot-assisted procedure (Fig. 3e).

Of the three included studies examining the mean number of para-aortic lymph nodes removal, two studies reported lower mean number of para-aortic lymph nodes removed in the robot-assisted group compared with the open hysterectomy group (13 ± 8 vs. 25 ± 14) [25]; (1.9 ± 0.4 vs. 3.5 ± 0.7) [50] (Fig. 3f). Of the four included studies,

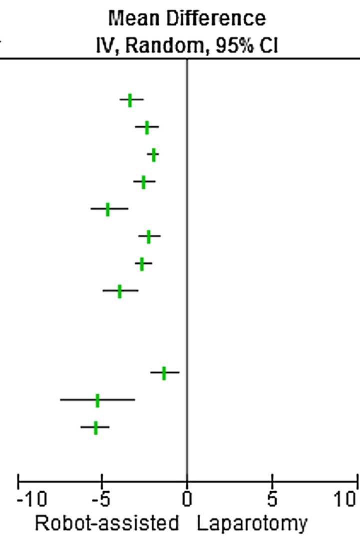
(a) Estimated Blood Loss

Study or Subgroup	Robot-assisted Mean	Robot-assisted SD	Robot-assisted Total	Laparotomy Mean	Laparotomy SD	Laparotomy Total	Mean Difference IV, Random, 95% CI	Year
2.7.1 Mean blood loss: endometrial cancer								
Lim, 2010	89	45	56	266	145	36	-177.00 [-225.81, -128.19]	2010
Goel, 2011	232	48	59	308	34	38	-76.00 [-92.34, -59.66]	2011
Subramaniam, 2011	96	109	73	409	290	104	-313.00 [-374.09, -251.91]	2011
Elshawi, 2011	119	45	155	185	304	150	-66.00 [-115.16, -16.84]	2011
Estape, 2012	108	94	102	412	312	78	-304.00 [-375.60, -232.40]	2012
Wei Mok, 2012	111	25	34	250	84	90	-139.00 [-158.28, -119.72]	2012
Coronado, 2012	99	75	71	232	110	192	-133.00 [-156.38, -109.62]	2012
Tang, 2012	160	150	129	292	226	110	-132.00 [-181.53, -82.47]	2012
2.7.2 Mean blood loss: cervical cancer								
Maggioni, 2009	78	95	40	222	132	40	-144.00 [-194.40, -93.60]	2009
Halliday, 2010	106	113	16	546	570	24	-440.00 [-674.67, -205.33]	2010
Nam, 2010	221	135	32	532	436	32	-311.00 [-469.14, -152.86]	2010
Sert, 2011	82	74	35	595	285	26	-513.00 [-625.26, -400.74]	2011



(b) Length of Hospital Stay

Study or Subgroup	Robot-assisted Mean	Robot-assisted SD	Robot-assisted Total	Laparotomy Mean	Laparotomy SD	Laparotomy Total	Mean Difference IV, Random, 95% CI	Year
2.2.1 Length of hospital stay in days for endometrial cancer								
Lim, 2010	1.6	0.7	56	4.9	1.9	36	-3.30 [-3.95, -2.65]	2010
Subramaniam, 2011	2.73	1.84	73	5.07	2.54	104	-2.34 [-2.99, -1.69]	2011
Goel, 2011	1.28	0.87	66	3.26	0.64	43	-1.98 [-2.26, -1.70]	2011
Elshawi, 2011	1.5	2	155	4	3	150	-2.50 [-3.07, -1.93]	2011
Coronado, 2012	3.5	3.4	71	8.1	4.8	192	-4.60 [-5.64, -3.56]	2012
Estape, 2012	1.9	1.5	102	4.1	2.3	78	-2.20 [-2.79, -1.61]	2012
Tang, 2012	1.5	1	129	4.1	2.2	110	-2.60 [-3.05, -2.15]	2012
Wei Mok, 2012	2.06	1.1	34	6.02	4.53	90	-3.96 [-4.97, -2.95]	2012
2.2.2 Length of hospital stay in days for cervical cancer								
Maggioni, 2009	3.7	1.2	40	5	2.4	40	-1.30 [-2.13, -0.47]	2009
Halliday, 2010	1.9	0.9	16	7.2	5.3	24	-5.30 [-7.47, -3.13]	2010
Sert, 2011	3.8	0.9	35	9.2	2	26	-5.40 [-6.22, -4.58]	2011



