

# Surgical approach in early stage cervical cancer: the Asian view point

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**Objective:** To examine the current practice of radical hysterectomy for early-stage cervical cancer in Asia after the Laparoscopic Approach to Cervical Cancer (LACC) trial. **Methods:** A cross-sectional study was conducted in Asia to examine the prevalence and management of women with early-stage cervical cancer. The study was conducted among gynecologic oncologists at leading hospitals in the Asian Society of Gynecologic Oncology Council members. A systematic literature review was performed to examine the association between survival outcomes and surgical approach after the LACC trial. **Results:** Seven countries participated voluntarily in the study. The incidence, mortality, and centralization of treatment in early-stage cervical cancer were different among the seven countries. The number of specialized centers per population density in Japan was higher than that in the other countries. Minimally invasive surgery (MIS) approach for cervical cancer was common in Korea (56%) and Hong Kong (80-90%), but not in the other countries (2-20%). In the systematic review, there was a significant difference in survival outcomes between MIS and open surgery (recurrence, hazard ratio 1.83, 95% confidence interval 1.27-2.62). MIS without a uterine manipulator or making a vaginal cuff closure produced similar recurrence rates compared with open surgery (MIS without uterine manipulator vs open-surgery: 10.5% vs 10.1%, and MIS with cuff closure vs open-surgery 7.2% vs 10.1%; all  $P > 0.05$ ). **Conclusion:** The prevalence of MIS for early-stage cervical cancer varies across Asian regions after the LACC trial. Surgical methods to avoid tumor spillage may be useful for improving survival.

## Keywords

Cervical cancer; Radical hysterectomy; Minimally invasive surgery; Uterine manipulator; Vaginal cuff closure; Survival

## 1. Introduction

Cervical cancer remains the fourth most common gynecologic malignancy in women. Worldwide, approximately 570,000 cases were newly diagnosed and 311,000 patients died in 2018 [1]. The standard surgical management of early-stage cervical cancer includes radical hysterectomy (RH). Multiple retrospective studies have shown the benefits of minimally invasive surgery (MIS) for RH for women with early-stage cervical cancer regarding quality of life and low

rate of intra- and postoperative complications. The utilization of MIS-RH, therefore, increased worldwide. However, a recent randomized trial, the Laparoscopic Approach to Cervical Cancer (LACC) trial [2] demonstrated that patients who underwent MIS-RH for early cervical cancer had worse survival compared to those who received the conventional open approach.

Therefore, it is essential to select patients who may benefit from MIS without worsening their oncologic outcomes. In the LACC trial, there was insufficient information about surgical management to prevent tumor spillages, such as using a uterine manipulator during surgery, or intracorporeal colpotomy under CO<sub>2</sub> pneumoperitoneum, and vaginal cuff closure before surgery. The lack of sufficient evidence for the safety of MIS-RH for early-stage cervical cancer is an obstacle to its implementation.

In Asia, before the LACC trial, skilled surgeons with clinical and oncological expertise had proposed and demonstrated surgical methods to prevent tumor cell spillage [3-5]. Currently, some obstetrics and gynecological societies in Asian countries have distributed position statements and have responded to the results of LACC trial. Therefore, we conducted a questionnaire survey to validate the management of MIS-RH in Asian countries after the LACC trial among women with early-stage cervical cancer. Furthermore, a systematic review was performed to examine the recurrence rates between MIS-RH and open-RH, when the proposed surgical approaches for preventing of tumor spillage are made in women with early-stage cervical cancer.

## 2. Materials and methods

### 2.1 Study design

#### 2.1.1 Questionnaire analysis

An Asian-wide questionnaire survey was conducted at leading institutions of the Asian Society of Gynecologic Oncology (ASGO). After receiving approval from the Institutional Review Board of the Tokai Ethics Committee, the study concept was disseminated, and participation was invited from institutions where RH was practiced during the

study period. A cross-sectional, descriptive study was carried out to examine the management and surgical indications of women in early-stage cervical cancer in Asia. The study design was a national questionnaire survey sent to gynecological oncologists who were ASGO Council members or executive committee members working at a leading hospital in Asia in June 2019. A questionnaire was constructed which appears in Table Supplemental S1.

