Comparison of Minimally Invasive Versus Abdominal Radical Hysterectomy for Early-Stage Cervical Cancer: An Updated Meta-Analysis

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Background: Although minimally invasive surgery (MIS) was commonly used to treat patients with early-stage cervical cancer, its efficacy remained controversial.

Methods: We systematically searched PubMed, Web of Science, and Cochrane Library databases until March 2021 to compare the prognosis of early-stage cervical cancer patients who underwent MIS (laparoscopic or robot-assisted radical hysterectomy) or ARH. The primary outcomes included rates of 3- and 5-year disease-free survival (DFS) and overall survival (OS). The study protocol was registered in PROSPERO: CRD42021258116.

Results: This meta-analysis included 48 studies involving 23346 patients (11220, MIS group; 12126, ARH group). The MIS group had a poorer medium-term (3-year) DFS (HR=1.08, 95% CI: 1.01-1.16, p=0.031) than the ARH group, without significant difference in medium-term OS as well as long-term (5-year) DFS and OS. Subgroup analysis of 3-year prognosis revealed that although patients in Western countries who underwent MIS had shorter DFS than those who underwent ARH (HR=1.10, p=0.024), no difference was observed in DFS among those in Asian countries. Moreover, MIS was linked to poorer 3-year DFS in patients with stage I cervical cancer (HR=1.07, p=0.020).

Notably, subgroup analysis of 5-year prognosis revealed that patients with tumor size ≥2 cm undergoing MIS exhibited a shorter DFS than those who underwent ARH (HR=1.65, p=0.041).

Conclusion: Patients with early-stage cervical cancer undergoing MIS may have a poorer prognosis than those undergoing ARH. Therefore, applying MIS in early-stage cervical cancer patients should be conducted with caution.

Systematic Review Registration: The study protocol was registered in PROSPERO: CRD42021258116.

Keywords: abdominal radical hysterectomy, early-stage cervical cancer, prognosis, meta-analysis, minimally invasive surgery
INTRODUCTION

Cervical cancer was ranked as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women. Most of these cases occurred in sub-Saharan Africa, Melanesia, South America, and South-Eastern Asia, with the highest morbidity and mortality rates in sub-Saharan African (1). Surgery was the primary treatment option for early-stage cervical cancer to treat stage IA, IB1, and selected IIA1 cases (2). Conization alone or simple hysterectomy was an appropriate treatment option for patients with stage IA disease, whereas radical hysterectomy was the preferred treatment modality for stage IB1 or IIA1 patients (3). Abdominal radical hysterectomy (ARH) was a standard and historical treatment for early-stage cervical cancer (4, 5). As the research progressed, minimally invasive surgery (MIS) became the preferred treatment option for early-stage cervical cancer over the past two decades (6, 7).

The feasibility and safety of MIS (laparoscopic or robot-assisted radical hysterectomy) were gradually widely accepted (7, 8). Several retrospective studies and reviews (9–11) highlighted MIS benefits in reducing blood loss, shortening hospital stay, accelerating recovery time, and reducing the risk of postoperative complications, with equal survival outcomes as ARH. Nevertheless, preliminary results from a phase 3 multicenter randomized controlled trial (RCT) (12), presented at the Society of Gynecological Oncology (SGO) meeting in March 2018, indicated that early-stage cervical cancer patients undergoing MIS had a lower disease-free survival (DFS) and overall survival (OS) than those undergoing ARH. The RCT results were unexpected and sparked a huge debate (2). Since then, the guidelines from National Comprehensive Cancer Network (NCCN) (2) and International Federation of Gynecology and Obstetrics (FIGO) (13) have been revised to indicate that ARH remains the gold standard for treating early-stage cervical cancer.

Consequently, the comparison of prognosis between MIS and ARH in patients with early-stage cervical cancer remains controversial. Then, some clinical trials and reviews (14–17) demonstrated that patients with early-stage cervical cancer who underwent MIS or ARH had similar OS, but those who underwent MIS exhibited shorter DFS. Therefore, we performed a meta-analysis of available evidence to compare and evaluate medium- (3-year) and long-term (5-year) survival outcomes in patients with early-stage cervical cancer who underwent MIS or ARH.

