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Short-term and Long-term Outcomes in Patients with Early-stage Cervical Cancer, Comparing Clinical and Adjuvant Therapy between Laparoscopic and Open Radical Hysterectomy: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: Cervical cancer represents one of the most common gynecological malignancies worldwide and the standard treatment has been radical abdominal hysterectomy (RAH). Recent surgical developments can be done through minimally invasive surgery (MIS) using laparoscopic radical hysterectomy (LRH), but the data regarding LRH are still conflicting.

AIM: Therefore, we undertook a systematic review and meta-analysis comparing the short-term and long-term outcomes of laparoscopic versus RAH in women with early-stage cervical cancer.

METHODS: A systematic search was performed within PubMed, Cochrane, Science Direct, and Google Scholar databases to research the outcome of LRH versus RAH in early-stage cervical cancer. Two reviewers independently reviewed titles, abstracts, and full article text to identify studies meeting inclusion and exclusion criteria. If there any discrepancies, it will be resolved by discussion. The Newcastle–Ottawa scale (NOS) was used to assess the risk of bias of non-randomized studies in this analysis. We used Review Manager 5.4 to calculate the result of 95% CI for the outcomes, odds ratio (OR), and mean differences (MD). The endpoints of interest are short-term, during operation, early post-operation, and long-term outcomes.

RESULT: The initial search identified 3.030 citations after a comprehensive review of the final 35 observational studies included, involving 6.919 early-stage cervical cancer patients. Pooled analysis showed that LRH had better intraoperative outcomes, estimated blood loss (EBL) significantly lower LRH (MD = 145.88 [95% CI: 132.84–158.92; $p < 0.0001$; $I^2 = 94\%$]), lesser intraoperative urinary tract injury (OR = 0.91), and vascular injury (OR = 0.76) but was not significant, number of pelvic lymph nodes resected tended to be higher in RAH with MD = 3.63 (95% CI: 3.10–4.15; $p < 0.0001$; $I^2 = 95\%$), shorter bowel recovery time post-operative (MD = 0.05 [95% CI: 0.34–0.66; $p < 0.001$]). Uniquely, the duration of surgery was not significantly different but still shorter in LRH with MD = 0.73. Long-term outcome was not significantly different for LRH from survival (OR = 1.17) and recurrence (OR = 0.83). LRH had shorter length of stay post-operative (MD = 13.23 [95% CI: 12.98–13.47; $p < 0.001$; $I^2 = 100\%$]) and tend to use significantly fewer adjunctive chemotherapy treatments (OR = 1.84 [95% CI: 1.38–2.45; $p < 0.001$; $I^2 = 73\%$]), the same was seen in radiotherapy treatment (OR = 1.27 [95% CI: 1.03–1.58; $p = 0.03$; $I^2 = 68\%$]).

DISCUSSION: The result demonstrated that for the long-term outcome, there was no significant difference between the two techniques. In general, LRH is considered to be associated with better recovery, smaller scar, and faster back to normal life than ARH. Some comparative studies have reported that survival outcome and perioperative complications after LRH are comparable to those after ARH. However, some study found that MIS was associated with a higher risk of death than open surgery for patients with tumor size ≥2 cm (HR 1.66, 95% CI: 1.19–2.30) and had significantly worse progression-free survival than those in the open surgery group with tumor size >2 cm and ≤4 cm ($p = 0.044$). This may be because of the use of uterine manipulator or because the difference approaches in handling the vaginal margin. Thus, avoiding tumor spillage and diminishing tumor handling during MIS may be beneficial. A Korean study demonstrated that LRH was associated with a lower total cost of care within 6-month postoperatively than RAH. It appeared that using laparoscopic approach was the least expensive approach from a societal perspective followed by robotic and then abdominal hysterectomy.

CONCLUSION: This systematic review and meta-analysis of observational studies found that among patients who underwent radical hysterectomy for early-stage cervical cancer, LRH had a better outcome in intraoperative, faster post-operative recovery time, and less need for adjunctive therapy.

Introduction

Cervical cancer represents one of the most common gynecological malignancies worldwide. It is the fourth most frequent cancer in women with an estimated 570,000 new cases in 2018 representing 6.6% of all female cancers [1]. According to the definition from the International Federation of Gynaecology and Obstetrics (FIGO), early stage cervical cancer refers to those at Stages IA1–IIA and constitutes the majority of incipient patients [2].

Surgery is the primary method of treatment in early stage cervical cancer. Radical hysterectomy

(RH) allows tumor removal and identification of risk factors for tailor adjuvant treatments. Accumulating data have highlighted the safety and effectiveness of radical hysterectomy (plus pelvic node dissection) in early stage cervical cancer [3], [4], [5]. Hence, the International Federation of Gynaecology and Obstetrics (FIGO) recommended the utilization of radical hysterectomy [6]. The National Comprehensive Cancer Network (NCCN) in 2017 and the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) in 2018 recommended the execution of radical hysterectomy through open or minimally invasive surgery (MIS) [7], [8].

Since then for patients with early-stage cervical cancer who do not wish to preserve fertility, radical hysterectomy with pelvic lymphadenectomy remains the standard treatment. Women with early-stage cervical cancer who undergo radical hysterectomy are usually cured, with 5-year disease-free survival rates exceeding 90% in some studies [9].

For more than a century, radical hysterectomy was performed predominantly through an open abdominal approach. Today minimally invasive surgery, including laparoscopic radical hysterectomy (LRH), had long been recognized as an alternative surgical approach to abdominal radical hysterectomy (ARH) with reduced operative morbidity and similar oncological safety [10]. Several studies have previously compared that the safety, feasibility, and clinical outcome of Abdominal Radical Hysterectomy and Laparoscopic Radical Hysterectomy suggest that short-term surgical outcomes are improved with Minimal Invasive Surgery techniques for Radical Hysterectomy, but ensuring that long-term cancer outcomes are not compromised is vital [11], [12], [13], [14]. The Laparoscopic Approach to Carcinoma of the Cervix (LACC) study which was an multicenter international randomized controlled trial showed the disadvantage for minimally invasive radical approach with higher recurrent rate and worse survival outcome [15], thus further evidence is still needed regarding this topic.

Therefore, we aim to evaluate the oncological safety of MIS in cervical cancer patients to appraise and synthesize the available real-world evidence stratified by characteristics of disease, publication, adverse event, recurrence, and overall survival between patients who underwent laparoscopic compared to open radical hysterectomy in patient with early-stage cervical cancer.

Methods

Literature search

This study strategy was undertaken according the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P). The literature search was conducted in Pubmed, Cochrane library, Science Direct and Google Scholar from January 2002 until September 2022 using these following terms: "Cervical cancer," "cervical carcinoma or cervical neoplasm," "early stage cervical cancer," "laparoscopic or laparoscopy," and "radical hysterectomy" with all studies must be comparative, in English and full text publication. Further manual search was performed by scanning the references of all included and relevant studies. Our study design is provided in Supplementary Table 1.

