Comparison of long-term outcomes of minimally invasive surgery versus open radical hysterectomy for cervical cancer: A meta-analysis

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Abstract

BACKGROUND The use of minimally invasive surgery (MIS) for cervical cancer remains controversial. OBJECTIVES To compare the long-term outcomes after experiencing the MIS robot-assisted laparoscopic radical hysterectomy (RRH) and total laparoscopic radical hysterectomy (LRH)) with traditional total open radical hysterectomy (ORH). SEARCH STRATEGY Five electronic databases including PubMed and Embase were searched from inception to January, 2020. SELECTION CRITERIA We included eligible studies of cervical cancer patients with outcomes of MIS and ORH. DATA COLLECTION AND ANALYSIS The pooled hazard ratio (HR) or relative risk (RR) and its 95% confidence interval (CI) of overall survival (OS), disease-free survival (DFS), progression-free survival (PFS) and recurrence (R) were pooled. MAIN RESULTS 37 studies (20,133 patients) were included. Overall, patients in MIS group showed similar prognosis with those in ORH group (OS HR = 1.11, P = 0.350; DFS HR = 1.08, P = 0.426; PFS HR = 1.04, P = 0.873; recurrence RR = 0.91, P = 0.166). For those with early stage cervical cancer, the ORH might be a better prognostic factor for OS than MIS (HR = 1.30, 95% CI: 1.08 - 1.56, P = 0.005), but no significant difference was observed for DFS, PFS and recurrence (P were 0.364, 0.760 and 0.349, respectively). The OS for LRH and RRH comparable to ORH (HR: 1.26 vs. 1.30, P interaction = 0.925). CONCLUSIONS We found that MIS, irrespective of LRH or RRH, might be a poor prognosis factor for early cervical cancer patients in OS compared to conventional ORH.

Introduction

Cervical cancer is the common malignancy among women worldwide[1]. It ranks fourth for both incidence and mortality among women worldwide with approximately 569,847 new cases and 311,365 deaths caused by cervical cancer globally in 2018 [2]. Despite advances in prevention and treatment during the past decade, due to substantial regional and global disparities in cervical cancer prognosis, various evidence-based management guidelines have been developed to improve the outcomes and quality of life for patients [1].

Open radical hysterectomy (ORH) is the standard care for the treatment of resectable cervical cancer [3]. The latest guidelines recommended by the National Comprehensive Cancer Network and the European Society of Gynecological Oncology suggest that minimally invasive surgery (MIS), including laparoscopic radical hysterectomy (LRH) and robot-assisted laparoscopic radical hysterectomy (RRH), is a newer alternative to open approaches for patients with cervical cancer.

MIS has been increasingly udy, including 6,355 patients who underwent radical hysterectomy, revealed that patients under LRH was associated with better OS [12]. Recently, a large and well-designed phase III randomized controlled trial (RCT) also suggested that MIS was associated with higher recurrence rate and worse OS for early-stage cervical cancer [13]. Till now, only two meta-analyses with no more than 2,000 patients have assessed the long term outcomes such as OS and DFS [8, 9] for cervical cancer.

Therefore, we performed this meta-analysis to clarify long-term outcomes of MIS (RRH or LRH) compared with ORH in the treatment of cervical cancer by using the current body of literature to determine whetsed in abdominal surgery. Several meta-analyses [4-10] showed that MIS might be associated with more short-term beneficial effects including less estimated blood loss, transfusion rate, operation time, length of hospital stay, febrile morbidity, recovery time, intraoperative and postoperative complications compared with ORH. However, the long-term outcomes were still in debate. With some studies[8-11] have shown that recurrence rates, disease-free survival (DFS) and overall survival (OS) rates did not differ significantly between the two approaches, whereas a recent large retrospective cohort study MIS could be as safe and effective as ORH.

Materials and methods

Literature search

We conducted a comprehensive literature search of studies from the following databases without language and date restriction: PubMed, Embase, the Cochrane Library, ClinicalTrial.gov and two Chinese databases (CNKI and Wan fang databases). The search was updated to January, 2020. The medical subject heading (MeSH) terms and free text terms searched for cervical cancer in title and abstract, individually and in combination, were as follows: "uterine cervical neoplasms", "cervical cancer", "cervix cancer", "cervical carcinoma", "cervix neoplasm". All fields were searched for MIS related terms such as "laparoscopy", "laparoscopic", "laparotomic", "minimally invasive", "robot-assisted laparoscopic", "radical hysterectomy", and "hysterectomy". We also searched the references of all related original and review articles to identify additional publications. Related articles generated by PubMed were also retrieved.