(c) Mean Number of Pelvic Lymph Nodes Removed

Study or Subgroup	Robot-assisted Mean	Robot-assisted SD	Robot-assisted Total	Laparotomy Mean	Laparotomy SD	Laparotomy Total	Mean Difference IV, Random, 95% CI	Year
2.3.1 Number of pelvic lymph nodes removed: endometrial cancer								
Lim, 2010	19	8	56	31	14	36	-12.00 [-17.03, -6.97]	2010
Coronado, 2012	16.1	7.6	71	17.1	8	192	-1.00 [-3.10, 1.10]	2012
Wei Mok, 2012	15	6.3	34	25.6	12.9	90	-10.60 [-14.00, -7.20]	2012
2.3.2 Number of pelvic lymph nodes removed: cervical cancer								
Sert, 2011	20	7	35	26	7	26	-6.00 [-9.55, -2.45]	2011

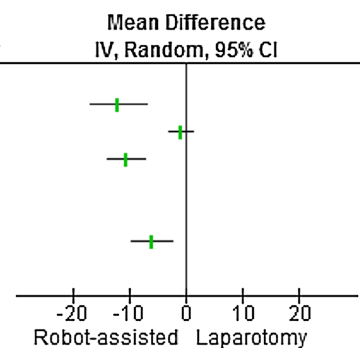
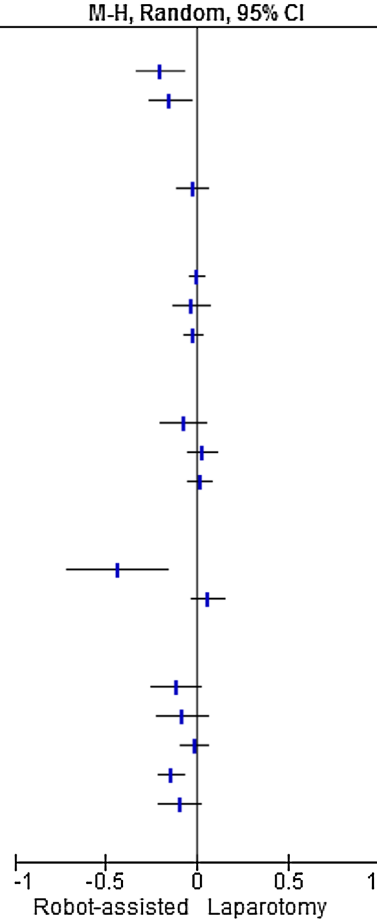


Fig. 3 Depicts a forest plot with different study estimates for the included studies comparing robotic hysterectomy with open hysterectomy/laparotomy; **a** shows the outcome of mean estimated blood loss among women who underwent hysterectomy for cervical and endometrial cancer separately as subgroups, **b** shows the outcome of mean number of hospital stay in days post-op for both the cervical and endometrial cancer cohort, **c** shows the outcome of mean pelvic lymph nodes removed, **d** shows complication rates including perioperative and intraoperative for both endometrial and cervical cancer, minor and major complications for women who underwent hysterectomy for endometrial and cervical cancer, **e** shows the mean operative time for both endometrial and cervical cancer, **f** shows mean number of para-aortic lymph nodes removed in the endometrial cancer cohort, **g** shows the number of total lymph nodes removed among both cohorts

(d) Complication Rates

Study or Subgroup	Robot-assisted Events	Robot-assisted Total	Laparotomy Events	Laparotomy Total	Risk Difference M-H, Random, 95% CI	Year
2.1.1 Perioperative complications: endometrial cancer						
Nevadunsky, 2010	2	66	10	43	-0.20 [-0.34, -0.07]	2010
Estape, 2012	11	102	20	78	-0.15 [-0.26, -0.03]	2012
2.1.2 Perioperative complications: cervical cancer						
Wright, 2012	9	67	258	1610	-0.03 [-0.11, 0.06]	2012
2.1.3 Intraoperative complications: endometrial cancer						
Lim, 2010	0	56	0	36	0.00 [-0.04, 0.04]	2010
Bernardini, 2011	2	45	3	41	-0.03 [-0.13, 0.07]	2011
Coronado, 2012	2	71	10	192	-0.02 [-0.07, 0.03]	2012
2.1.4 Intraoperative complications: cervical cancer						
Maggioni, 2009	2	40	5	40	-0.07 [-0.20, 0.05]	2009
Nam, 2010	1	32	0	32	0.03 [-0.05, 0.11]	2010
Wright, 2012	5	67	94	1610	0.02 [-0.05, 0.08]	2012
2.1.5 Minor complications						
Halliday, 2010	3	16	15	24	-0.44 [-0.71, -0.17]	2010
Lim, 2010	5	56	1	36	0.06 [-0.03, 0.15]	2010
2.1.6 Major complications						
Lim, 2010	3	56	6	36	-0.11 [-0.25, 0.02]	2010
Halliday, 2010	0	16	2	24	-0.08 [-0.23, 0.06]	2010
Cantrell, 2010	3	63	4	64	-0.01 [-0.09, 0.06]	2010
Paley, 2011	24	377	27	131	-0.14 [-0.22, -0.07]	2011
Goel, 2011	2	59	5	38	-0.10 [-0.21, 0.02]	2011