METHODS

Search Strategy
We conducted a systematic search of PubMed, Web of Science, and Cochrane Library to identify relevant reports published from inception until March 2021. The search terms included (uterine cervical neoplasms OR cervical cancer OR cervix cancer OR cervical carcinoma) AND (minimally invasive OR laparoscopic OR robotic OR robot-assisted OR Davinci) AND (open OR abdominal OR traditional) AND (radical hysterectomy OR surgery OR hysterectomy OR surgical procedure OR operation). Additionally, potential studies were identified by manually searching the references of included articles. From the initial search to the final selection of studies, the entire review process was mapped using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram. The study protocol was registered in PROSPERO: CRD42021258116.

Eligible Criteria
The included studies met the following criteria: (1) the articles were observational studies or RCTs comparing patients with early-stage cervical cancer who underwent MIS (laparoscopic and/or robot-assisted radical hysterectomy) or ARH. (2) The studies contained detailed data on prognosis (DFS and OS) for patients with early-stage cervical cancer. (3) At least 3-year survival data was provided in the study. (4) The articles were published in English.

Data Extraction and Quality Assessment
Two independent researchers extracted data from each relevant article, and a third researcher arbitrated disagreements. We recorded information on author, year of publication, country, age, number of patients, study design, MIS type, primary FIGO tumor stage, tumor size, pathologic type, lymph node metastasis, lymph-vascular space invasion, tumor differentiation, and follow-up time. Additionally, this meta-analysis used medium- and long-term prognosis endpoints, including 3- and 5-year DFS and OS. Following that, the methodological quality of included RCTs and observational studies was assessed using Cochrane Collaboration’s tool and Newcastle-Ottawa Quality Assessment Scale, respectively.

Statistical Analysis
All statistical analyses were performed using Stata 12.0 (18). Medium- and long-term prognoses in MIS and ARH groups were analyzed using a hazard ratio (HR) with a 95% confidence interval (95% CI) (19). Moreover, heterogeneity of HR was assessed based on I² statistics. Due to differences in study design and surgical treatment, a random-effects model was used to improve the credibility of results. Furthermore, Egger’s test used p<0.05 as the significance level to evaluate publication bias (20). Sensitivity analysis for the stability of results was performed. All statistical tests were two-sided, and p<0.05 was considered statistically significant.

Abbreviations: MIS, minimally invasive surgery; ARH, Abdominal radical hysterectomy; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; RCT, randomized controlled trial.
RESULTS

Characteristics of Eligible Research
The initial search resulted in 2600 relevant studies from different electronic databases. Following screening, 48 studies (10–12, 14–17, 21–61) encompassing 23346 patients fulfilled the inclusion criteria. The detailed screening process of articles is summarized in Figure 1. The basic characteristics of selected studies are listed in Table 1. Two studies were RCTs (12, 29), and the remaining were observational studies (10, 11, 14–17, 21–28, 30–61) (n=46). Three treatment modalities were adopted by contrast: MIS (laparoscopic radical hysterectomy plus robot-assisted radical hysterectomy) versus ARH (involved 10 studies), and robot-assisted radical hysterectomy versus ARH (involved 10 studies). Of 48 studies, 23 were conducted in Asian countries and 24 in Western countries. The remaining study was conducted in both Asian and Western countries. Among the studies conducted in Asian countries, 11 were conducted in China, 10 in Korea, 1 in Singapore, and 1 in Turkey. Of the studies conducted in Western countries, 7 were conducted in America, 1 in Brazil, 1 in Canada, 1 in Denmark, 1 in France, 4 in Italy, 3 in multicenters, 2 in the Netherlands, 1 in Poland, 1 in Spain, 1 in Sweden, and 1 in the United Kingdom. All studies were published between 2004 and 2021. In these eligible studies, the number of patients was a minimum of 14 and a maximum of 1305. Almost all patients underwent hysterectomy versus ARH (involved 31 studies), and robot-assisted radical hysterectomy versus ARH (involved 10 studies). Of 48 studies, 23 were conducted in Asian countries and 24 in Western countries. Among the studies conducted in Asian countries, 11 were conducted in China, 10 in Korea, 1 in Singapore, and 1 in Turkey. Of the studies conducted in Western countries, 7 were conducted in America, 1 in Brazil, 1 in Canada, 1 in Denmark, 1 in France, 4 in Italy, 3 in multicenters, 2 in the Netherlands, 1 in Poland, 1 in Spain, 1 in Sweden, and 1 in the United Kingdom. All studies were published between 2004 and 2021. In these eligible studies, the number of patients was a minimum of 14 and a maximum of 1305. Almost all patients were diagnosed with FIGO stage IA-IIA cervical cancer. In addition, the proportion of patients with tumor size ≥2 cm ranged from a minimum of 18.8% to a maximum of 78.6%. Squamous cell carcinoma was the most common pathological type of cervical cancer in our study. Additional details of included studies are presented in Supplementary Table 1.