Selection criteria

We identified all available randomized controlled trials, non-randomized controlled trials, and cohort studies. The detail inclusion criteria were: (1) studies that focused on patients with cervical cancer; (2) comparative studies between MIS and traditional ORH, MIS included RRH or LRH; (3) studies that reported or had enough data to calculate the hazard ratios (HRs) or relative risks (RRs) with their 95% confidence intervals (CIs) for at least one of our pre-specified outcomes of interest, including OS, progression-free survival (PFS), and DFS, or reporting the number of recurrence (R) for each group; (4) the mean follow-up time for each group at least 12 months. For researches that had repeated data or duplicate analysis, only the most relevant ones with the largest dataset were included in the final analysis.

Data extraction and quality assessment

Two authors (LJ and CT) independently extracted the data and assessed the qualities of included studies. The following items were extracted from each included study: first author, year of publication, baseline characteristics of patients, study design, total number of cases, treatment strategy, HRs with 95% CIs for OS, DFS, and PFS. HRs were extracted from multivariate analyses or Kaplan-Meier survival curves. If only Kaplan-Meier curves were provided, we extracted data from the survival curves and estimate the approximate data of HRs and their 95% CIs by using the methods illustrated by Burdett Sarah *et al.*[14]. As for recurrence rate, all the number of event data were extracted between the two groups. Because meta-analysis was performed based on data from previous reports, ethics approval and patient written informed consent were not required in this study.

The quality for cohort studies was assessed by using Newcastle-Ottawa Scale (NOS), which is a tool for assessing the quality of nonrandomized studies in meta-analysis [15]. The scoring system consists of three parts: patient selection (0 - 4 stars), study group comparability (0 - 2 stars) and exposure or outcome assessment (0 - 3 stars). The NOS scores ranged from 0 to 9 stars, and 6 or greater stars were assigned as a high quality of studies. The sum of stars for each part were the total score for this study. Study quality of RCT was quantified using the revised Jadad scoring system [16]. The scoring system consists of four domains: generation of allocation sequence, allocation concealment, investigator blindness, and description of withdrawals and dropouts. The Jadad scores ranged from 0 to 7 stars, and 4 or greater stars were assigned as a high quality of studies.

Statistics analysis

All related data analyses were performed by using stata 11.0 (College Station, TX, USA). Aside from recurrence that analyzed by relative risks (RR), pooled RRs and their 95% CIs were pooled for the prognostic values of MIS versus ORH for cervical cancer. A HR/RR > 1 demonstrated a worse prognosis in cervical cancer patients with treatment of MIS. Statistical heterogeneity was examined by the I^2statistic and chi-squared test; I^2 values $> 50\%$ or P for heterogeneity < 0.10 demonstrated statistical heterogeneity in the studies and random-effects model was adopted, otherwise, a fixed-effects model was used [17]. Subgroup analysis was performed to identify the possible sources heterogeneity and to check for the potential effects of duration of follow-up and surgery approach. The Begg's and Egger's regression tests were used to detect any publication bias [18]. Meanwhile, influence analysis was also applied to assess the effect of single study on the pooled estimates. Except for the P for heterogeneity, all of these tests were two-sided and significance was set at P lesser than 0.05.

Results

Literature search

A total of 2,171 potentially relevant articles were identified from electronic databases, and 2,075 were excluded through assessment of titles and abstracts. 96 full-text were further screened. According to the pre-specified inclusion and exclusion criteria, 37 qualified studies were finally included for this meta-analysis. The procedures of literature selection were summarized in Figure 1.

Characteristics of included studies

The basic characteristics of the included studies were shown in Table 1. There were thirty-seven studies with 20,133 cases (MIS 10,191 and ORH 9,942) met the inclusion criteria, including one RCT[13], five prospective cohort studies [19-23], thirty retrospective cohort studies[12, 24-52], and one nonconcurrence cohort study [53]. Twenty-eight studies had selected patients with early stage cervical cancer, seven studies had selected patients with early stage and advanced cervical cancer, and two studies [12, 20] lacked of specific data on clinical stage of cervical cancer. Of these included studies, thirty-four studies [13, 19-23, 25-30, 32-53] mentioned the recurrence rate, twenty-seven [12, 13, 19-22, 24-31, 35-38, 40-46, 49, 50] studies reported the survival related data and survival curves. In addition, eleven studies were conducted among America, ten among Europe, and sixteen among Asia. The quality score of NOS ranged from 6 to 9 with median of 8 for cohort studies, and the quality score of Jadad was 7 for RCT.