Eligible criteria and study selection

The population was women diagnosed with early-stage cervical cancer that underwent radical hysterectomy and the types of publication were prospective or retrospective. Two reviewers independently reviewed titles, abstracts, and full article text to identify studies meeting inclusion and exclusion criteria, if there any discrepancies, it will be resolved by discussion. The Newcastle–Ottawa scale (NOS) was used to assess the risk of bias of non-randomized studies in this analysis. The entire study assessment summary is provided in Supplementary Table 2.

Outcome measures

The study primary outcome was the survival outcome and secondary outcomes were operative outcome and adverse events such as oncologic outcome included 5-year disease-free survival rate, 5-year overall survival rate, and recurrent rate. Pathological outcome included the number of LN retrieved, tumor size, vaginal margin involvement, and lymph node metastases. Operative outcome included hospital stay, bladder dysfunction perioperative complication, estimated blood loss, and operative time.

Statistical analysis

Categorical variables had been analyzed as proportion. Data had been pooled using the Mantel-Haenszel fixed-results fashions with odd ratio (OR) because the impact degree with the associated 95% confidence interval (CI). Statistical heterogeneity among companies become measured the usage of Higgins I^2 statistic. Specifically, a $I^2 = 0$ indicated no heterogeneity even as we taken into consideration excessive heterogeneity primarily based totally at the values of I^2 as above 50%. Publication bias becomes evaluated in step with evaluation of the funnel plot asymmetry. All analyses had been done by Review Manager 5.4.1 (the Nordic Cochrane Centre, The Cochrane Collaboration, 2020). $p < 0.05$ (two-sided) was considered statistically significant.

Results

Search outcomes and study selection process

The initial search identified 3.030 citations (1.850 from Scholar, 897 from Science Direct, 265 from PubMed, and 18 from Cochrane), 2.725 were excluded by review of title and abstract, 14 studies excluded due to duplicate. We further undertake a complete assessment of 291 observational studies observational studies comparing laparoscopic with open radical hysterectomy for inclusion and exclusion criteria. One hundred and ninty-seven studies excluded because it was not full text, 30 studies were reviews, 24 studies compared other surgical plans, and five of them excluded because of unusable form. Finally, 35 eligible studies with 6.919 patients were identified. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram Figure 1 [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [10], [40], [41], [42], [43], [44], [45], [46], [47], [48] shows the entire review process from the original search to the final selection of studies.

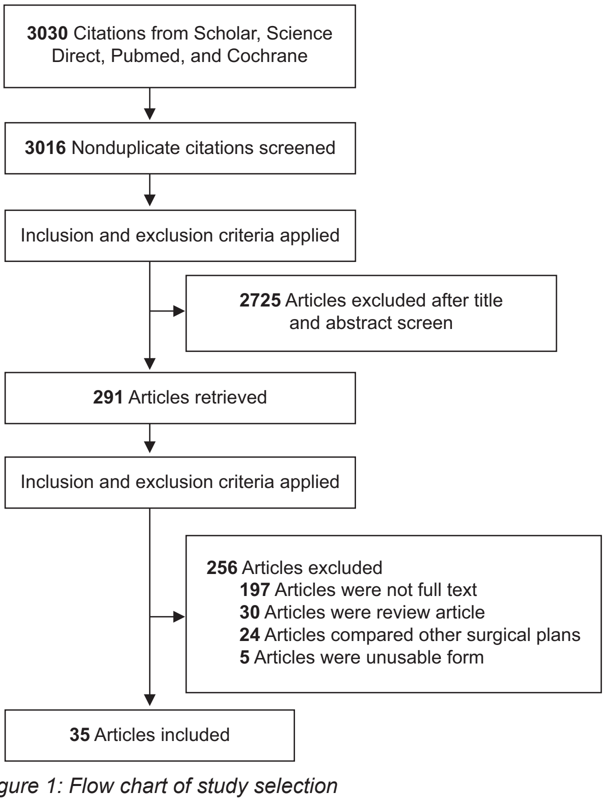

Figure 1: Flow chart of study selection

Main characteristics and quality assessment of included studies

Data quality of the studies assessed using the Newcastle-Ottawa quality assessment form for Cohort studies, which was divided into three qualities. Three or four stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain was concluded in good quality. Fair quality was 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Poor quality were 0 or 1 star in selection domain OR = 0 stars in comparability domain OR = 0 or 1 stars in outcome/exposure domain. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram reveals the entire review process from the original search to the final selection of the citations in this study. Most of our selected study are fall into good quality studies.

The majority of the study have been prospective or retrospective observational studies and most were non Asian, thus the majority of the patient in these studies were Non-Asian origin. A total of 6.985 patients were included in the study, 4.187 patients were Western and 2.798 were Asian. The research baselines are provided in Supplementary Table 3 [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [10], [40], [41], [42], [43], [44], [45], [46], [47], [48], most of the studies have been reported and statistically compare the independent variables between LRH and ARH groups such as age, BMI, and follow-up duration. Supplementary Tables 4 and 5 are the each study characteristic for staging and histology findings. The mean age among the groups were varying from 40.5 to 69.4 in LRH group and 42.7 to 70 in ARH group. The BMI among groups appeared to vary from varied from 22 to 31.8 kg/m^2 and it was comparable between two groups. The tumor histology was not reported in one study.

Pooled analysis for clinical outcomes

The forest plot of overall survival rate is shown in Figure 2 and disease recurrence is shown in Figure 3. Twenty studies analyzed overall survival rate between two groups including 5.250 patients (3.115 LRH and 2.235 ARH). The result revealed no significant difference (OR = 1.17, 95% CI [0.95–1.43] I^2 = 16% p = 0.14). A total of 4.669 patients (2.810 LRH and 1.859 ARH) were included in the analysis of disease recurrence and the result was also no significant difference (OR = 0.83, 95% CI [0.68–1.02] p = 0.08; I^2 = 19%). The shape of the funnel plots of the meta-analyses was symmetrical on both sides of the perpendicular line which indicates that the publication bias of these studies was not obvious.

Few pathological factors are thought to influence risk of disease recurrence and the rate of progression free survival after patient underwent a radical surgery. Large tumor diameter, lymph vascular invasion, deep stromal invasion, tumor involvement of the parametrium, vaginal margin involvement, and lymph node metastases were some of the risk factors. Adjuvant therapy usually considered to decrease the risk of disease progression, which consists of radiation with or without concurrent chemotherapy. Figure 4 shows the result between LRH and ARH for adjuvant chemotherapy, we found significant difference of the patients received adjuvant therapy especially chemotherapy (OR = 1.84, 95% CI [1.38–2.45] $I^2 = 73\%$ $p < 0.0001$). Similarly in Figure 5, we found a significance difference for patient received radiotherapy (OR = 1.27, 95% CI [1.03–1.58] p = 0.03; $I^2 = 68\%$).