Quality Assessment
Cochrane collaboration’s tool was employed to assess the quality of RCT enrolled in the study. For observational studies, quality assessment was performed based on the Newcastle-Ottawa Quality Assessment Scale, and only high-quality studies with a total score ≥6 were included in the final analysis. Details on quality assessment are displayed in Supplementary Table 2.

Prognostic Analysis
Random effect analysis of 14 of 48 reports on 3-year DFS encompassing 7003 patients with early-stage cervical cancer revealed a statistically significant difference, suggesting that the MIS group had a shorter 3-year DFS than the ARH group (HR=1.08, 95% CI: 1.01-1.16, p=0.031; Figure 2). Besides, 14 studies involving 7118 patients with early-stage cervical cancer were assessed for 3-year OS, without observing a significant difference in 3-year OS between MIS and ARH groups (HR=1.09, 95% CI: 0.99-1.20, p=0.082; Figure 3).

There were 32 studies that provided 5-year DFS, including 13025 patients with early-stage cervical cancer. Among them, there were 6471 cases in the MIS group and 6312 cases in the ARH group. The results revealed that MIS had no significant effect on long-term DFS in patients with early-stage cervical cancer compared with ARH (HR=1.02, 95% CI: 0.98-1.07, p=0.266; Figure 4). Moreover, 15551 patients were evaluated for 5-year OS in 32 studies. The results illustrated that long-term OS of patients undergoing MIS was similar to that of patients undergoing ARH (HR=1.01, 95% CI: 0.97-1.05, p=0.795; Figure 5).

Subgroup Analysis of 3- and 5-Year Survival
Of 14 studies that provided 3-year DFS, a subgroup analysis was performed on cervical cancer stage, including nine studies for stage I (HR=1.07, 95% CI: 1.01-1.14, p=0.020) and five studies for IA-IB1 (HR=1.23, 95% CI: 1.02-1.49, p=0.034). Patients with stages I and IA-IB1 who underwent MIS had a poorer 3-year DFS than those with ARH. Additionally, five studies were conducted in Western countries (HR=1.10, 95% CI: 1.01-1.20, p=0.024), whereas eight studies were conducted in Asian countries (HR=1.04, 95% CI: 0.96-1.12, p=0.381). Overall, the pooled subgroup results demonstrated that in Western countries, patients treated with MIS exhibited a significantly shorter 3-year DFS than those treated with ARH. Nevertheless, in studies of Asian countries, no difference in DFS was observed between MIS and ARH groups. Regarding patients with tumor size <2 cm, a subgroup analysis revealed no statistically significant difference in 3-year DFS between both groups (HR=1.04, 95% CI: 0.98-1.09, p=0.186) (Table 2).

Likewise, there were 14 studies that reported 3-year OS, with nine reporting stage I (HR=1.06, 95% CI: 0.99-1.14, p=0.096), five reporting stage IA-IB1 (HR=1.42, 95% CI: 0.71-2.85, p=0.321) and three reporting stage IB1-II (HR=1.02, 95% CI: 0.92-1.13, p=0.689). The subgroup analysis indicated that compared with patients undergoing ARH, no statistical difference was observed in 3-year OS in patients with stage I, IA-IB1, and IB1-II cervical
TABLE 1 | Characteristics of all studies included in the meta-analysis.