Surgical approaches and survival outcome in cervical cancer

The estimated risks for OS, DFS, PFS were provided in twenty-two studies (MIS 9,153 cases and ORH 8,922 cases), fifteen studies (MIS 2,845 cases and ORH 2,709 cases) and nine studies (MIS 1,229 cases and ORH 1,578 cases), respectively. In addition, the overall recurrence rate reported in thirty-four studies (MIS 5,676 cases and ORH 5,165 cases). The pooled data showed that, when comparing MIS with ORH, no significance difference was observed for OS (HR = 1.11, 95% CI: 0.89 - 1.40;$I^2 = 60.8\%$), for DFS (HR = 1.08, 95% CI: 0.90 - 1.29;$I^2 = 15.4\%$), for PFS (HR = 1.04, 95% CI: 0.62 - 1.74; $I^2 = 68.8\%$), and for recurrence (RR = 0.91, 95% CI: 0.79 - 1.04; $I^2 = 22.3\%$; Table 2; Figures S1, S2, S4, S6).

Surgical approaches and survival outcome in early cervical cancer

Nineteen studies with 9,870 cases (MIS 4,933 patients and ORH 4,937 patients) reported the data for OS in early cervical cancer patients. Pooled data from these studies revealed a significantly worse OS after MIS than ORH with the combined HR of 1.30 (95% CI: 1.08-1.56, $P= 0.005$; Table 2, Figure 2) with mild heterogeneity ($I^2 = 11.9\%$). Fourteen studies with 5,424 patients (MIS 2,780 cases and ORH 2,644 cases) assessed the risk for DFS and eight studies with 2,466 patients (MIS 1,161 cases and ORH 1,305 cases) for PFS and observed no significantly difference for the early stage cervical cancer (DFS HR = 1.09, 95% CI: 0.90 - 1.32,$I^2 = 19.0\%$; PFS HR = 1.09, 95%CI: 0.64 - 1.85, $I^2 = 71.7\%$; Table 2, Figures S3 and S5). The overall recurrence rate for MIS compared with ORH reported in twenty-six studies with 8,086 patients (MIS

4,176 cases and ORH 3,910 cases) and the pooled data analysis also showed no significant differences without significant heterogeneity (RR = 0.93, 95% CI: 0.80 - 1.08, I^2 = 28.9%; Table 2, Figure S7).

Subgroup and sensitivity analyses

Stratified analyses suggested that the association did not differ among different approaches (HR for LRH vs. RRH: 1.26 vs. 1.30, *P*interaction = 0.925), studies design (HR for retrospective vs. prospective: 1.29 vs. 1.88, *P* interaction = 0.395), and sample size (HR for sample size [?] 400 vs. < 400: 1.37 vs. 1.13, *P* interaction = 0.361;Table 2).

The results of sensitivity analyses comparing OS between MIS and ORH radical surgical for early-stage cervical cancer indicated that the results might keep relative robust after omitting any study in this group (Table S1). The influence analyses indicated that the pooled HRs were not obviously influenced by any single study, including the one RCT by Ramirez *et al.* [13], for all survival outcomes (data not shown).

Publication bias

The Begg's and the Egger's tests were adopted to assess publication bias. The Begg's test and Egger's test did not indicate significant publication bias in the meta-analyses for OS, DFS, PFS and recurrence rate (Table S2). The funnel plots of the included studies all showed symmetrical distribution, demonstrating that the bias of reference adopted in our study was small (Figure 3, Figures S8 to S13).

Discussion

We quantitatively assessed long-term outcomes of MIS (RRH or ORH) compared with ORH. To the best of our knowledge, this meta-analysis was the most comprehensive study that evaluated long-term survival outcomes between MIS and ORH among women with cervical cancer. We combined long-term outcomes of 20,133 cervical cancer from thirty-seven studies, suggesting that OS, DFS, PFS and recurrence rate for patients undergoing MIS were comparable to ORH in women with cervical cancer, whereas MIS might be a poor prognosis factor for early cervical cancer in OS compared to conventional ORH. These findings may provide helpful information for both clinicians and patients in decision making for early stage cervical cancer.