Pooled analysis showed LRH had better intraoperative outcomes, estimated blood loss (EBL) significantly lower in LRH patients (MD = 145.88, 95% CI [132.84–158.92] $p < 0.0001$ $I^2 = 94\%$)], Supplementary Table 4 shows that almost all studies found that LRH significantly had lower blood loss during intraoperative, other intraoperative outcomes found that LRH had lesser intraoperative urinary tract injury (OR = 0.91, 95% CI [0.57–1.45]) and vascular injury (OR = 0.76, 95% CI [0.32–1.77])

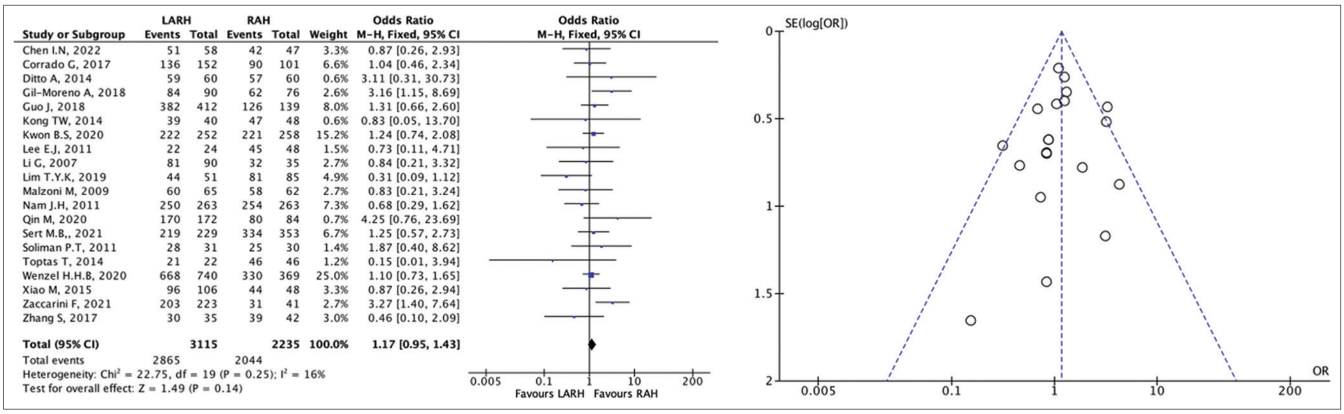

Figure 2: Forest plot of overall survival rate
LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy

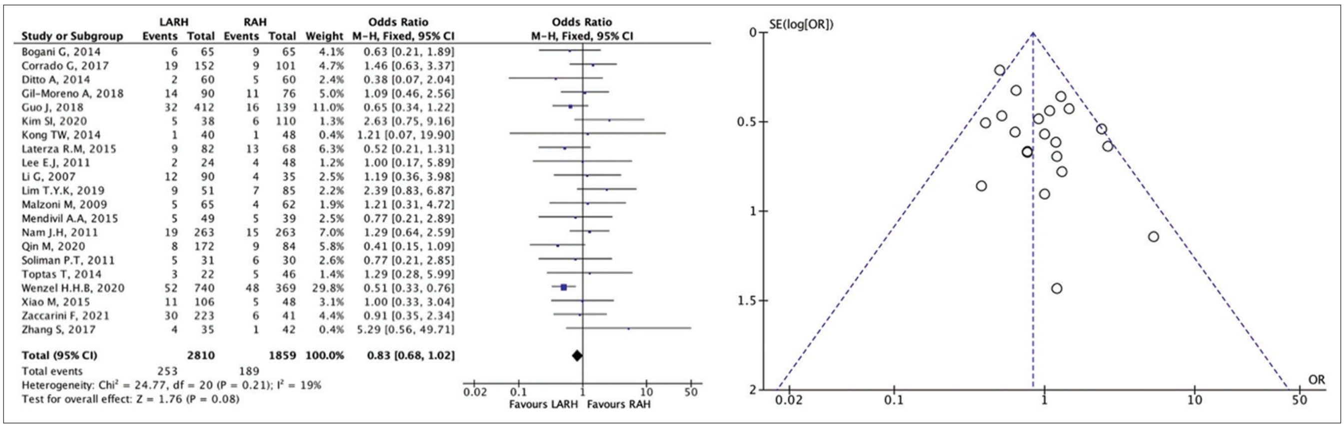

Figure 3: Forest plot of disease recurrence
LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy

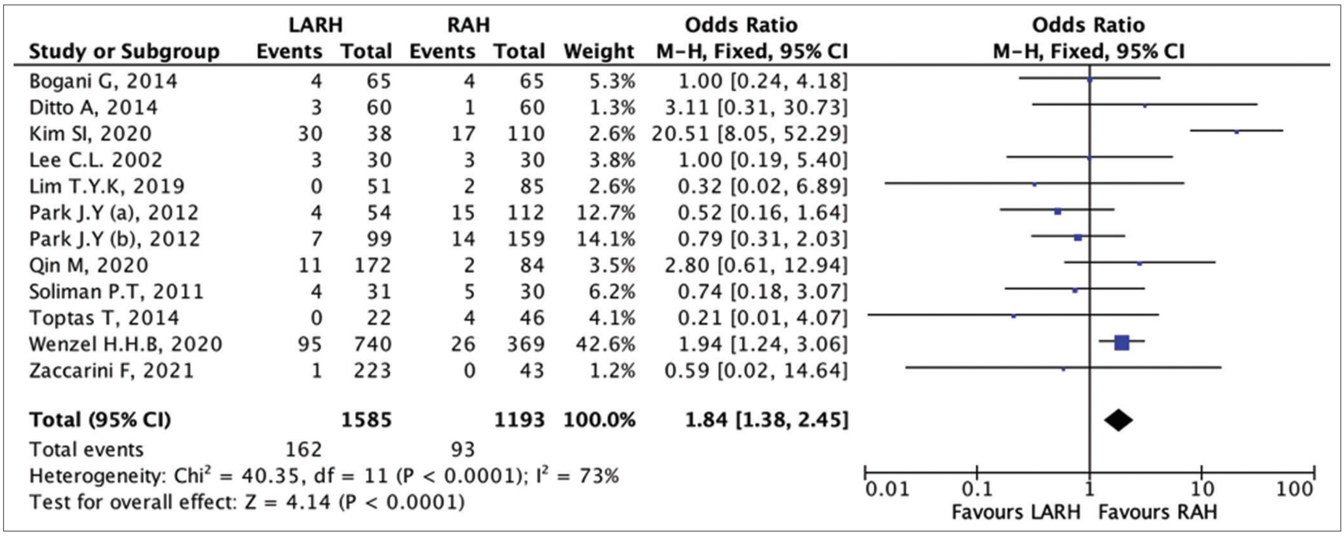

Figure 4: Forest plot of adjuvant chemotherapy
LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy

but was not significant. Number of pelvic lymph nodes resected tended to be higher in RAH MD = 3.63, 95% CI (3.10–4.15); $p < 0.0001$; $I^2 = 95\%$, 12 studies found no difference in the number of pelvic lymph node retrieved between two groups. However, 12 studies reported that there was a significance difference in the number of pelvic lymph node retrieved between two groups. The result of operative time varied widely, 16 studies reported that the surgical time was significantly longer for LRH than for ARH.