| Author Year | Group | Country | Tumor stage (FIGO) | Patients number | Tumor size (% ≥2cm) | Pathologic type (%) |
|-------------|-------|---------|-------------------|-----------------|---------------------|---------------------|
|             |       |         |                   |                 | MIS | Control | MIS | Control | MIS | Control | MIS | Control |
|             |       |         |                   |                 | SCC | ACC | ASC | Other | SCC | ACC | ASC | Other |
| Li 2021     | MIS   | Korea   | IA-I/IIA          | 282             | 51.8 | 59.6 | 62.4 | 31.6 | 3.9 | 2.1 | 68.6 | 24.6 | 4.6 | 2.1 |
| Kim 2021    | MIS   | Korea   | IA-I/IIA1         | 67              | 34.3 | 31.8 | 76.1 | 22.4 | 1.5 | 0.0 | 68.2 | 27.3 | 4.5 | 0.0 |
| Kim 2021    | MIS   | Korea   | IB-I/IIA2         | 110             | 70.0 | NA | 25.5 | 4.5 | 0.0 | 71.1 | 26.3 | 2.6 | 0.0 |
| Zaccarini 2021 | MIS   | French  | IA-II/B           | 223             | 66.4 | 26.9 | 0.0 | 6.7 | 63.4 | 24.4 | 0.0 | 12.2 |
| Chiva 2020  | MIS   | European | IB1               | 291             | 43.3 | 60.2 | NA | NA | NA | NA | NA | NA | NA |
| Levine 2020 | MIS   | America  | IA-I/II-B         | 82              | 42.7 | 54.5 | 43.9 | 47.6 | 8.5 | 0.0 | 65.9 | 27.3 | 6.8 | 0.0 |
| Upal 2020   | MIS   | America  | IA-I/II-B         | 560             | 55.0 | 40.7 | 4.3 | 0.0 | 60.0 | 35.7 | 4.3 | 0.0 |
| Gil-Moreno 2019 | MIS | Spain | IA-I/II-B | 112 | 60.7 | 33.9 | 0.0 | 5.4 | 61.8 | 30.2 | 0.0 | 7.8 |
| Cusimano 2019 | MIS | Canada | IA-II             | 473             | 51.6 | 48.4 | NA | NA | 56.1 | 43.9 |
| Ramirez 2018 | MIS | multicenter | IA-I/II-B     | 319             | 67.1 | 27.3 | 2.8 | 2.8 | 67.3 | 25.6 | 1.9 | 5.10 |
| Campos 2021 | LRH   | Brazil   | IA-I/II-B         | 16              | 65.0 | 31.1 | 3.9 | 0.0 | 67.0 | 28.1 | 4.9 | 0.0 |
| Rodriguez 2021 | LRH | multicenter | IA-I/II-B    | 681             | 26.5 | 27.8 | 65.0 | 31.1 | 3.9 | 2.1 | 67.0 | 28.1 | 4.9 | 0.0 |
| Li 2021     | LRH   | China    | IB1               | 574             | NA | NA | 82.4 | 15.2 | 2.4 | 0.0 | 85.2 | 11.5 | 3.3 | 0.0 |
| Dai 2020    | LRH   | China    | IB                | 213             | NA | NA | 75.6 | 22.5 | 1.9 | 0.0 | 68.5 | 27.2 | 4.2 | 0.0 |
| Abe 2020    | LRH   | America  | II                | 410             | 76.6 | 78.6 | NA | NA | NA | NA | NA | NA | NA |
| Kwon 2020   | LRH   | Korea    | IA-I/II-B         | 252             | 73.4 | 24.6 | 0.0 | 2.0 | 69.8 | 27.1 | 0.0 | 3.1 |
| Qin 2020    | LRH   | China    | IA-I/II-B         | 172             | 29.7 | 35.7 | 76.8 | 20.3 | 2.9 | 0.0 | 85.7 | 9.5 | 4.8 | 0.0 |
| Hu 2020     | LRH   | China    | IA-I/II-B/IIA1    | 406             | 88.0 | 9.1 | 1.7 | 1.2 | 88.9 | 8.4 | 1.5 | 1.2 |
| Chen 2020   | LRH   | China    | IB1               | 129             | 79.8 | 14.7 | 3.1 | 2.3 | 84.2 | 11.7 | 3.1 | 1.0 |
| Wenzel 2020 | LRH   | Netherlands | IA-I/II-A     | 369             | 67.0 | 29.0 | 4.0 | 0.0 | 66.0 | 29.0 | 5.0 | 0.0 |
| Pedone 2020 | LRH   | Italy    | IA-I/II-B        | 206             | 67.5 | 32.5 | 65.0 | 35.0 |
| Anchora 2019 | LRH | China | IB-II/III-B      | 217             | 86.6 | 11.5 | 1.8 | 0.0 | 89.4 | 5.0 | 5.6 | 0.0 |
| Wang 2019   | LRH   | China    | IA-I/II-B         | 99              | 50.5 | 53.5 | 82.8 | 14.1 | 3.1 | 0.0 | 82.8 | 13.1 | 4.1 | 0.0 |
| Yuan 2019   | LRH   | China    | IA-I/II-A2        | 222             | 66.7 | 27.9 | 5.4 | 0.0 | 75.2 | 18.9 | 5.9 | 0.0 |
| Kim 2019    | LRH   | Korea    | IB                | 119             | 68.9 | 31.1 | 0.0 | 0.0 | 72.0 | 28.0 | 0.0 | 0.0 |
| Paik 2019   | LRH   | Korea    | IB-I/II-A1        | 271             | 80.1 | 15.9 | 4.0 | 0.0 | 88.1 | 8.9 | 3.0 | 0.0 |
| Liu 2019    | LRH   | China    | IB                | 51              | 41.2 | 49.0 | 3.9 | 5.9 | 58.8 | 31.8 | 3.5 | 5.9 |
| Lim 2019    | LRH   | Singapore | IA-I/II-B       | 412             | 82.5 | 17.5 | 79.1 | 20.9 |
| Guo 2018    | LRH   | China    | IA-I/II-B        | 152             | 72.3 | 24.3 | 0.0 | 3.4 | 67.3 | 22.8 | 5.9 | 4.0 |