### 2.1.2 Systematic review

A systematic review of the literature and meta-analysis was performed to examine the association between survival outcomes and surgical approach taken after the LACC trial. The MIS-RH procedure to avoid tumor cell spillage was also evaluated. In September 2020, a literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses [6]. PubMed/MEDLINE was searched for relevant articles between September 2020 and November 2018, after the publication of the LACC trial, using the entry keywords “cervical cancer [all fields]”, “minimally invasive surgery [all fields]”, and “radical hysterectomy [all fields]” (Supplemental Table S1). Among women with stage I-II cervical cancer, according to the International Federation of Gynecology and Obstetrics (FIGO) staging system, eligible studies compared MIS-RH to the open approach in terms of surgical technique are: type of colpotomy, uterine manipulation, and vaginal cuff closure. All the studies of cervical cancers, randomized clinical trials, meta-analyses, and case-control series reported in the English literature, with adequate data on demographics and survival outcomes, were included. Each selected article’s references were reviewed, and any articles that met the inclusion criteria were assessed for inclusion. Systematic reviews and case reports were excluded.

### 2.2 Study definitions

MIS was defined as total laparoscopic as well as robotic-assisted surgery. In the analysis, the cancer stage was classified based on the 2009 FIGO classification [7]. The type of colpotomy performed was defined as either intracorporeal or vaginal (Supplemental Fig. S1A) [8]. Vaginal cuff closure was performed at the top of the vagina as part of the MIS-RH, near where the cervix is usually located. It was created by stitching together the top part of the vagina to prevent cancer cell spillage (Supplemental Fig. S1B) [3]. The population density was typically expressed as the number of people per square kilometer of land area. Certification for surgeon or institution was made by the obstetrics and gynecology board in each Asian country. Disease recurrence was defined as the time interval between hysterectomy and the first disease recurrence. Overall survival (OS) was defined as the time interval between hysterectomy and death due to cervical cancer or any other reasons.

### 2.3 Statistical analysis

Time-to-event data were calculated using the Parmer method, [9] and the logarithm of the hazard ratio (HR) and

95% confidence interval (CI) were calculated. The number of women in each treatment arm who experienced an event was compared to estimate the risk ratio [10]. The heterogeneity of each study was determined by visual inspection of forest plots and statistical evaluation using Cochran’s Q test and the  $I^2$  test [11]. The synthesis of data from the studies was performed to obtain overall estimates of the treatment effects. Meta-analysis was performed using random-effects models with inverse variance weighting. A  $P$  value  $< 0.05$  was considered statistically significant (two-tailed hypothesis). Statistical software for Review Manager (The Cochrane Collaboration, version 5.4, Copenhagen) was used for the statistical analyses.

## 3. Results

### 3.1 Questionnaire

A cross-sectional, descriptive study was carried out in Asia to examine the management and surgical indications of women in early-stage cervical cancer surgery, when MIS was performed during the study period. Seven countries voluntarily participated in the study. Gynecological oncology leaders in Asian countries who responded to this study, answered approximately 95% of the questionnaires (Supplemental Table S1).

The incidence, mortality, and proportion of women with cervical cancer were significantly different among the seven countries in Asia. Women in Japan and western Asian countries, including Thailand, Malaysia, and India, had a higher proportion of cervical cancer than women in Korea and Hong Kong (Fig. 1A). The majority of women with cervical cancer in Japan and Korea had stage I disease (54.2% and 56.2%, respectively). In other Asian countries, women with stage I disease represented only a quarter of all cervical cancer. Each country in Asia had different targets for the treatment of cervical cancer (Fig. 1B).