(e) Operative Time

Study or Subgroup	Robot-assisted Mean	Robot-assisted SD	Robot-assisted Total	Laparotomy Mean	Laparotomy SD	Laparotomy Total	Mean Difference IV, Random, 95% CI	Year
2.6.1 Operative time: endometrial cancer								
Lim, 2010	163	53	122	137	32	122	26.00 [15.01, 36.99]	2010
Goel, 2011	185	4	59	175	5	38	10.00 [8.11, 11.89]	2011
Elshawi, 2011	127	40	155	141	28	150	-14.00 [-21.73, -6.27]	2011
Subramaniam, 2011	246	75	73	138	53	104	108.00 [88.01, 127.99]	2011
Wei Mok, 2012	167	71	34	125	51	90	42.00 [15.91, 68.09]	2012
Coronado, 2012	189	34	71	157	33	192	32.00 [22.82, 41.18]	2012
Estape, 2012	109	38	102	84	39	78	25.00 [13.63, 36.37]	2012
Tang, 2012	237	65	129	177	50	110	60.00 [45.40, 74.60]	2012
2.6.2 Operative time: cervical cancer								
Maggioni, 2009	272	42	40	200	66	40	72.00 [47.76, 96.24]	2009
Nam, 2010	219	78	32	210	88	32	9.00 [-31.74, 49.74]	2010
Halliday, 2010	351	51	16	283	63	24	68.00 [32.51, 103.49]	2010
Sert, 2011	264	70	35	163	27	26	101.00 [75.59, 126.41]	2011