Previous meta-analyses[4, 6, 54] which compared LRH or RRH surgeries with ORH suggested that RRH or LRH should be considered as an alternative option for surgical treatment of cervical cancer. However, these studies [4, 6, 54] just focused on short-term operative effects but without paying attention to the long-term outcomes. As to long-term outcomes, only two meta-analysis mentioned the OS and DFS. Two meta-analyses [8, 9]showed that survival was similar between these two groups. Based on long-term outcomes, Wang *et al.* [9].compared the effectiveness between LRH and ORH in the treatment of early-stage cervical cancer, with only five studies with 975 cases were included to summarized the OS (n = 3) and DFS (n = 5), and no significant results were found between the LRH and ORH procedures (5-year OS HR = 0.91, 95% CI: 0.48 - 1.71; 5-year DFS HR = 1.45 95% CI: 0.56 - 1.68) in this study. Furthermore, Cao *et al.* [8] evaluated the prognostic and safety roles of LRH in cervical cancer (included early-stage and advanced cervical cancer) by meta-analysis. Pooled ten studies with 1,822 patients, six studies with 1,503 patients and thirteen studies with 2,274 cases were assessed the OS and DFS, recurrence rate, respectively, but none of these studies found significant difference between LRH and ORH surgeries OS in OS, DFS and recurrence rate (OS HR = 0.98, 95% CI: 0.86 - 1.11; DFS HR = 1.01, 95% CI: 0.90 - 1.16; Recurrence rate OR = 0.82, 95% CI: 0.61 - 1.11). In the present study, we observed that MIS and ORH were comparable in DFS and recurrence rate, but MIS might be a poor prognosis factor for early cervical cancer in OS compared to conventional ORH. Overall, our findings of OS, DFS and recurrence rate were consistent with a previous review [8]. However, the result of OS for early-stage cervical cancer was inconsistent with previous study[9]. Larger sample size always means higher adequate power for detecting effects, so the discrepancy might be ascribed to difference in sample size between this study and theirs, with only five studies including 975 cases in study by Wang *et al.*[9] and nineteen studies including 20,133 populations were included in our study.

Several reasons may explain the differences in OS between MIS and ORH. First, MIS requires CO_2 gas insufflation for long time to form a pneumoperitoneum, which significantly enhanced the proliferation

and colony formation of cervical cancer cells[55]. Furthermore, the change and instability of intraoperative CO_2pneumoperitoneum by MIS may increase the risk of cancer cells entering the abdominal cavity [56, 57]. Another study[58] have also suggested that CO_2pneumoperitoneum might cause a decrease in pH in the abdominal cavity so that it could damage the body's local defense mechanism and inhibited the immune function. Second, there is more problem of diffusion caused by the compression of the cancerous foci with MIS because large curved forceps are used to clamp the bilateral uterine horns. In contrast, cancerous foci are not touched or stimulated by ORH[55]. Last, the whole or part of the cancer is exposed to the abdominal cavity, may cause abdominal pelvic cavity planting. Additionally, if the lymph node has metastasized, the removed lymph node stays in the abdominal cavity for 1 hour or longer, which is a process of exposing the tumor cells to the abdominal cavity [55]. Thus, MIS might increase the risk of abdominal pelvic cavity planting. Nevertheless, further clinical studies are required to confirm these speculations.

When the subgroup analysis was limited to specific types of surgery (RRH vs. ORH and LRH vs. ORH), no significant interaction was observed (P interaction = 0.925). Previous studies also indicated that RRH and LRH have similar complication rates, OS, and PFS, whereas RRH has been suggested to be associated with significantly less operative time and blood loss than LRH [11]. However, only four studies with 1,005 patients (RRH 491cases and ORH 514 cases) compared RRH with ORH, and the insufficient sample size might limit its testing power. Hence, further studies with larger sample size were warranted examine the association between RRH and ORH in overall survival among women with early cervical cancer.

There are several strengths in this study. First of all, with the large number of literatures examined, it could improve the statistical power for discovering potential effects in our study. In addition, we observed consistent results after sensitivity analysis, indicating that our results might be relatively stable. Finally, all included studies had relatively higher NOS score (median score = 8, ranged from 6 to 9) for NOS and quality of Jadad was 7 for RCT, suggesting that the studies we included were in relatively high quality.