The number of specialized centers for gynecological cancer treatment and population density (people/km<sup>2</sup>) in each country was shown in Fig. 1C. The centralization of gynecological cancer treatment differed among the countries. The number of specialized centers per population density in Japan (241 hospitals and 334.5 people/km<sup>2</sup>) was higher than that in other Asian countries. Therefore, the number of specialized hospitals per patient with stage I cervical cancer in Japan was higher than that in Korea and Taiwan based on the same population density area (Fig. 1D). Therefore, Japan has a greater number of board-certified hospitals, gynecologic oncologists, and obstetrics gynecology laparoscopists than the other countries (Table 1).

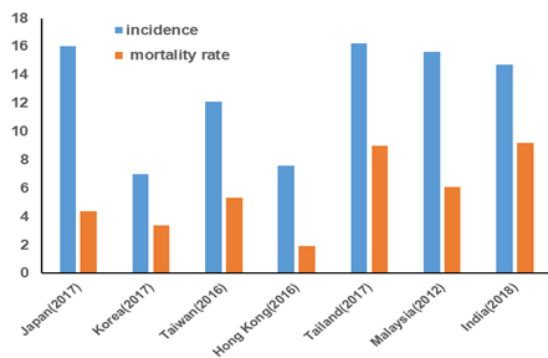
The common surgical approach and management of early-stage cervical cancer differed among Asian countries (Table 1). MIS-RH for stage I cervical cancer was common in Korea (56%) and Hong Kong (80-90%), but not in other countries (2-20%). Contributors in Japan, Taiwan, Korea and Hong Kong answered that they tried to improve the results with MIS-RH by avoiding the uterine manipulator and perform-

**Table 1. Treatment characteristics for early-stage cervical cancer in participating Asian countries**

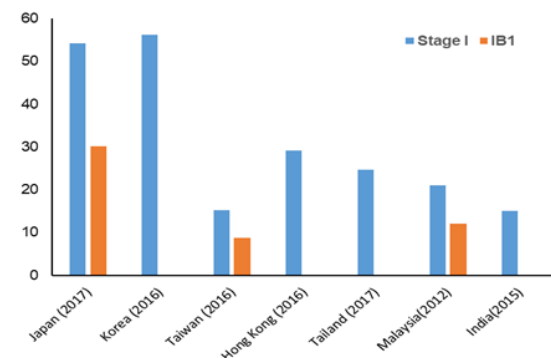
Country	No. of certified Institutions (Gy Oncology.)	No. of certified Gy. Oncologist	No. of certified Institutions (MIS)	No. of certified Gy Laparoscopist	Majority of approaches for early-stage CxCA	Estimated frequency of MIS for stage I CxCA	MIS-RH covered by National Health Insurance
Japan	241	915	312	807	Abdominal	20.90%	Yes (not for robotics)
Korea	64	268	n.a	n.a	MIS	55.60%	Yes (not for robotics)
Taiwan	33	207	44	313	Abdominal	20%	Yes (not for robotics)
Hong Kong	5	18	8	370	MIS / Robotic	Before LACC trial: 80-90% After LACC trial: 80% (Tumor Size < 2 cm)	Yes (Both laparoscopic and robotic)
Thailand	27	311	6	310	Abdominal	2%	No
Malaysia	6	30	0	5	Abdominal	5%	Yes
India	n.a	n.a	n.a	n.a	Abdominal	Exact information not available. Approximately 20-25%	Covered by private insurance

The number of board certified institutions, gynecological oncologists, and gynecological laparoscopists are shown. Among the entire cohort in each Asian country, the current proportions of MIS for early stage cervical cancer are shown. \* Board certified. Abbreviations: No. number; Gy, gynecologist; MIS, minimally invasive surgery; CxCA, cervical cancer; and n.a, not available.