(Continued)
In addition, six studies were conducted in Western countries (HR=1.04, 95% CI: 0.95-1.14, \(p=0.36\)), while the remaining seven were conducted in Asian countries (HR=1.12, 95% CI: 0.96-1.31, \(p=0.134\)). Additionally, a subgroup analysis based on tumor size revealed that compared with patients undergoing ARH, those with early-stage cervical cancer undergoing MIS included tumor size <2 cm (HR=1.01, 95% CI: 0.98-1.05, \(p=0.441\)) and tumor size \(\geq 2\) cm (HR=2.26, 95% CI: 0.64-7.94, \(p=0.203\)), but no statistically significant difference was observed in 3-year OS (Table 2).

Of 32 studies on 5-year DFS, 16 were for stage I cervical cancer (HR=1.03, 95% CI: 0.98-1.09, \(p=0.247\)), 13 were for...
stage IA-IB1 (HR=1.04, 95% CI: 0.99-1.09, p=0.157), and 12 were for stage IB1-II (HR=1.06, 95% CI: 0.99-1.13, p=0.111). A total of 17 of 32 studies were conducted in Western countries (HR=1.03, 95% CI: 0.98-1.07, p=0.243), whereas 15 studies were conducted in Asian countries (HR=1.03, 95% CI: 0.92-1.17, p=0.53). All above subgroup analyses revealed that MIS was not linked to long-term DFS in patients with early-stage cervical cancer. Notably, for early-stage cervical cancer patients with tumor size ≥2 cm, the pooled results disclosed that the MIS group may have a significantly shorter 5-year DFS than ARH group (HR=1.65, 95% CI: 1.02-2.66, p=0.041) (Table 2).

5-year OS was assessed in 32 studies, including 16 for stage I cervical cancer (HR=1.01, 95% CI: 0.96-1.06, p=0.665), 13 for stage IA-IB1 (HR=1.01, 95% CI: 0.97-1.05, p=0.626), 14 for stage IB1-II (HR=1.01, 95% CI: 0.97-1.06, p=0.606), and 2 for stage II (HR=1.03, 95% CI: 0.88-1.20, p=0.745). Moreover, 18 of 32 studies were performed in Western countries (HR=1.02, 95% CI: 0.95-1.10, p=0.597), while the remaining studies (n=14) were conducted in Asian countries (HR=1.00, 95% CI: 0.96-1.04, p=0.665).
Briefly, in the above subgroup analyses, the results revealed that MIS was not correlated with 5-year OS in patients with early-stage cervical cancer. Additionally, subgroup analyses of 5-year OS were performed for patients with various tumor sizes. According to the results for patients with tumor size <2 cm, long-term OS was not statistically different between the MIS and ARH groups (HR=1.03, 95% CI: 0.98-1.07, p=0.25). Although patients with tumor size ≥2 cm undergoing MIS had a poorer long-term OS than those undergoing ARH, the difference was not statistically significant (HR=1.76, 95% CI: 0.97-3.19, p=0.063) (Table 2).