However, there were also several limitations required to be cautiously considered in this meta-analysis. First, heterogeneity is an inevitable problem in meta-analysis since it may affect the interpretation of the results of all meta-analysis. The presence of heterogeneity may derive from many factors, including different sample size, disease stage, follow-up time and other clinical factors. Although the random-effect model was taken to minimize the heterogeneity, but it could not eliminate heterogeneity. Second, with only one RCT included, most studies we included were cohort studies, which might limit the testing power in our study. Third, we included thirty-seven studies and the bias existed due to the lack of information for every interest outcome. As for DFS, OS and PFS, the HRs and their 95% CIs were directly derived from original studies, whereas data for other studies which only reported survival curves data were calculated by us. The difference in data synthesis might lead to the inaccuracy in survival data and further damage our results. Fourth, although we grimly performed subgroup analyses to discover potential confounders, many unknown factors such as surgery quality may not have been precluded. For example, it has been shown that cases with a tumor size of lager than two cm might have better OS and PFS with open surgery than minimally invasive surgery [25]. Nevertheless, due to the lack of accurately data, it was impossible to perform subgroup analyses by tumors size, more detail stage distribution, nodal metastasis, and other clinical factors, and we could not acquire the effect of the above factors on the survival results between these two approaches.

In conclusion, the MIS is worse than conventional ORH in terms of OS for early cervical cancer patients. This study pooled the largest studies that compares the survival outcomes of MIS and ORH in treating cervical cancer with estimated that will be helpful in patients counseling and decision-making.

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Disclosures *of Interests*

The authors have declared no conflicts of interest.

Author contribution

The authors' responsibilities were as follows: F.F.Z and D.H.W: study concept and design;, J.L, T.C and M.Q.L: completed the literature search and data extraction; D.F.C and X.X.Y: performed the statistical analyses; J.L and T.C: drafted the manuscript; S.N.L and Y.H.L: assisted in the revision of the manuscript.

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Table 1. The characteristics of included studies.

First author	Year	Country	Study design	Number of patients	Age [a] (year)	BMI [a] (Kg/m2)	Follow-up [a] (months)	FIGO stage					
								Ia1	Ia2	Ib1	Ib2	IIa	IIb
MIS													
Diver [33]	2017	USA	Retrospective cohort	101	45.8 (10.6)	27.6 (7.7)	61.2 (50.4)	-	32	67	-	1[e]	-
Nitschmann [31]	2017*	USA	Retrospective cohort	190	44.1	-	60	-	-	-	-	-	-
Ramirez [13]	2018	USA	RCT	319	46.1 (11.0)	27.2 (5.6)	30 (0-75.6)	5	21	293	-	-	-
ORH													
Li [52]	2007	China	Retrospective cohort	35	44 (11)	-	26(5-84)	-	-	22[d]	-	13	-
ZAKASHANSKY [23]	2007	USA	Prospective cohort	30	46.6 (31–78)	-	41	1	6	19	2	2	-
Dıaz-Feijoo [51]	2008	Spain	Retrospective cohort	30	52.4 (13.3)	27.6 (4.9)	35(5–57)	-	1	25	1	3	-
Malzoni [50]	2009	Italy	Retrospective cohort	62	42.7 (8.6)	29(19–35)	52.5 (4-89)	3	11	48	-	-	-
Sobiczewski [49]	2009	Poland	Retrospective cohort	58	51.19 (12)	-	47	-	8[c]	46	-	4	-

First author	Year	Country	Study design	Number of patients	Age [a] (year)	BMI [a] (Kg/m^2)	Follow-up [a] (months)	FIGO stage I	FIGO stage II	FIGO stage III	FIGO stage IV	FIGO stage V	FIG
Leigh [48]	2010	USA	Retrospective cohort	64	41.5(20-72)	25(19-37)	28	0	5	51	7	1	0
Nam [53]	2010	Korea	Nonconcurrent cohort	32	45.9 (34-66)	22.3 (18.0-29.8)	40.6	-	2	24	4	-	2
Schreuder [47]	2010	Netherlands	Retrospective cohort	14	46 (32–68)	-	42 (31-54)	-	-	12	1	-	0
Lee [46]	2011	Korea	Retrospective cohort	48	50.2 (34–67)	23.9 (15.8–34.6)	75	-	-	10	26	48	-
Park [45]	2012	Korea	Retrospective cohort	159	70.0 (65–86)	24.69 (13.67–35.11)	45 (3-152)	-	5	123	6	25	-
Park [44]	2012	Korea	Retrospective cohort	112	52.1 (11.8)	31.7 (1.5)	45 (3-152)	-	3	81	13	15	-
Nam [22]	2012	Korea	Prospective cohort	263	46.5	23.2	127 (26-159)	-	40	194	21	8	-
Ghezzi [21]	2013	Italy	Prospective cohort	273	49 (25–79)	23.9 (15.8–45)	41 (3–143)	-	-	-	93	56	124
Jackson** [43]	2013	USA	Retrospective cohort	97	44.3 (17–75)	27.7 (16–50)	24.7 (0–82.1)	-	-	-	-	-	-
Park [42]	2013	Korea	Retrospective cohort	188	48.1 (25–84)	23.7 (17.63–34.75)	30 (3–142)	-	-	-	146	42	-
Bogani [20]	2014	Italy	Prospective cohort	65	50.9 (14)	25.9 (6.1)	106.2 (69.8)	-	-	-	-	-	-
Kong [40]	2014	Korea	Retrospective cohort	48	48.0 (11.0)	23.4 (3.3)	58.0 (17.0)	-	-	27	14	7	-
Ditto [19]	2015	Italy	Prospective cohort	60	45.5 (15-78)	24.0 (4.3)	48.7 (27.3)	-	10	50	-	-	-
Yang [38]	2015	China	Retrospective cohort	477	-	-	24 (1-177)	-	23	175	33	178	68
Xiao [39]	2015	China	Retrospective cohort	48	45.7 (11.3)	24.7 (3.8)	64.64 (8–147)	-	1[c]	-	35[d]	11	1
Laterza [32]	2016	Austria	Retrospective cohort	68	48 (26—85)	24.52 (19.3–43.3)	121.2 (5.9-266.2)	9	2	53	-	4	-