In post-operative outcome, LRH had shorter bowel recovery time post-operative (MD = 0.05 [95% CI: 0.34–0.66]; $p < 0.001$) in Figure 6, but only three studies compare between two groups. LRH had shorter length of stay post-operative (MD = 13.23, 95% CI [12.98–13.47] $p < 0.001$; $I^2 = 100\%$) in Figure 7.

Discussion

Until today, radical hysterectomy is the standard treatment of early-stage cervical cancer; however, it has several surgical morbidities, thus laparoscopic has been developed since. The feasibility and its long-term safety remains unclear. This study was aimed to integrate multiple evidences and make a comprehensive analysis to compare the respective advantages between LRH and ARH in treating early stage cervical cancer, which can be helpful in patient counseling and decision-making for equipment procurement.

The result demonstrated that for the long-term outcome, there was no significant difference between the two techniques, either from the overall survival rate or recurrence of the disease. The study found that LRH was associated with lower EBL, less intraoperative, and post-operative complication, and shorter hospital stays. The results of operative time actually varied widely between studies, this may due to differences between surgeon experience or may because differences between each operating room. The same also can be found in the number of lymph-node resected, it may because in differences between surgeons. We have to take note that almost half of the included studies observed that LRH may take longer

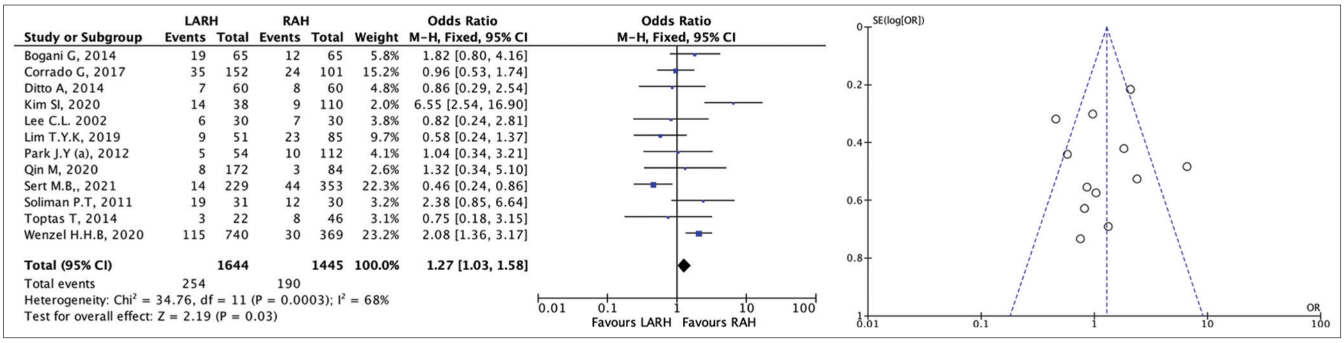

Figure 5: Forest plot of adjuvant radiotherapy
LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy

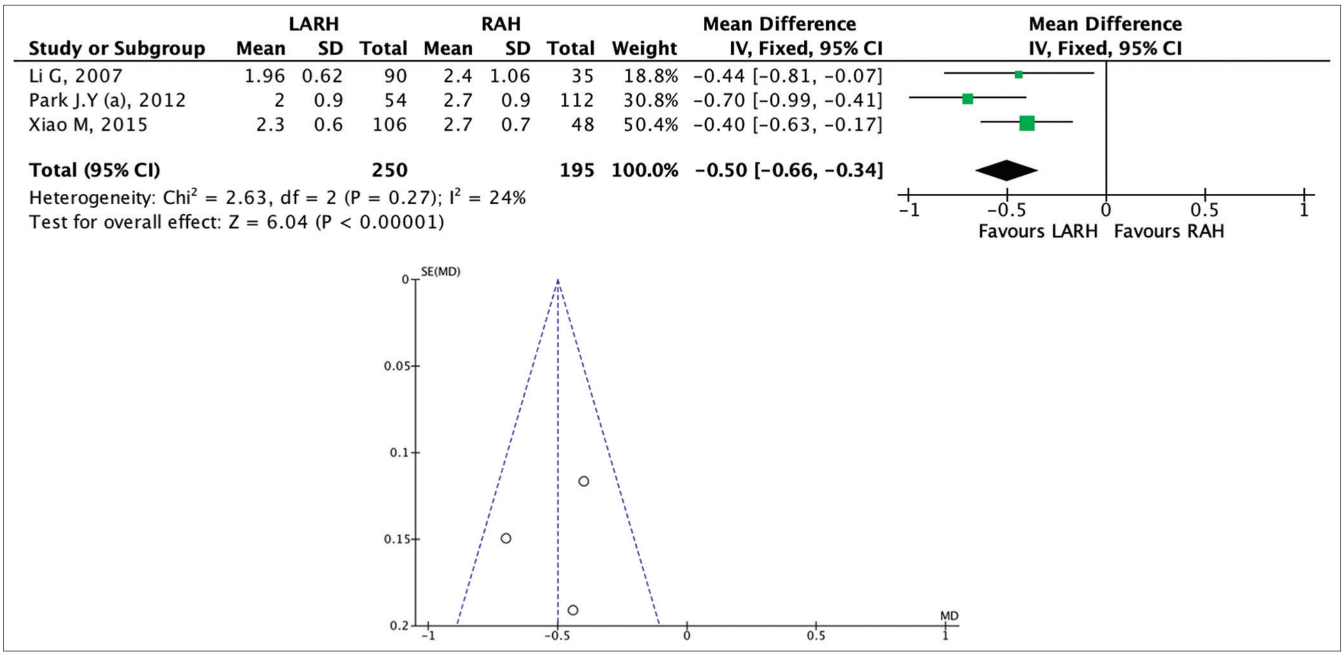

Figure 6: Forest plot of bowel recovery time
LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy

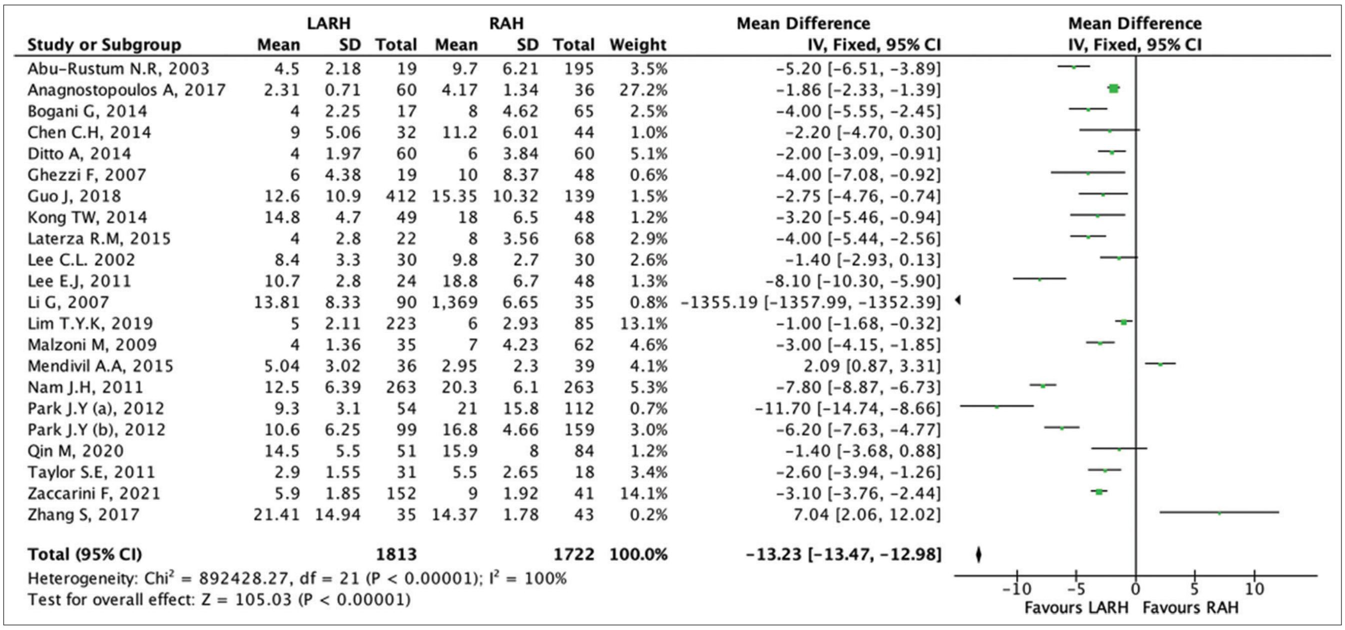

Figure 7: Forest plot of length of stay post operative
LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy

operative time and lower number of lymph node retrieved.

In general, LRH is considered to be associated with better recovery, smaller scar, and faster back to normal life than ARH. Some comparative studies have reported that survival out-come and perioperative complications after LRH are comparable to those after ARH in patients with uterine cervical cancer. The Laparoscopic Approach to Carcinoma of the Cervix (LACC) trial which was a multicenter and randomized controlled trial (RCT) [49] evaluating the oncological outcomes between MIS and open abdominal radical hysterectomy demonstrated that minimally invasive radical hysterectomy such as LRH was associated with lower rates of overall survival and higher recurrence compared to ARH. The LACC trial has been conflicting with a long-standing consensus that minimally invasive and open surgery is both acceptable approaches to radical hysterectomy for cervical cancer [50].

A study conducted in Korea, using the Korean nationwide database to identify women with cervical cancer who underwent radical hysterectomy from, 2011 to 2014 [51]. The study showed an opposite result, LRH was associated with better overall survival with a hazard ratio of 0.52. The study also showed lower rates of complications and lower cost of care, this study is the largest cohort study which included more than 6000 patients in 4 years. Whereas, a multicenter LACC trial recruited only 630 patients in 10 years. Patients who underwent LRH had a lower risk of intraoperative complications, post-operative complications, and surgical site complications even after propensity matching. This may due to an important benefit of minimally invasive surgery is lower rates of perioperative morbidity. Numerous retrospective studies comparing LRH and laparotomy for cervical cancer have consistently shown lower complication rates [52].

As LRH was associated with a lower risk of complications, this benefit may translate to a decrease in all-cause mortality. LRH patients significantly had lower risk of serious complication such as such as bowel obstruction, cardiopulmonary arrest, renal failure, and sepsis, than with abdominal radical hysterectomy [52]. There is a different story in the setting of cervical cancer patients with tumor size above 2 cm and there are several studies which confirmed that laparoscopic surgery has a worse survival rate than open surgery. Melamed, *et al.*, found that MIS was associated with a higher risk of death than open surgery for patients with tumor size ≥2 cm (HR = 1.66, 95% CI: 1.19–2.30) [52]. Other study was also found who underwent minimally invasive surgery had significantly worse progression-free survival than those in the open surgery group with tumor size >2 cm and ≤4 cm (p = 0.044), that the harm associated with this approach is said may be independent of surgeon experience [53], [54].

There is still back and forth regarding which is safer for patients with early stage cervical cancer, this study found that there was no significant difference in overall survival or in disease recurrence between LRH and ARH patients. There are several potential reasons that may account for the inferior survival outcomes of laparoscopic surgery. Some suggest that it may be because the use of uterine manipulator or because the difference approaches in handling the vaginal margin. A study showed that the recurrence rate was 16.3% in the MIS group with intracorporeal colpotomy, if compared to patients with vaginal colpotomy (5.1%, p = 0.06), and they also found that the rate of a positive surgical margin was higher in the intracorporeal colpotomy group. This may suggest avoiding tumor spillage and diminishing tumor handling during MIS may be beneficial [30]. Carbon dioxide (CO_2) also said may increase the proliferation of cervical cancer cells and cause tumor spillage, but further research still needed regarding this theory [52].

Adjuvant therapy is usually performed based on pathologic findings after the patient underwent radical hysterectomy surgery. In this study, we found that adjuvant therapy, radiation, and chemotherapy in women who underwent LRH was used less frequently. This may suggests that surgeons tend to choose laparoscopic radical hysterectomy for small volume tumors and select abdominal radical hysterectomy for large volume tumors [55].

One should note that Kim *et al.* suggest that laparoscopic radical hysterectomy was associated with a lower total cost of care within 6-month postoperatively than open radical hysterectomy. It appeared that using laparoscopic approach was the least expensive approach from a societal perspective followed by robotic and then abdominal hysterectomy. These findings might result from favorable operative outcomes, such as lower complication rates, a shorter hospital stay, and fewer blood transfusions, of laparoscopic surgery. This may be because the characteristic of the population, medical insurances, and comorbidities [52].

Limitations

Important limitations of this systematic review and meta-analysis include the possibility of bias because of residual confounding in the included studies. This study has some limitations that should be recognized when interpreting the results. First, the cohort studies might be subjected to selection bias. Second, case selection may have caused the more advanced cervical cancer cases not to be considered for LRH. We were not able to evaluate factors that may modify the association between MIS and survival outcomes between groups, such as tumor size and surgical technique used during the surgery.