**DISCUSSION**

Academics had cast doubt on previous surgical findings following the publication of 2018 Laparoscopic Approach to Cervical Cancer (LACC) trial. Additionally, the impact of MIS and ARH on the prognosis of patients with early-stage cervical cancer has been controversial. The RCT findings (12) revealed that MIS was associated with poorer DFS and OS than ARH, but some limitations were found. On the one hand, the trial of patients in the MIS group was terminated prematurely, and some patients received insufficient follow-up time. On the other hand, the results were inapplicable to assessing survival outcomes in “low-risk” cervical cancer patients. Moreover, the trial lacked specific preoperative imaging and central pathology (62). As a result, this meta-analysis systematically evaluated and compared prognosis (3- and 5-year DFS and OS) of patients with early-stage cervical cancer in MIS and ARH groups, and subgroup analyses of associated factors were conducted.

Our meta-analysis included 48 studies with 23346 patients. Based on evaluating 3-year prognosis, the results revealed that patients with early-stage cervical cancer undergoing MIS had a poorer 3-year DFS than those undergoing ARH, without observing a statistical difference in 3-year OS. In a multi-institution retrospective study, Uppal et al. (15) indicated that patients undergoing MIS had a poorer DFS, but no difference was observed in OS compared to those undergoing ARH, consistent with our findings. Meanwhile, subgroup analyses of tumor stage, region, and tumor size were performed on a 3-year prognosis. The pooled results of 3-year prognosis revealed that patients with stage I cervical cancer undergoing MIS exhibited poorer DFS than those undergoing ARH. Similarly, the pooled results in 3-year DFS demonstrated that patients with stage IA-IB1 and Western countries undergoing MIS indicated a shorter DFS than those undergoing ARH. Besides, no significant difference was observed in other subgroup analyses. For patients with stage I and IA-IB1, the poor results may be influenced by the frequency of the use of postoperative adjuvant therapy. In a Norwegian study (63), the incidence of postoperative radiotherapy was low in the MIS and ARH groups (6.1% vs. 12.5%). This study indicated that early-stage cervical cancer patients with stage IB1 and tumor size <2 cm who...
underwent MIS had significantly worse DFS than those with ARH. Nevertheless, a population-based study from Denmark (FIGO Stage IA2-IB1) (61) and a population-based study from Sweden (FIGO Stage IA1-IB1) (58) indicated a relatively high incidence of adjuvant therapy in the MIS and ARH groups (21.9% vs. 31.9%; 30.6% vs. 31.9%, respectively), with no difference in survival outcomes between the two groups. Since there was no difference in surgical techniques among the 3 closely related countries, it was tempting to speculate that the use of adjuvant radiotherapy had an impact on the survival outcomes. This speculation needs to be further confirmed. For patients from Western countries, DFS of MIS group was obviously inferior to that of ARH group. There was no clear explanation for this result. We suspected that it may be related to the different types of adjuvant therapy available in different geographic areas. Additionally, the frequency of use of adjuvant treatment in a study may influence the result. The relatively high number of patients receiving adjuvant therapy was likely to reduce the difference in survival between the two groups. NCCN guidelines (2) stated that for patients with stage IA2, IB1, or IIA1 who had negative lymph nodes after surgery but had other risk factors, pelvic external-beam radiation therapy was recommended with (or without) concurrent chemotherapy. A multicenter retrospective study from some Western countries (30) implicated that the incidence of postoperative adjuvant therapy was lower in the MIS group and the ARH group (29.2% vs. 30.7%), and the MIS group had worse prognosis after adjuvant therapy adjustment. By contrast, in a multi-center retrospective study from China (31), postoperative adjuvant therapy consisted of chemotherapy, radiotherapy or chemoradiotherapy. The study implicated that the incidence of postoperative adjuvant therapy was relatively high in the MIS and ARH groups (57.7% vs. 59.6%), with no significant difference between the two groups. Unfortunately, additional confirmation is required due to the scarcity of studies on adjuvant therapy and prognosis.