First author	Year	Country	Study design	Number of patients	Age [a] (year)	BMI [a] (Kg/m^2)	Follow-up [a] (months)	FIGO stage I	FIGO stage II	FIGO stage III	FIGO stage IV	FIGO stage V	FIG
Park [37]	2016	Korea	Retrospective cohort	107	47.3 (28–73)	23.58 (17.13–35.96)	58.8 (4.2–189.4)	-	4	97	5	1	-
Serta [36]	2016	USA	Retrospective cohort	232	46.7 (12.2)	27.4 (6.6)	46.7 (12.2)	-	22[c]	-	183[d]	24[g]	-
Wang [35]	2016	China	Retrospective cohort	203	44.47 (8.32)	22.08 (3.83)	83.26 (26-158)	-	12	110	25	26	-
Zanagnolo [34]	2016	Italy	Retrospective cohort	104	47.0 (12.4)	23.1 (4.1)	50.38(19.74-79.61)	-	5	78	16	5	-
Diver [33]	2017	USA	Retrospective cohort	282	45.1 (11.6)	25.9 (5.7)	61.2 (50.4)	-	92	178	-	7[e]	5[f]
He [29]	2017	China	Retrospective cohort	792	45.9	22.4	69(14-101)	-	66	456	95	175	-
Nitschmann [31]	2017	USA	Retrospective cohort	306	44.1	-	60	-	-	-	-	-	-
Shah [30]	2017	USA	Retrospective cohort	202	45.4 (19–88)	29.1 (18.3–55.7)	-	15	22	127	23	-	-
Guo [28]	2018	China	Retrospective cohort	139	40.52 (23–62)	23.19 (13.88–36.63)	39 (11-170)	-	12[c]	-	105[d]	22	-
Melamed [24]	2018	USA	Retrospective cohort	1236	-	-	45	-	127	1109	-	-	-
Ramirez [13]	2018	USA	RCT	312	46 (10.6)	26.2 (5.3)	30 (0-75.6)	5	20	287	-	-	-
David [25]	2019	USA	Retrospective cohort	56	40.6 (10.7)	27.6 (7.1)	25.4 (0.2-95.1)	-	-	56	-	-	-
Kim [12]	2019	Korea	Retrospective cohort	3235	-	-	-	-	-	-	-	-	-
Kim [b 26]	2019	Korea	Retrospective cohort	435	49.5 (11.5)	-	114.8	-	-	-	-	-	-
Matanes [27]	2019	Canada	Retrospective cohort	24	47 (24-69)	26.2 (20.6-38.5)	95.7 (0-165.6)	2	3	16	1	2	-
RRH													
Leigh [48]	2010	USA	Retrospective cohort	63	43(17-75)	28(18-49)	12.2 (0.2-36.3)	4	5	49	3	1	1
Nam [53]	2010	Korea	Nonconcurrent cohort	32	45.4 (33-75)	21.8 (17.0-31.6)	15.3	-	2	25	3	-	2