Conclusion

In this systematic review and meta-analysis of, laparoscopic radical hysterectomy was as safe and effective as open abdominal hysterectomy. LRH was associated with reduced blood loss, hospital stays, and post-operative complications. In addition, it also may need lower adjuvant therapy post-operation. These results provide real-world evidence that may aid patients and clinicians engaged in shared decision-making about surgery for early-stage cervical cancer. However, the patients should also be informed about conflicting data and extensively discussed before treatment.

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Supplementary Tables

Table 1: Supplement for study design

Patients	Early stage cervical cancer patients who underwent abdominal radical hysterectomy. Laparoscopic radical hysterectomy for the primary treatment with or without lymph node dissection
Literature search	Keyword search in PubMed, Cochrane, Science Direct, and Scholar
Limits	Only comparable studies, Jan 2002–Sep 2022 In English
Keywords	Cervical cancer, cervical carcinoma, or cervical neoplasm Stage IB, Stage IB1, StageIB2, Stage IIA, or early stage cervical Cancer Radical hysterectomy Laparoscopic or laparoscopy
Eligibility criteria	Article in full text No duplicate articles Reported each of the interested outcomes: Type of publication (prospective and retrospective trial), duration of follow-up, patient characteristics (number, age, and pathological stage), intraoperative outcomes, and postoperative outcomes (mean operative time, length of hospital stay, estimated blood loss, adjuvant treatment, recurrent rate, disease free survival, or overall survival rate) Outcome reported in a usable form (each surgical approach was reported as a separate cohort, no missing or unreliable data)
Exclusion criteria	Duplicate patient population, where some or all of the same patients were included in a different study reporting on the same parameters (prevents double counting) Total sample size <10
Data extraction	Articles needed to report and contain each of outcomes of interest to be included in the analysis. Two reviewers independently reviewed titles of full article text to identify studies meeting inclusion and exclusion criteria. Discrepancies were resolved by discussion before data analysis. All primary outcomes were then double checked and any discrepancies resolved.
Primary outcomes	Recurrence of the disease Overall survival (OS) rate
Secondary outcomes	Adjuvant treatment Intraoperative outcomes Operative time Bladder dysfunction Perioperative complication Estimated blood loss Pelvic LN retrieved Hospital stay

Table 2: Supplement Risk of bias assessment

Checklist	Lee *et al.*	Li *et al.*	Lim *et al.*	Kim *et al.*	Qin *et al.*	Xiao *et al.*	Lee *et al.*	Sert *et al.*	Taylor *et al.*	Park *et al.* (a)	Park *et al.* (b)	Nam *et al.*
Selection												
Representativeness of exposed cohort	*	*	*	*	*	*	*	*	*	*	*	*
Selection of non-exposed cohort	*	*	*	*	*	*	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*	*	*	*	*	*	*
Non presence of outcome at beginning	NA	NA	*	*	*	NA	NA	NA	NA	NA	NA	NA
Comparability												
Comparability of cohorts	**	**	*	**	**	**	**	**	**	**	**	**
Outcome												
Assessment of outcome	*	*	*	*	*	*	*	*	*	*	*	*
Enough follow-up time	*	*	*	*	*	*	*	*	*	*	*	*
Adequacy of follow-up	*	*	*	*	*	*	*	*	*	*	*	*
Checklist	**Kong *et al.***	**Frumovitz *et al.***	**Toptas *et al.***	**Bogani *et al.***	**Chen *et al.***	**Ditto *et al.***	**Laterza *et al.***	**Mendivil *et al.***	**Zhang *et al.***	**Anagnostopoulos *et al.***	**Guo *et al.***	**Gil-Moreno *et al.***
Selection												
Representativeness of exposed cohort	*	*	*	*	*	*	*	*	*	*	*	*
Selection of non-exposed cohort	*	*	*	*	*	*	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*	*	*	*	*	*	*
Non-presence of outcome at beginning	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Comparability												
Comparability of cohorts	**	**	*	**	*	**	*	**	**	**	**	**
Outcome												
Assessment of outcome	*	*	*	*	*	*	*	*	*	*	*	*
Enough follow-up time	*	*	*	*	*	*	*	*	*	*	*	*
Adequacy of follow-up	*	*	*	*	*	*	*	*	*	*	*	*
Checklist	**Ghezzi *et al.***	**Zaccarini *et al.***	**Wenzel *et al.***		**Kwon *et al.***	**Abu-Rustum *et al.***		**Soliman *et al.***	**Corrado *et al.***		**Malzoni *et al.***	**Estape *et al.***
Selection												
Representativeness of exposed cohort	*	*	*		*	*		*	*		*	*
Selection of non exposed cohort	*	*	*		*	*		*	*		*	*
Ascertainment of exposure	*	*	*		*	*		*	*		*	*
Non-presence of outcome at beginning	NA	*	*		*	NA		NA	NA		NA	NA
Comparability												
Comparability of cohorts	**	**	**		**	**		**	**		*	**
Outcome												
Assessment of outcome	*	*	*		*	*		*	*		*	*
Enough follow-up time	*	*	*		*	*		*	*		*	*
Adequacy of follow-up	*	*	*		*	*		*	*		*	*