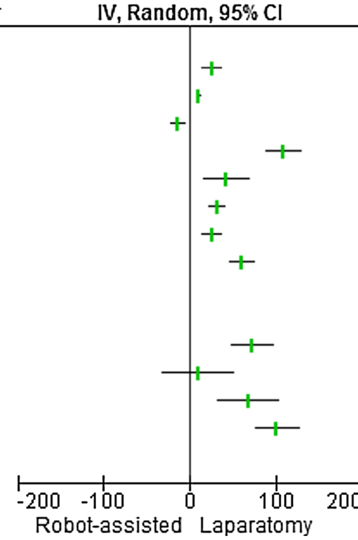


Fig. 3 continued

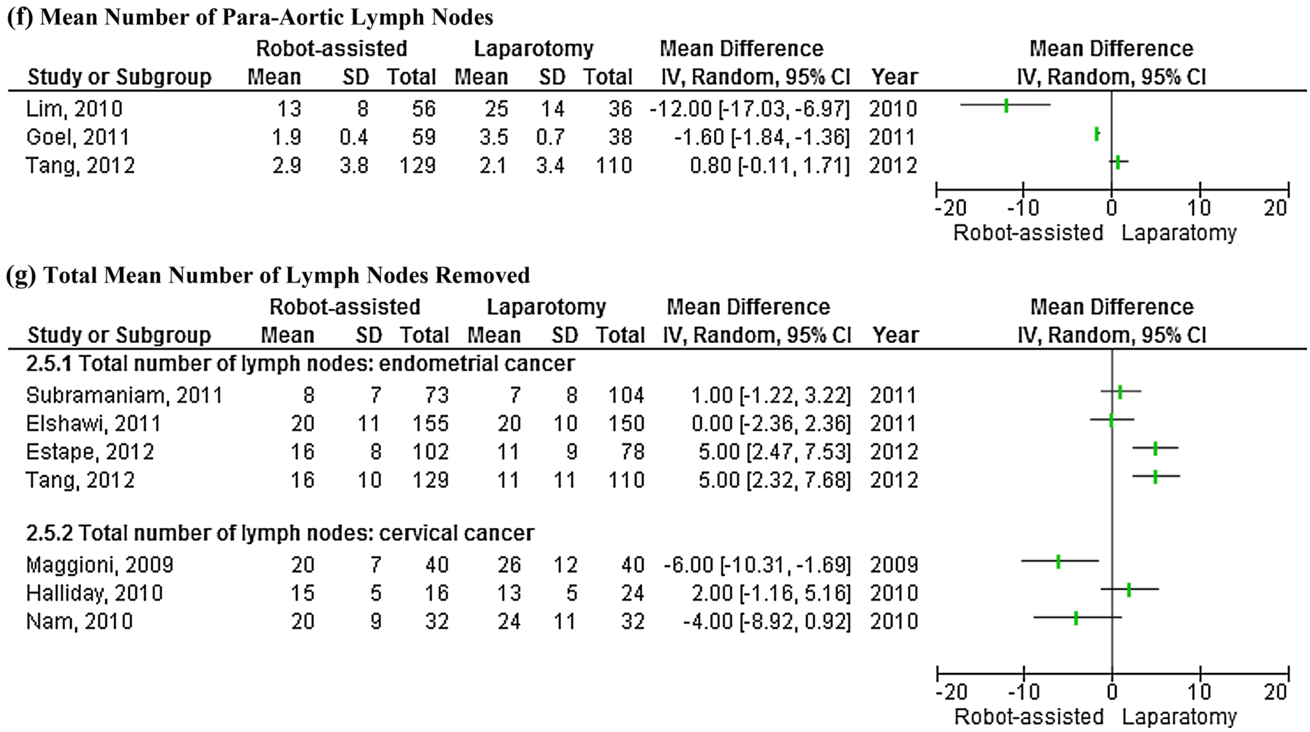


Fig. 3 continued

comparing the mean total number of lymph nodes removed, two studies showed no difference [20, 31], whereas two studies reported higher number of total lymph nodes removed among the robot-assisted hysterectomy group (16 ± 8 vs. 11 ± 9) [34]; (16 ± 10 vs. 11 ± 11) [32] (Fig. 3g).

Cervical cancer

Among the 12 studies that examined the outcomes in women with cervical cancer, 2 studies compared robot assisted with laparoscopic hysterectomy [38, 47], 7 studies compared robot assisted with open procedure [37, 39–44], and 3 studies compared all the 3 techniques [45, 46, 48]. Of the 12 studies, 5 studies were prospective cohort studies with a historic control [38, 41–43, 45], 1 was a prospective cohort study [40], and 6 studies were retrospective cohort studies [37, 39, 44, 46–48]. Five studies were from USA [37, 39, 46–48], two from Korea [38], one study each from Italy [42], Netherlands [44], Turkey [40], Canada [41], and Norway [45]. Sample size ranged from 7 to 1610 among the 12 included studies. Only three studies reported the length of follow-up which ranged from 2 days to 15 months post-op [43, 45, 47].

Robot assisted compared with laparoscopic hysterectomy for cervical cancer

When robot-assisted hysterectomy was compared with laparoscopic hysterectomy for cervical cancer, we found one study favoring the robot-assisted procedure (55 ± 32 vs. 202 ± 148) [38], and one study showing less blood loss with laparoscopic procedures (157 ± 7 vs. 95 ± 5) [47] (Fig. 2a).

Mean length of hospital stay was shorter among the robot-assisted group in two of the three studies that reported this outcome [45, 47] (Fig. 2b). Only one of the included studies reported complication rates comparing robot assisted with laparoscopic hysterectomy, demonstrating fewer perioperative complication events in robot-assisted group (7/50 vs. 13/50) [38] (Fig. 2d).

Comparing the mean operative time between the two procedures, one study reported that laparoscopic surgery was less time consuming compared to the robot assisted (323 ± 30 vs. 255 ± 25) [47], whereas the other study reported otherwise (211 ± 47 vs. 230 ± 36) [38] (Fig. 2e). The number of pelvic (Fig. 2c) and para-aortic lymph nodes (Fig. 2f) removed did not differ among the comparison groups [45, 47]. One study that reported conversion to open surgery did not find a difference between the two groups (Fig. 2h) [38].