First author	Year	Country	Study design	Number of patients	Age [a] (year)	BMI [a] (Kg/m^2)	Follow-up [a] (months)	FIGO stage I	FIGO stage II	FIGO stage III	FIGO stage IV	FIGO stage V	FIGO stage VI
Schreuder [47]	2010	Netherlands	Retrospective cohort	13	43 (31–78)	-	26 (17-32)	-	-	11	1	-	1
Jackson** [43]	2013	USA	Retrospective cohort	147	44.3 (17–75)	27.7 (16–50)	24.7 (0-82.1)	-	-	-	-	-	-
Serta [36]	2016	USA	Retrospective cohort	259	44.5 (11.7)	27.6 (6.5)	44.5 (11.7)	-	36[c]	-	206[d]	17[g]	-
Zanagnolo [34]	2016	Italy	Retrospective cohort	203	44.7 (9.7)	23.1 (4.1)	35.84 (15.89-57.92)	-	11	162	27	3	-
Shah [30]	2017	USA	Retrospective cohort	109	45.2 (25–84)	27.9 (17.6–51.6)	-	5	16	69	4	-	-
Matanes [27]	2019	Canada	Retrospective cohort	74	48 (29-77)	26.4 (18.2-42.1)	46.4 (0-110.5)	9	12	44	7	2	
David [25]	2019	USA	Retrospective cohort	49	44.1 (10.7)	28.7 (6.7)	25.4 (0.2-95.1)	-	-	49	-	-	-
LRH													
Li [52]	2007	China	Retrospective cohort	90	42 (9)	-	26.0(5-84)	-	-	72[d]	-	18	-
ZAKASHANSKY [23]	2007	USA	Prospective cohort	30	48.3 (29–78)	-	20	1	8	17	2	2	-
Dıaz-Feijoo [51]	2008	Spain	Retrospective cohort	20	44.9 (9.2)	24.01 (3.0)	22.5(2-52)	-	2	18	0	0	-
Malzoni [50]	2009	Italy	Retrospective cohort	65	40.5 (7.7)	26(19–35)	71.5 (5-151)	5	21	39	-	-	-
Sobiczewski [49]	2009	Poland	Retrospective cohort	22	45.44 (9)	-	26.0	-	7[c]	15	-	0	-
Lee [46]	2011	Korea	Retrospective cohort	24	48.4 (39–68)	23.4 (18.2–32.4)	78.0	-	-	5	13	24	-
Nam [22]	2012	Korea	Prospective cohort	263	46.4	23.9	63 (25-150)	-	36	197	25	5	-
Park [44]	2012	Korea	Retrospective cohort	54	49.4 (11.5)	31.8 (1.39)	54 (3-152)	-	2	45	2	5	-
Park [45]	2012	Korea	Retrospective cohort	99	69.4 (65–78)	24.13 (17.8–29.4)	54 (3-152)	-	10	74	8	7	-

First author	Year	Country	Study design	Number of patients	Age [a] (year)	BMI [a] (Kg/m^2)	Follow-up [a] (months)	FIGO stage	FIGO stage	FIGO stage	FIGO stage	FIGO stage	FIGO
Ghezzi [21]	2013	Italy	Prospective cohort	68	49 (25–79)	23 (15–49)	35 (6–112)	-	-	-	33	18	17
Park [42]	2013	Korea	Retrospective cohort	115	48.5 (25–77)	23.1 (15.62–34.80)	30 (3–142)	-	-	-	81	34	-
Bogani [20]	2014	Italy	Prospective cohort	65	48.9 (13.5)	25.1 (5.2)	58.8 (27.8)	-	-	-	-	-	-
Kong [40]	2014	Korea	Retrospective cohort	40	45.0 (10.6)	22.3 (2.9)	28.0 (20.0)	-	-	22	12	6	-
Toptas [41]	2014	Turkey	Retrospective cohort	22	46.5 (40–57)	-	42.5 (38.4–55.42)	-	9	13	-	-	-
Ditto [19]	2015	Italy	Prospective cohort	60	46 (29-79)	24.3 (2.9)	31 (19.9)	-	13	47	-	-	-
Xiao [39]	2015	China	Retrospective cohort	106	43.7 (9.3)	23.8 (3.9)	48.2 (8–125)	-	15[c]	-	75[d]	15	1
Yang [38]	2015	China	Retrospective cohort	1052	-	-	24 (1-177)	-	76	587	105	237	47
Laterza [32]	2016	Austria	Retrospective cohort	82	43 (24–77)	23.44 (16.9–39.76)	44.67 (3.4-158.1)	21	5	53	-	3	-
Park [37]	2016	Korea	Retrospective cohort	186	45.3 (27–71)	23.69 (17.19–34.97)	58.8 (4.2–189.4)	-	10	156	16	4	-
Wang [35]	2016	China	Retrospective cohort	203	45.15 (8.62)	23.94 (3.84)	68.33 (26-156)	-	13	109	28	53	-
He [29]	2017	China	Retrospective cohort	1071	46.2	22.3	52 (13-95)	-	70	632	132	237	-
Guo [28]	2018	China	Retrospective cohort	412	44.19 (25–76)	22.81 (14.33–35.61)	39 (11-170)	-	35[c]	-	331[d]	46	-
Melamed [24]	2018	USA	Retrospective cohort	1225	-	-	45	-	159	1066	-	-	-
Kim [12]	2019	Korea	Retrospective cohort	3100	-	-	-	-	-	-	-	-	-
Kim [b 26]	2019	Korea	Retrospective cohort	158	52.9 (12)	-	114.8	-	-	-	-	-	-