Table 3: Base characteristic of the study

Author	Year	Population			Age (year) Mean ± SD		BMI (kg/m^2) Mean ± SD		Follow-up duration (month)
		Total	LARH	RAH	LARH	RAH	LARH	RAH	
Lee *et al.*	2002	60	30	30	46.2 ± 7.2	48 ± 6.8	NR	NR	24–60
Li *et al.*	2007	125	90	35	42 ± 9	44 ± 11	NR	NR	26
Lee *et al.*	2011	72	24	48	48.4 ± 3	50.2 ± 4	23.4 ± 8.02	23.9 ± 8.65	2.49–2.5
Park *et al.*	2012	166	54	112	49.4 ± 11,5	52.1 ± 11.8	31.8 ± 1.39	31.7 ± 1.5	60
Park *et al.*	2012	258	99	159	69.4 ± 2	70 ± 8	24.13 ± 6.4	24.69 ± 6.77	60
Nam *et al.*	2011	526	263	263	NR	NR	NR	NR	24
Chen *et al.*	2014	76	32	44	51.2 ± 3	51.9 ± 2	23.2 ± 1.51	24.9 ± 9.94	NR
Xiao and Zhang	2015	154	106	48	43.7 ± 9.3	45.7 ± 11.3	23.8 ± 3.9	24.7 ± 3.8	48
Zhang *et al.*	2017	77	35	42	46.6 ± 1.92	45 ± 8.65	24.07 ± 3.3	22.68 ± 3.1	19–84
Guo *et al.*	2018	551	412	139	44.19 ± 7.49	40.52 ± 6.94	22.81 ± 1.05	23.19 ± 7.15	39
Abu-Rustum *et al.*	2003	214	19	195	42.6 ± 2.17	43.6 ± 2.69	23.1 ± 7.73	24.6 ± 1.51	NR
Ghezzi *et al.*	2007	98	50	48	47 ± 1.44	53 ± 8.69	23 ± 7.53	25 ± 5.92	10
Frumovitz *et al.*	2007	89	35	54	42.5 ± 1.05	40.8 ± 3.77	28.2 ± 1.53	28.1 ± 8.03	13
Malzoni *et al.*	2009	127	65	62	40.5 ± 7.7	42.7 ± 8.6	26 ± 0.5	29 ± 8.41	71,5
Estape *et al.*	2009	31	17	14	52.8 ± 4.23	42 ± 0.83	28.1 ± 7.03	29.5 ± 3.96	NR
Soliman *et al.*	2011	61	31	30	44.2 ± 7.4	48.1 ± 8.65	29.5 ± 4.25	26.2 ± 4.97	NR
Bogani *et al.*	2014	130	65	65	48.9 ± 1.51	50.9 ± 4.81	25.1 ± 9.15	25.9 ± 9.95	NR
Taylor *et al.*	2011	27	9	18	41.4 ± 0.59	41.1 ± 2.17	26.3 ± 4.27	26.9 ± 4.37	60
Sert and Abeler	2011	33	7	26	45 ± 7.81	44.8 ± 4.19	22.5 ± 5.96	25 ± 8.13	36
Toptas and Simsek	2014	68	22	46	46.5 ± 7.15	50 ± 1.98	22 ± 6.42	24.04 ± 7.32	42,5
Ditto *et al.*	2014	120	60	60	46 ± 1.75	45.5 ± 3.64	24.3 ± 7.61	24 ± 9.83	60
Laterza *et al.*	2015	150	82	68	43 ± 6.03	48 ± 4.34	23.44 ± 4.62	24.52 ± 3.78	44,67
Anagnostopoulos *et al.*	2017	72	36	36	44.6 ± 5.79	41.2 ± 8.79	25.8 ± 3.8	26.4 ± 4.7	36
Gil-Moreno *et al.*	2018	166	90	76	46.31 ± 11.04	50.5 ± 13.67	26 ± 1.31	26.5 ± 1.02	112,4
Mendivil *et al.*	2015	88	49	39	51.3 ± 12.47	47.8 ± 12.02	29.2 ± 6	27.9 ± 5.71	39
Corrado *et al.*	2017	153	152	101	45 ± 1.68	50 ± 8.42	23.5 ± 9.33	24.8 ± 8.9	41,7
Kong *et al.*	2014	88	40	48	45 ± 10.6	48 ± 11	22.3 ± 2.9	23.4 ± 3.3	28
Zaccarini *et al.*	2021	264	223	41	48.3 ± 11.7	51 ± 15.4	24.6 ± 4.7	27.2 ± 6	39,6
Wenzel *et al.*	2020	1109	740	369	46 ± 1.51	44 ± 2.51	25 ± 5.51	25 ± 6	49
Lim *et al.*	2019	136	51	85	47 ± 7.74	49 ± 3.1	22.9 ± 6.75	23.4 ± 7.45	27
Kim *et al.*	2020	148	38	110	51.6 ± 10.8	48.9 ± 10.1	30.82 ± 7.98	25.08 ± 2.68	42,1
Qin *et al.*	2020	256	172	84	44.3 ± 8.2	42.8 ± 8.3	23.1 ± 2.8	23.2 ± 3	59
Sert *et al.*	2021	582	229	353	42 ± 4.04	45 ± 3.29	24.18 ± 2.83	22.78 ± 1.52	74
Kwon *et al.*	2020	539	252	258	50 ± 3.86	49 ± 8.83	26.27 ± 4.35	28.05 ± 5.92	80,4
Chen *et al.*	2022	105	58	47	48.5 ± 6.57	52 ± 8.43	23.1 ± 5.24	22.7 ± 6.19	62

LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy; SD: Standard deviation; NR: Not reported.

Table 4: Staging characteristics in the study

Author	Year	LARH					RAH				
		IA2	IB	IB1	IB2	IIA	IA2	IB	IB1	IB2	IIA
Lee *et al.*	2002	NR	17	NR	NR	13	NR	19	NR	NR	11
Li *et al.*	2007	NR	72	NR	NR	18	NR	22	NR	NR	13
Lee *et al.*	2011	5	15	13	2	4	10	NR	26	4	8
Park *et al.*	2012	2	47	45	2	5	3	NR	81	13	15
Park *et al.*	2012	10	82	74	8	7	5	NR	123	6	25
Nam *et al.*	2011	36	223	197	26	5	40	NR	194	21	8
Chen *et al.*	2014	27	NR	NR	NR	5	34	NR	NR	NR	10
Xiao and Zhang	2015	15	75	NR	NR	15	1	35	NR	NR	11
Zhang *et al.*	2017	2	28	20	8	8	4	NR	13	20	6
Guo et al	2018	35	331	NR	NR	46	12	105	NR	NR	22
Abu-Rustum *et al.*	2003	6	NR	11	NR	NR	24	NR	162	NR	NR
Ghezzi *et al.*	2007	7	36	30	6	7	2	NR	26	13	7
Frumovitz *et al.*	2007	8	43	42	1	NR	2	NR	28	NR	NR
Malzoni *et al.*	2009	39	NR	NR	11	NR	48	NR	NR	39	NR
Estape *et al.*	2009	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Soliman *et al.*	2011	20	NR	NR	4	NR	20	NR	NR	20	NR
Bogani *et al.*	2014	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Taylor *et al.*	2011	6	NR	NR	6	NR	12	NR	NR	6	NR
Sert and Abeler	2011	5	NR	NR	2	NR	23	NR	NR	5	NR
Toptas and Simsek	2014	13	NR	NR	39	NR	7	NR	NR	13	NR
Ditto *et al.*	2014	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Laterza *et al.*	2015	53	NR	3	2	NR	53	NR	4	53	NR
Anagnostopoulos *et al.*	2017	33	NR	2	NR	NR	36	NR	NR	33	NR
Gil-Moreno *et al.*	2018	33	34	6	3	NR	17	46	8	33	34
Mendivil *et al.*	2015	15	13	7	4	NR	18	15	9	15	13
Corrado *et al.*	2017	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kong *et al.*	2014	22	12	6	NR	NR	27	14	7	22	12
Zaccarini *et al.*	2021	NR	NR	12	5	32	NR	NR	NR	NR	NR
Wenzel *et al.*	2020	711	NR	26	4	NR	358	NR	7	711	NR
Lim *et al.*	2019	39	3	NR	NR	NR	62	14	2	39	3
Kim *et al.*	2020	69	26	5	NR	NR	10	19	3	69	26
Qin *et al.*	2020	155	NR	NR	3	NR	80	NR	NR	155	NR
Sert *et al.*	2021	156	36	NR	30	NR	200	94	NR	156	36
Kwon *et al.*	2020	119	125	NR	13	NR	108	137	NR	119	125
Chen *et al.*	2022	38	3	8	2	NR	29	8	7	38	3

LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy; NR: Not reported.