Robot-assisted compared with open hysterectomy for cervical cancer

When robot-assisted hysterectomy was compared with laparotomy in women with cervical cancer, there was an overall decrease in mean estimated blood loss in robot-assisted group as demonstrated in all four included studies

(78 ± 95 vs. 222 ± 132) [42]; (106 ± 113 vs. 546 ± 570) [41]; (221 ± 135 vs. 532 ± 436) [43]; (82 ± 74 vs. 595 ± 285) [45] (Fig. 3a).

Mean length of hospital stay was also consistently shown in all three included studies to be reduced by robot-assisted surgery (3.7 ± 1.2 vs. 5 ± 2.4) [42]; (1.9 ± 0.9 vs. 7.2 ± 5.3) [41]; (3.8 ± 0.9 vs. 9.2 ± 2) [45] (Fig. 3b). Less number of pelvic lymph nodes were removed in the robot-assisted procedure compared to laparotomy in one study that reported this outcome (20 ± 7 vs. 26 ± 7) [45] (Fig. 3c). Mean operative time was lower in the laparotomy group compared with robot-assisted hysterectomy [41, 42, 45] (Fig. 3e). One study showed decreased number of mean total lymph nodes removed in robot-assisted group (20 ± 7 vs. 26 ± 12) [42], while two other studies showed no difference between the two groups [41, 43] (Fig. 3g).

GRADE evidence profile

The quality of evidence for all reported outcomes was considered as very low quality using the GRADE evidence profile. This was primarily based on risk of bias, inconsistency, indirectness, imprecision, and publication bias (Online Appendix Tables 5 and 6). Since all included studies were observational, they started as low quality and further downgraded for serious risk of bias. In majority of studies, inadequate reporting of patient selection process and/or inadequate adjusting in the analysis for the level of surgeon experience were the reasons for downgrading. In addition, these confounding factors contributed to high degree of inconsistency across the included studies. Indirectness of the reported outcomes also contributed as a serious limitation in the quality of evidence. Examples of these include complication rates not being adequately defined in studies and the number of removed lymph nodes being reported as a surrogate outcome for cancer staging.

Discussion

Our systematic review found that for endometrial cancer, robot-assisted hysterectomy compared to both laparoscopy and laparotomy showed reduced mean estimated blood loss and length of hospital stay although compared to laparoscopy it was not statistically significant. There was no difference in complications and although not significant, there was a trend toward more conversions to open surgery with laparoscopy compared to robot-assisted surgery. Secondary outcome measures of lymph node count did not favor one modality over another although studies did show an increase in pelvic lymph node count removal with laparoscopy compared to robotic surgery but the clinical significance is unclear. Furthermore, the variation in histologic lymph node counting, location of lymph nodes and operator bias make this difficult to interpret. The data from the current analysis can be considered an early snapshot in the adoption of robotic-assisted technology form the management of endometrial and cervical cancers as the data represent the initial work in the field. Our results are consistent with a recently published population-based registry study of women with newly diagnosed endometrial cancer. Women who underwent robot-assisted hysterectomy had reduced days to normal activity of daily living, return to work, blood loss, and length of hospital stay compared to abdominal hysterectomy [51]. In other recently published studies, robotic hysterectomy was found to be superior to laparoscopy in terms of intra- and post-operative complications, conversion rates, length of hospital stay as well as better health-related quality of life score after surgery [52, 53]. Similar results were obtained in morbidly obese women with endometrial cancer. Minimally invasive robotic or laparoscopic surgeries were associated with fewer complications, less days of hospitalization relative to open surgery and found to be safe and feasible in this population [54, 55].

For cervical cancer, robot-assisted hysterectomy demonstrated a reduction in estimated blood loss compared to open surgery but not compared to laparoscopy. Length of hospital stay was also consistently reduced among the robot-assisted group compared with both laparoscopy and laparotomy. Few of the recently published studies concluded that robot-assisted hysterectomy was safe, reliable, and feasible in women undergoing hysterectomy for cervical cancer [56–58]. Similarly, a few of the published systematic reviews and meta-analyses suggest robot-assisted hysterectomy to be superior to open hysterectomy with shorter hospital stay, reduced blood loss, and fewer wound related complications [59–61]. In another study, 5 year disease free and overall survival outcomes did not differ much among women with cervical cancer, irrespective of operative approach [62]. Overall, our results were consistent with the recently published literature on this topic. There is also an ongoing randomized control trial comparing minimally invasive radical hysterectomy and open surgery for women with cervical cancer. This study includes laparoscopy and robot-assisted surgeries in the minimally invasive arm and will hopefully provide some important insight into the respective benefits.