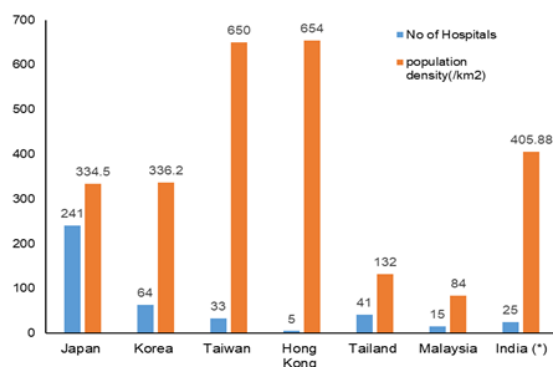
**A. Estimated incidence and mortality rate of CxCA**



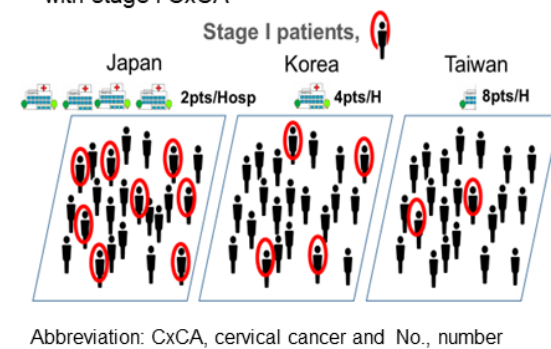
**B. Proportion of stage I CxCA in Asia**



**C. No. of specialized hospitals in gynecologic oncology**



**D. No. of specialized hospitals per patients with stage I CxCA**



**Fig. 1. Epidemiology of cervical cancer in Asia.** (A) Estimated incidence and mortality rate of cervical cancer, (B) Proportion of stage I cervical cancer in Asia, (C) Number of hospitals specializing in gynecologic cancer treatment, and (D) Number of specialized hospitals per patient with stage I cervical cancer.

ing vaginal cuff closure or colpotomy vaginally (Supplemental Table S1, No 30). National Health Insurance covered the MIS-RH in most Asian countries except Thailand and India.

Our study asked contributors about the possibility of

a randomized clinical trial for MIS-RH with standardization of surgical procedure in early-stage cervical cancer, the surgeon's proficiency, the possibilities of lawsuits after the LACC trial, and the value of the patient's surgical prefer-

**Table 2. The board position for MIS-RH with early-stage cervical cancer in Asian countries**

	Can you perform RCT?	Surgical procedure can be standardized?	Could the surgical outcome by the standardized procedure be similar for all surgeons?	Possibility of lawsuit	Which do you think more important: survival or patients' preference?	Position statement from the board
Japan	No	Yes	No	small	Patents' preference	Yes
Korea	No	Yes	No	small	Per tumor condition	Yes
Taiwan	Yes	Yes	No	small	Patents' preference	Yes
Hong Kong	Possible	Yes	Yes	small	Patient's preference (if technically feasible)	No
Thailand	Yes	Yes	No	small	Survival	No
Malaysia	No	Yes	No	highly possible	Survival	No
India	Yes	Yes	No	Highly possible	Survival	No

Abbreviations: RCT, randomized clinical trials.

ence in each Asian country (Table 2). All contributors, except Hong Kong, answered that the surgical outcome by the usual procedure for MIS-RH could not be standardized between surgeons. Whether or not intervention with MIS for early-stage cervical cancer may result in a lawsuit received different responses from each Asian country. In Japan, the possibility of a lawsuit was estimated to be small, and the patient's preference for the surgical approach may affect the surgeon's decision. The majority of contributors in Asia thought that the standardization of MIS-RH procedures is possible and that the outcome of standardized MIS-RH might even depend on the surgeon's proficiency.

### 3.2 Systematic review

The literature search identified 139 articles published during the target period (Supplemental Table S2). Among them, 116 articles were excluded because they did not meet the criteria: without survival outcomes, non-surgical management, systematic review articles, or non-English articles. The remaining 23 articles met the criteria for further assessment. These studies compared MIS-RH for early-stage cervical cancer, and a full content review of these articles was performed. Finally, 13 articles were identified, which enrolled women with FIGO stage I-II cervical cancer and met the inclusion criteria for this review (Table 3) [2, 3, 12–22]. The review included a total of 6,224 women, including 3,154 women who underwent MIS and 3,070 women who underwent open surgery.