Table 5: Histology characteristics of the study

Author	Year	LARH			RAH		
		SCC	Adenocarcinoma	Other	SCC	Adenocarcinoma	Other
Lee *et al.*	2002	27	3	NR	25	5	NR
Li *et al.*	2007	81	5	4	25	4	6
Lee *et al.*	2011	19	4	1	38	8	2
Park *et al.*	2012	39	11	4	91	16	5
Park *et al.*	2012	92	7	NR	145	14	NR
Nam *et al.*	2011	214	41	8	207	46	10
Chen *et al.*	2014	26	5	1	33	10	1
Xiao and Zhang	2015	96	6	4	42	5	1
Zhang *et al.*	2017	32	3	NR	40	2	NR
Guo *et al.*	2018	340	72	NR	110	29	NR
Abu-Rustum *et al.*	2003	10	7	2	132	55	8
Ghezzi *et al.*	2007	38	7	5	33	13	2
Frumovitz *et al.*	2007	15	17	3	33	16	5
Malzoni *et al.*	2009	56	7	2	53	6	3
Estape *et al.*	2009	NR	NR	NR	NR	NR	NR
Soliman *et al.*	2011	16	12	3	13	16	1
Bogani *et al.*	2014	20	45	NR	22	43	NR
Taylor *et al.*	2011	5	4	NR	11	7	NR
Sert and Abeler	2011	5	2	NR	19	6	1
Toptas and Simsek	2014	18	1	3	29	5	12
Ditto *et al.*	2014	NR	NR	NR	NR	NR	NR
Laterza *et al.*	2015	NR	NR	NR	NR	NR	NR
Anagnostopoulos *et al.*	2017	25	11	NR	20	16	NR
Gil-Moreno *et al.*	2018	57	27	6	47	23	6
Mendivil *et al.*	2015	38	9	2	27	5	7
Corrado *et al.*	2017	110	37	5	68	23	10
Kong *et al.*	2014	30	7	3	39	7	2
Zaccarini *et al.*	2021	148	60	15	26	10	5
Wenzel *et al.*	2020	490	214	36	248	107	14
Lim *et al.*	2019	21	25	5	50	27	8
Kim *et al.*	2020	NR	NR	NR	NR	NR	NR
Qin *et al.*	2020	132	35	5	72	8	4
Sert *et al.*	2021	141	81	7	221	120	12
Kwon *et al.*	2020	185	62	5	180	70	8
Chen *et al.*	2022	33	18	7	33	12	2

LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy; NR: Not reported; SCC: Squamous cell carcinoma.

AQ6 **Table 6: Intraoperative characteristics in the study**

Author	Year	Pelvic in resected		p	OP time (min)		p	EST blood loss (ml)		p
		LARH	RAH		LARH	RAH		LARH	RAH	
Lee *et al.*	2002	15.3	22	0.001	221	206	0.16	450	962	<0.001
Li *et al.*	2007	21.28	18.77	0.15	262.99	217.2	0.001	369.78	455.14	0.12
Lee *et al.*	2011	26.3	26.8	NR	334.8	326.8	NA	414.3	836	<0.001
Park *et al.*	2012	33.4	32.2	0.5	271	270	0.98	494	620	0.009
Park *et al.*	2012	29.8	29.4	0.55	253.8	271.9	0.035	433.6	605.2	0.014
Nam *et al.*	2011	34.3	30.6	0.001	246.8	247.2	0.98	379.6	541.1	<0.001
Chen *et al.*	2014	29.7	27.8	0.82	245	259	<0.05	200	500	<0.05
Xiao and Zhang	2015	20.5	24.3	0.008	270.8	310.2	0.02	232.6	797.9	<0.001
Zhang *et al.*	2017	36.19	23.71	<0.05	169.33	182.74	NR	861.91	502.86	<0.05
Guo *et al.*	2018	24.35	20.24	<0.001	238.177	258.94	0.01	292.78	439.89	<0.001
Abu-Rustum *et al.*	2003	25.5	30.7	0.08	371	296	<0.01	301	693	<0.01
Ghezzi *et al.*	2007	21	23	0.07	250	232	0.8	185	450	<0.001
Frumovitz *et al.*	2007	18.7	13.5	0.001	307	344	0.03	548	319	0.009
Malzoni *et al.*	2009	23.5	25.2	<0.01	196	152	<0.01	55	145	<0.1
Estape *et al.*	2009	18.6	25.7	<0.001	132	114	NR	209	621.4	NR
Soliman *et al.*	2011	15.6	19	0.26	338	265	0.002	100	350	<0.001
Bogani *et al.*	2014	23.3	27.4	0.13	245	259.5	0.26	200	500	<0.01
Taylor *et al.*	2011	11.2	13.9	0.23	231.7	207.2	0.43	161.1	394.4	0.059
Sert and Abeler	2011	15.4	26.1	NR	364.2	163.4	<0.001	164.2	295	<0.005
Toptas and Simsek	2014	28	32	NR	NR	NR	NR	NR	NR	NR
Ditto *et al.*	2014	25.4	34.6	<0.001	215.9	175.2	<0.01	20	200	<0.001
Laterza *et al.*	2015	20	31	0.001	NR	NR	NR	100	400	<0.001
Anagnostopoulos *et al.*	2017	12.6	16.9	<0.05	206	159	<0.05	189	934	<0.05
Gil-Moreno *et al.*	2018	19	20	0.8	289	244.87	<0.0001	291.63	502.63	<0.001
Mendivil *et al.*	2015	12.8	11.2	NR	143.4	106.8	<0.001	475	312	<0.0001
Corrado *et al.*	2017	20	28	0.01	195	195	0.21	100	190	0.01
Kong *et al.*	2014	22.7	21.5	0.14	254.5	246	0.589	449.1	588	<0.001
Zaccarini *et al.*	2021	NR	NR	NR	228	278	0.17	NR	NR	NR
Lim *et al.*	2019	23	24	0.43	262	228	<0.001	300	500	0.002
Qin *et al.*	2020	NR	NR	NR	176.9	248.8	<0.001	200.9	670.2	<0.001

LARH: Laparoscopic radical hysterectomy; RAH: Radical abdominal hysterectomy; NR: Not reported; SCC: Squamous cell carcinoma.

Author Queries???
AQ5: Kindly provide significant value
AQ6: Kindly cite supplementary table 6 in the text part