Likewise, 5-year prognosis was assessed in patients with early-stage cervical cancer. The results demonstrated no statistically significant difference between MIS and ARH groups. Brandt et al. (43) evaluated 196 cases and presented similar results that MIS had no association with a 5-year prognosis in patients with early-stage cervical cancer. Additionally, Abel et al. (33) revealed that stage II cervical cancer undergoing MIS or ARH revealed comparable 5-year survival rates. Nonetheless, some recent studies have demonstrated that early-stage patients undergoing MIS had poorer DFS and OS than those undergoing ARH. According to Dai et al. (32), patients with stage IB undergoing ARH had better DFS and OS than those undergoing MIS (5-year

### TABLE 2 | Subgroup analysis of the 3- and 5-year survival of early-stage cervical cancer patients.

| Subgroup Analysis | No. of studies | HR (95%CI) | p-value | Heterogeneity (I²) (%) |
|-------------------|----------------|------------|---------|------------------------|
| **3-year disease-free survival** | | | | |
| I                 | 9              | 1.07 (1.01-1.14) | 0.020 | 59.6                    |
| IA-IB1            | 5              | 1.23 (1.02-1.49) | 0.034 | 69.2                    |
| Western           | 5              | 1.10 (1.01-1.20) | 0.024 | 30.9                    |
| Asia              | 8              | 1.04 (0.96-1.12) | 0.381 | 69.3                    |
| Tumor size<2cm    | 3              | 1.04 (0.98-1.09) | 0.186 | 0.0                     |
| **3-year overall survival** | | | | |
| I                 | 9              | 1.06 (0.99-1.14) | 0.006 | 48.4                    |
| IA-IB1            | 5              | 1.42 (0.71-2.85) | 0.321 | 70.4                    |
| IB1-II            | 3              | 1.02 (0.92-1.13) | 0.689 | 0.0                     |
| Western           | 6              | 1.04 (0.95-1.14) | 0.360 | 13.0                    |
| Asia              | 7              | 1.12 (0.96-1.31) | 0.134 | 69.4                    |
| Tumor size<2cm    | 3              | 1.01 (0.98-1.05) | 0.441 | 17.4                    |
| Tumor size>2cm    | 2              | 2.26 (0.64-7.94) | 0.203 | 71.1                    |
| **5-year disease-free survival** | | | | |
| I                 | 16             | 1.03 (0.98-1.09) | 0.247 | 68.5                    |
| IA-IB1            | 13             | 1.04 (0.99-1.09) | 0.157 | 65.0                    |
| IB1-II            | 12             | 1.06 (0.99-1.13) | 0.111 | 73.2                    |
| Western           | 17             | 1.03 (0.98-1.07) | 0.243 | 58.3                    |
| Asia              | 15             | 1.03 (0.92-1.17) | 0.577 | 54.4                    |
| Tumor size<2cm    | 9              | 0.86 (0.54-1.37) | 0.530 | 50.9                    |
| Tumor size>2cm    | 6              | 1.65 (1.02-2.66) | 0.041 | 69.6                    |
| **5-year overall survival** | | | | |
| I                 | 16             | 1.01 (0.96-1.06) | 0.665 | 56.2                    |
| IA-IB1            | 13             | 1.01 (0.97-1.05) | 0.626 | 37.2                    |
| IB1-II            | 14             | 1.01 (0.97-1.06) | 0.606 | 51.4                    |
| II                | 2              | 1.03 (0.88-1.20) | 0.745 | 0.0                     |
| Western           | 18             | 1.02 (0.95-1.10) | 0.597 | 55.1                    |
| Asia              | 14             | 1.00 (0.96-1.04) | 0.900 | 6.3                     |
| Tumor size<2cm    | 9              | 1.03 (0.98-1.07) | 0.250 | 0.0                     |
| Tumor size>2cm    | 5              | 1.76 (0.97-3.19) | 0.063 | 65.1                    |
DFS rate, 94.1% vs. 87.5%; 5-year OS rate, 98.1% vs. 92.3%). Chiva et al. (25) reported in an international European cohort observational study that early-stage cervical cancer patients undergoing MIS increased the risk of recurrence and death compared with those undergoing ARH. In addition, we observed that in many retrospective studies (28, 30, 33, 41, 47, 51, 57, 59), the MIS group had a shorter follow-up time than that of the ARH group. In order to objectively evaluate the effect of MIS and ARH on the prognosis of patients with early-stage cervical cancer, more adequate follow-up time is needed. Furthermore, 5-year prognosis subgroups were analyzed based on tumor stage, region, and tumor size. Except for tumor size ≥2 cm, no statistical difference was observed in other subgroup analyses. The lack of discrepancy in stage II may be due to the relatively small number of studies.