A systematic review of data from the 14 retrospective studies yielded the following results (Fig. 2). There was a significant difference in OS and disease recurrence between the MIS group and the open surgery group (MIS versus Open: OS rates 7% versus 4.5%, HR: 1.83, 95% CI 1.27–2.62,  $P = 0.001$ , and recurrence rates 10.8% versus 7.8%, HR: 1.89, 95% CI 1.56–2.30,  $P < 0.001$ ; Fig. 2A and 2B). Use of the uterine manipulator was significantly more likely to be associated with recurrence in the MIS group than in the open surgery group (19.9% versus 10.6%, RR: 2.13, 95% CI 1.53–2.97,  $P < 0.001$ ; Fig. 2C). When a uterine manipulator was not used during MIS, there was no significant difference in recurrence between the two groups (MIS versus Open: 10.5% versus

10.1%, RR: 1.27, 95% CI 0.79–2.03,  $P = 0.32$ ; Fig. 2D). Undergoing vaginal cuff closure before the colpotomy in MIS gave similar recurrence rates between the MIS group and the open surgery group (7.2% versus 10.1%, RR: 0.90, 95% CI: 0.43–1.90,  $P = 0.78$ ; Fig. 2E).

## 4. Discussion

### 4.1 Principal findings

Our study found that the common surgical approach and management of early-stage cervical cancer with MIS-RH after the LACC trial differed in each Asian country. MIS-RH for stage I cervical cancer was still common in Korea and Hong Kong, but not in other countries. The MIS-RH procedure with a vaginal cuff closure, vaginal colpotomy, and the non-use of a uterine manipulator to prevent tumor cell spillage were reported in these countries.

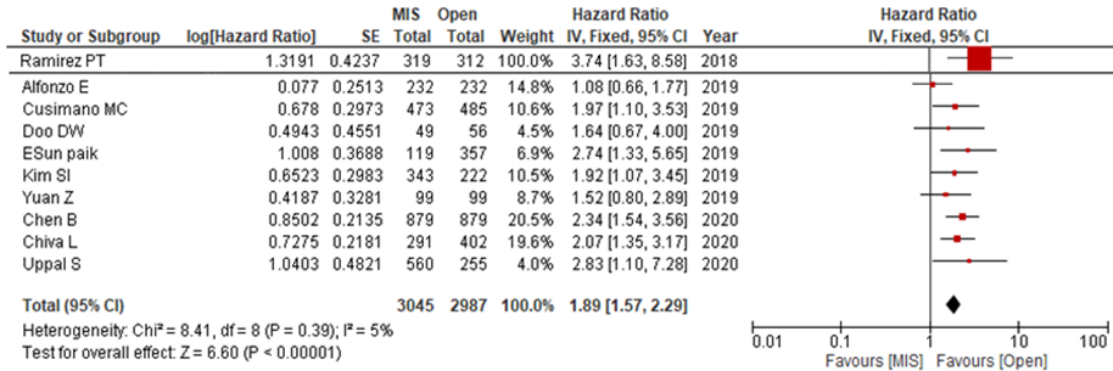
Additionally, our study suggested that these surgical techniques to prevent tumor cell spillage was the key to providing favorable survival through MIS for early-stage cervical cancer. When surgical management of the MIS included vaginal cuff closure and the non-use of a uterine manipulator, the oncologic outcome after MIS-RH was acceptable. In contrast, when MIS-RH was performed without further management, the recurrence risk was considerably higher.