Notes: a, mean (range), median (range), mean (SD), mean; b, stage IB1–IIA2; c, represent the number of stage Ia1 plus stage Ia2; -, not reported; *, IA-IB; **, early cervical cancer; e, stage IIA or IIb; f, others; g, early-stage cervical cancer, stage [?] IB2.

Abbreviations: OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; R, recurrence; ORH, open radical hysterectomy; MIS, minimally invasive surgery (RRH or LRH); RRH, robot-assisted laparoscopic radical hysterectomy; LRH, total laparoscopic radical hysterectomy.

Table 2. Summary of the meta-analysis results.

Analytical models	**N**	**Citation numbers of studies**	**Fixed-effects model**	**Fixe**
			HRs/RRs (95% CIs)	***P* va**
Over all*				
OS	22	12, 24, 13,19-22, 25-31, 35-38, 41,42, 44,45	0.95 (0.86, 1.05)	0.303
PFS	9	21, 25-28, 30, 31, 41, 43	1.20 (0.93, 1.55)	0.164
DFS	15	13, 19, 20, 22, 29, 35-37, 40, 42, 44-46, 49, 50	1.07 (0.91, 1.25)	0.393
Recurrence	34	13, 19-23,25- 30, 32-53	0.91 (0.79, 1.04)	0.166
For early-stage cervical cancer				
OS	19	24, 13, 19, 20, 22, 25-31, 35-39, 41,42, 44,45	1.33 (1.13, 1.56)	0.001
Subgroup1: approaches				
LRH vs. ORH	13	24, 19, 20, 22, 26, 28, 29, 35, 37, 41, 42, 44, 45	1.26 (1.06, 1.50)	0.008
RRH vs. ORH	4	25, 27, 30, 36	1.30 (0.69, 2.43)	0.416
P **for interaction**			0.925	
Subgroup 2: studies design				
Retrospective study	15	24, 25-31, 35-37, 41,42,44,45	1.29 (1.09, 1.52)	0.003
Prospective study	4	13**,** 19, 20, 22	1.90 (1.05, 3.41)	0.033
P **for interaction**			0.215	
Subgroup 3: sample size				
Sample size [?] 400	9	24, 13, 22, 26, 28, 29, 31, 35, 36	1.41 (1.17, 1.70)	<0.00
Sample size < 400	10	19, 20, 25, 27, 30, 37, 41, 42, 44, 45	1.13 (0.83, 1.54)	0.439
P **for interaction**			0.230	
PFS	8	25-28, 30, 31, 41, 43	1.22 (0.94, 1.58)	0.132
DFS	14	13, 19, 22, 29, 35-37, 40, 42, 44-46, 49, 50	1.08 (0.92, 1.27)	0.330
Recurrence	26	13, 19, 22,23,25-30, 32, 34-37, 40-46, 49-52	0.93 (0.80,1.08)	0.349

SNotes: *, cervical cancer included early-stage and advanced stage.

Abbreviations: N, number of studies; HRs, hazard ratios; RR, relative risks; 95% CIs, 95% confidence intervals; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; ORH, open radical hysterectomy; MIS, minimally invasive surgery (LRH or RRH); RRH, robot-assisted laparoscopic radical hysterectomy; LRH, total laparoscopic radical hysterectomy.

Figure legends

Figure 1. Flow chart of study selection.

Figure 2. Forest plot depicting overall survival for early cervical cancer; Error bars indicate 95% confidence intervals. Abbreviations: HR, hazard ratio; 95%CI, 95% confidence intervals.

Figure 3. Funnel plot of studies evaluating HRs of overall survival for early cervical cancer. Abbreviation: HR, hazard ratio.