Of note, these data are derived from small observational studies with overall low methodological quality. While there is a clinical consensus that it is safe for women to undergo robot-assisted hysterectomy compared with other techniques for hysterectomy, the magnitude of the benefit is unclear. In addition, there is no clear evidence as to the degree of risk involved at various stages of cancer, which is an important information needed to make an informed decision. The results from our systematic review warrant a need for future large multicenter randomized controlled trials to better quantify the benefits and risks associated with robot-assisted hysterectomy. Unfortunately, for endometrial cancer, this is unlikely ever to happen in large part because randomized controlled data already exist favoring laparoscopy to open surgery [63] and as mentioned above, the only randomized trial in cervix cancer is combining robot assisted and laparoscopy in a minimally invasive arm.

Our systematic review has a number of strengths. It is one of the most comprehensive reviews that complement other recent reviews on this topic [59–61, 64–66]. It also presents an "early" representation of the data which allows people to compare differences over time. We did a comprehensive search to identify relevant literature in accordance with published guidelines and a pre-specified protocol. During our protocol phase, we had discussions with other methodologists as to what type of study designs should be included in our review. We determined a priori that randomized controlled studies, prospective cohorts with comparison groups and retrospective cohorts with comparison groups should be included to obtain reasonable valid effect estimates. Our literature search was comprehensive and reproducible. One recent study was not captured in our search because it was indexed (July 2014) after our search was completed (June 2014), this study compared robot-assisted hysterectomy with open hysterectomy [67]. The authors of this study found elderly women with endometrial cancer who underwent robot-assisted surgery had a significantly lower rate of minor complications, less operative blood loss, and shorter hospitalization [67]. Other studies published after our search date have been included in "Discussion". We do not expect any publication bias, as review of gray literature for unpublished studies did not yield any results.

The quality of studies included in this review inherently limits the conclusions that can be drawn. Thus, this review serves efficiently to summarize past studies but is not definitive as to what benefits or risks can be quoted to women who opt to have robot-assisted hysterectomy. Confounding factors such as surgeon's experience, tumor staging, women's age at the time of surgery, Body Mass Index, uterine weight, parity, comorbidities at the time of surgery etc. may distort the association between the exposure and outcome [68, 69]. In many of the studies, these confounding factors were not adequately addressed in the study design or in the statistical analysis. Studies were either retrospective relying on administrative database or prospective with a historic control where there was a possibility of differential misclassification, selection bias, and ascertainment bias [70]. For example, there were baseline differences between the comparison groups in many of the included studies; time period effects were of concern in most of the included studies where a group was compared with a historic control. Furthermore, a dose-response relationship between tumor staging and clinical risks was not considered in many of the included studies.

Given the rapid diffusion of robot-assisted hysterectomy world-wide, women opting for robot-assisted hysterectomy may assume that the technology is safe and effective compared to laparoscopic or open hysterectomy. The data from this report is consistent with other published literature (including randomized data) showing that minimally invasive surgery is superior to open surgery for endometrial cancer and likely for cervical cancer management but differences between robot assisted and laparoscopy are difficult to interpret. Nonetheless, appropriate counseling can reduce anxiety and avoid bias in patient preference. This review summarizes key published information on the overall clinical effectiveness of robot-assisted surgery compared to laparoscopic and/or open hysterectomy. This review provides surgeons with evidence and underscores the limitations of the current published literature. Surgeons and other healthcare professionals can integrate this information with their surgical expertise when they counsel women before hysterectomy.

Conclusions

This systematic review provides important information for decision-makers and policy-makers to make recommendations based on clinical effectiveness of robot-assisted hysterectomy. This systematic review of observational studies also highlights the need for future methodologically rigorous studies to estimate the magnitude of benefits or risks associated with robot-assisted hysterectomy. The clinical benefits of robotic surgery compared to laparoscopy are less clear. Until such data become available, health care professionals can use currently available evidence, along with their clinical expertise and patient preferences to guide decisions on robot-assisted hysterectomy.

Compliance with ethical standards

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Conflict of interest Authors IN, BV, CH, ID, DU, and MB declare that they have no conflict of interest.

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