### 4.2 Results and clinical Implication

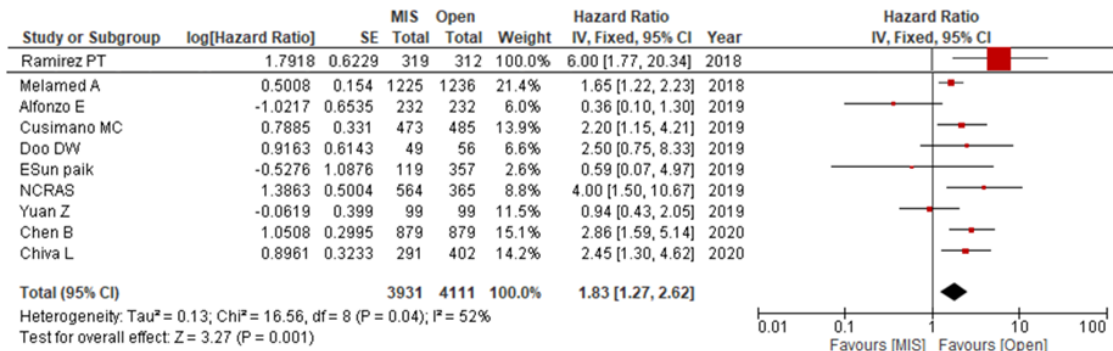
Surgical techniques in RH are varied and extremely difficult to control with any randomization or multivariate adjustment process. Randomized control trials have the highest level of evidence but certainly can also be subject to many biases, and the surgical quality and technique bias among individual surgeons and institutions are nearly impossible to overcome [23]. In our study, the majority of leaders in Asian countries considered that the surgical outcome by the standardized procedure for MIS-RH could not be similar for all surgeons and thought it might depend on the surgeon's proficiency.

The basic principles of oncologic surgery include careful tumor manipulation, resection in tumor-free margins, and the avoidance of tumor spillage [24]. In Asia, skilled gynecological surgeons with clinical and oncological expertise have

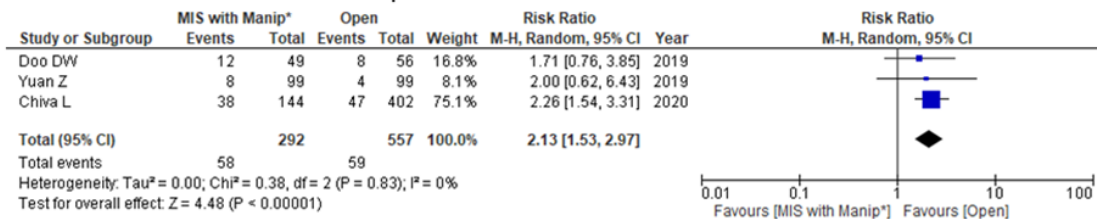
### A. Disease Recurrence



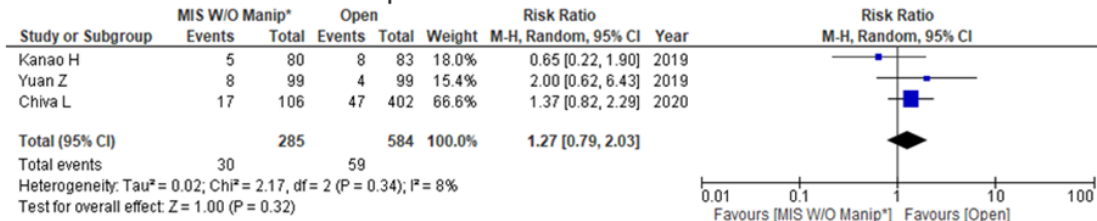
### B. Overall survival



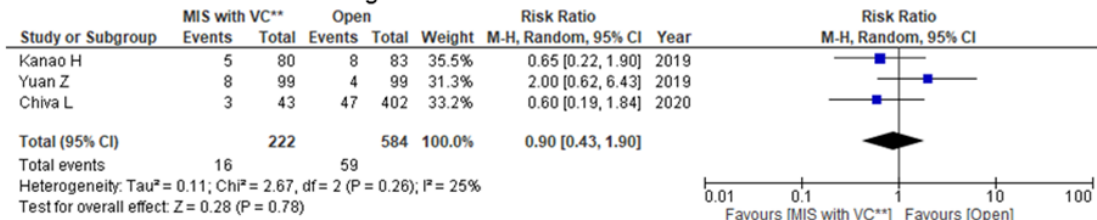
### C. Estimated risk of Uterine manipulator use



### D. Estimated risk of uterine manipulator non-use



### E. Estimate risk of MIS with vaginal cuff closure



**Fig. 2. Forest plots for comparison of MIS-RH versus open-RH in early-stage cervical cancer.** (A) Disease recurrence, (B) Overall survival, (C) Estimated recurrence risk with the use of a uterine manipulator, (D) Estimated recurrence risk without the use of a uterine manipulator and estimated recurrence risk of MIS with vaginal cuff closure are shown for the MIS-RH and open-RH groups. The study of Ramirez PT in the LACC trial was used as a reference. All 14 studies were retrospective. Weights were obtained from a fixed-effects model. Abbreviations: MIS, Minimally invasive surgery; Manip, uterine manipulator; VC, vaginal cuff closure; and W/O, without.