Specifically, the pooled results revealed that patients with tumor size ≥2 cm treated with MIS had a poorer long-term prognosis than those treated with ARH. Consistent with the results of Li et al. (21) and Chen et al. (64), patients with tumor size ≥2 cm undergoing MIS had a shorter DFS than those treated with ARH. The following reasons may be responsible for poorer DFS in patients with tumor size ≥2 cm undergoing MIS: (1) Wagner et al. (65) pointed out that tumor size was an independent prognostic factor for each stage and greatly influenced the prognosis of cervical cancer patients. Larger tumors have a higher risk of lymphatic metastasis (66–69), requiring greater tumor resection (66). However, MIS might be less thoroughly resected than ARH. (2) Pressing the tumor while using a uterine manipulator may spread cancer or increase lymphatic vascular space infiltration (70–72). The SUCCOR study (25) indicated that the risk of recurrence was 2.76-fold higher in patients undergoing MIS with a uterine manipulator compared to those undergoing ARH. (3) When tumors are large, selection bias of surgical methods may affect the results (73). MIS probably brings some surgical difficulties to surgeons (21, 22, 66, 70, 74), reducing the surgical effect. (4) Pneumoperitoneum environment may be a prognostic factor in patients undergoing MIS. An in vitro study (75) demonstrated that when cervical cancer cells were stimulated in CO₂ pneumoperitoneum environment in vitro, their proliferation ability was enhanced following a short period of inhibition. A retrospective analysis by Kong et al. (76) found that patients with early-stage cervical cancer undergoing MIS in pneumoperitoneal conditions increased the risk of recurrence and intraperitoneal tumor spread. In addition, the SUCCOR study (25) proposed that implementing a preoperative protective vaginal closure in patients undergoing MIS dramatically reduced the risk of recurrence and peritoneal metastasis compared to those undergoing ARH.

Compared with other studies, the strengths of this meta-analysis included the division of patients’ prognoses into medium- (3-year) and long-term (5-year) categories, as well as subgroup analyses for various factors such as tumor stage, region, and tumor size. Indeed, our meta-analysis had several limitations. First, only two of the included studies were RCTs, while the remaining were observational studies, resulting in inevitable risks such as selection bias. Second, the baseline characteristics of studies varied, such as tumor stage and surgical procedure. Besides, sentinel lymph node and adjuvant therapy assessments were not performed due to limited data. Furthermore, the sample size of our study was impacted by language restrictions associated with included literature. Finally, the retrieval time span was relatively long, allowing for MIS technology development, resulting in studies that may not accurately reflect changes in survival outcomes over time.

**CONCLUSION**

In patients with Western countries and stage I cervical cancer, MIS was linked to a shorter medium-term DFS, particularly in stage IA–IB1. Regarding long-term prognosis, patients with tumor size ≥2 cm were unsuitable for MIS and had shorter DFS than ARH. Accordingly, MIS should be chosen with caution in patients with early-stage cervical cancer. Nevertheless, more large-scale RCTs, including two ongoing trials (NCT03739944, NCT03719547), and clinical studies are required to provide relevant data.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

Each author contributed significantly to concept and development of the present paper. LYY and MZ designed the research process. WD and MZ searched the database for corresponding articles and extracted useful information from the articles above. YXS and YTS used statistical software for analysis. XL, KJ, and JS drafted the meta-analysis. All authors had read and approved the manuscript and ensured that this was the case.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.762921/full#supplementary-material

**Supplementary Table 1** | Characteristics of all studies included in the meta-analysis.

**Supplementary Table 2** | Quality assessment of included studies in this meta-analysis.
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