**Table 3. Survival impact of MIS-RH versus open-RH with early-stage cervical cancer**

Study Country	No.	Type of study	Recurrence rates	Overall survival	Uterine manipulator	Type of colpotomy	Vaginal cuff closure
Ramirez PT <i>et al.</i> (Ramirez <i>et al.</i> 2018) USA (2018)	631	Prospective Phase III	3ys: 8.8% vs 5%	3ys: 94% vs 99%	Use	unknown	unknown
Melamed A <i>et al.</i> (Melamed <i>et al.</i> 2018) USA (2018)	2,461	Retrospective National registry study	n.a	4ys: 91% vs 95%	unknown	unknown	unknown
NCRAS study (2019) Public Health England UK (2019)	929	Retrospective National registry study	n.a	4.5 ys 94% vs 98%	unknown	unknown	unknown
Doo DW <i>et al.</i> (Doo <i>et al.</i> 2019) USA (2019)	105	Retrospective Single institution	5ys: 24% vs 14%	5ys: 14% vs 5%	Use	unknown	per Surgeon preference
Kim SI <i>et al.</i> (Kim <i>et al.</i> 2019) Korea (2019)	565	Retrospective 2 institutions	3ys: 15% vs 8%	n.a	unknown	Unknown	unknown
Cusimano MC <i>et al.</i> (Cusimano <i>et al.</i> 2019) Canada (2019)	958	Retrospective National registry study	5ys: 16.2% vs 8.4%	5ys: 87% vs 95%	unknown	unknown	unknown
Paik E.S <i>et al.</i> (Paik <i>et al.</i> 2019) Korea (2019)	738	Retrospective Multi-institutions	5ys: 13.3% vs 4.8%	5ys: 5.0% vs 0.3%	unknown	unknown	unknown
Kanao H <i>et al.</i> (Kanao <i>et al.</i> 2019) Japan (2019)	163	Retrospective Single institution	2.5ys: 6% vs 10%	2.5ys: 100% vs 96%	Non use	Intracorporeal	performed
Alfonzo E <i>et al.</i> (Alfonzo <i>et al.</i> 2019) Swedish (2019)	864	Retrospective National registry study	5ys: 16% vs 15%	5ys: 92% vs 92%	unknown	unknown	unknown
Zhen Yuan <i>et al.</i> (Yuan <i>et al.</i> 2019) China (2019)	198	Retrospective Single institution	3ys: 8% vs 4%	3ys: 92% vs 96%	Non use	unknown	performed
Uppal S <i>et al.</i> (Uppal <i>et al.</i> 2020) USA (2020)	815	Retrospective Multi-institutions	5ys: 9.1% vs 7.5% Size < 2 cm: 8.8% vs 2.4%	n.a	unknown	unknown	unknown
Chen B <i>et al.</i> (Chen <i>et al.</i> 2020) China (2020)	6,930	Retrospective Multi-institutions	3ys: 8.9% vs 4.6%	3ys: 94.4% vs 97.8%	unknown	unknown	unknown
Chiva L <i>et al.</i> (Chiva <i>et al.</i> 2020) European countries -2020	693	Retrospective Multi-institutions	4.5ys: 20.6% vs 11.7%	4.5ys: 89% vs 97%	Non use* Recurrence: Use vs Non vs Open 26.3% vs 16% vs 11.7%	Intracorporeal intracorporeal (95%) vaginal (5%)	Performed* Recurrence: Yes vs No vs Open 7% vs 25% vs 11.7%
Brandt B <i>et al.</i> (Brandt <i>et al.</i> 2020) USA (2020)	196	Retrospective Single institution	5ys: 13.0% vs 13.4%	5ys: 96.5% and 87.4%	Use (93%)		unknown

\* Recurrence and overall survival rates were shown as MIS versus open surgery.

proposed a procedure based on those principles, since before the LACC trial. For instance, variations of techniques concerning MIS-RH, associated with the utility of uterine manipulators and colpotomy, have been proposed [3–5]. Surgeons refrain from using a uterine manipulator to push tumor cells into the lymph vascular cavity, always create a tumor-covering vaginal cuff via a transvaginal approach, and open the vaginal cuff transvaginally or laparoscopically above the closure rim at parametrial resection to prevent the tumor cells from spreading within the peritoneal cavity by circulating carbon dioxide.

In our systematic review, the MIS included vaginal cuff closure and the non-use of a uterine manipulator contributed to improved survival outcomes. While open surgery remains the leading surgical management for early-stage cervical cancer worldwide, the role of MIS using these techniques in improving survival outcomes and patients' quality of life merits further investigation. The MITOR study (Minimally Invasive Therapy versus Open Radical hysterectomy study) organized by the Asia-Pacific Association for Gynecologic Endoscopy and Minimally Invasive Therapy (APAGE) is ongoing. This trial comparing the survival of women with early-stage cervical cancer undergoing MIS-RH using these surgical techniques versus open-RH, is being conducted by the most experienced surgeons in the high-case-load centers.

Recently, the relationship between the centralization of treatment centers and clinical outcomes in a variety of malignancies has been increasing. Our study showed that women with early-stage cervical cancer were treated in centralized centers in some Asian countries, but not in all countries. In this observational study, there were existing disparities in Asia concerning the centralization of treatment centers for cervical cancer. Resolving centralization disparity and surgical technique problems might bring about nationwide improvements in cervical cancer outcomes.

#### 4.3 Strengths and limitations

This study's strength is that it is the first to reveal, in Asian countries, the medical practice for early-stage cervical cancer with MIS-RH after the LACC trial. The systematic review enhanced the statistical rigor of our findings and strengthened the robustness of the investigation. However, several limitations of this study must be acknowledged. First, an unmeasured bias inherent to the nature of retrospective studies exists. For instance, our study did not manage to interview all members of the ASGO in Asian countries, and the quality of certification for surgeons or hospitals were based on the obstetrics gynecology board in each country. Thus, information on data quality and completeness is missing. There were inadequate details regarding the precise methods of MIS-RH, the surgeon's experience in performing this surgery, and the social system of cancer treatment, all of which may have impacted the outcome.

## 5. Conclusions

Recently, the LACC trial reported that MIS negatively influences the survival of women with early-stage cervical cancer. Simultaneously, the advantages of MIS regarding the quality of life and low rate of intra- and postoperative complications are well known. Therefore, it is essential to select patients who may benefit from MIS without worsening their oncologic outcomes. The prevalence of MIS for early-stage cervical cancer varies across Asian regions after the LACC trial. Surgical methods to avoid tumor spillage may be useful for improving survival. Additionally, our findings may reassure women with early-stage cervical cancer who want to undergo MIS.

### Author contributions

Conceptualization: MM; Data curation: HM and MM. Formal analysis: HM, MM.; Funding acquisition: None; Investigation: all authors; Methodology: MM, HY, HM; Project administration: MM; Resources: MM; Software: HM; Supervision: HY, MM.; Validation: all authors; Visualization: HM, MM; Writing - original draft: HM, MM Writing - review & editing: all authors.

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### Conflict of interest

The authors declare no competing interests.

### Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://ejgo.imrpress.com/EN/10.31083/j.ejgo.2021.01.2270>.

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Plenary Session at the 6<sup>th</sup> Biennial Meeting of Asian Society of Gynecologic Oncology on October 10-12<sup>th</sup> 2019, Incheon, Korea.

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