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Systematic Review

# Laparo-assisted vaginal radical hysterectomy as a safe option for Minimal Invasive Surgery in early stage cervical cancer: A systematic review and meta-analysis

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## HIGHLIGHTS

- Laparo-Assisted Vaginal Hysterectomy could represent a valid and safe option to Abdominal Radical Hysterectomy in Early stage Cervical Cancer.
- Vaginal Cuff creation prevent tumor's spillage
- Laparo-Assisted Vaginal Hysterectomy does not appear to affect Disease Free Survival and Overall Survival in Early stage Cervical Cancer.

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## ABSTRACT

*Background.* Radical hysterectomy and pelvic lymphadenectomy are considered the standard treatment for early-stage cervical cancer (ECC). Minimal Invasive approach to this surgery has been debated after the publication of a recent prospective randomized trial (Laparoscopic Approach to Cervical Cancer, LACC trial). It demonstrated poorer oncological outcomes for Minimal Invasive Surgery in ECC. However, the reasons are still an open debate. Laparo-Assisted Vaginal Hysterectomy (LAVRH) seems to be a logical option to Abdominal Radical Hysterectomy (ARH). This meta-analysis has the aim to prove it.

*Methods.* Following the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, the Pubmed database and Scopus database were systematically searched in January 2022 since early first publications. No limitation of the country was made. Only English article were considered. The studies containing data about Disease-free Survival (DFS) and/or Overall Survival (OS) and/or Recurrence Rate (RcR) were included.

*Results.* 19 studies fulfilled inclusion criteria. 9 comparative studies were enrolled in meta-analysis. Patients were analyzed concerning surgical approach (Laparo-Assisted Vaginal Radical Hysterectomy) and compared with ARH Oncological outcomes such as DFS and OS were considered. 3196 patiets were included for the review. Meta-analysis of 1988 0f them highlighted a non-statistic significant difference between LARVH and ARH (RR 0.8 [95% CI 0.55–1.16] $p = 0.24$; $I^2 = 0\%$; $p = 0.98$). OS was feasible only for 4 studies (RR 0.84 [95% CI 0.23–3.02] $p = 0.79$; $I^2 = 0$ $p = 0.44$). Sub-analysis for tumor with a maximum diameter greater than 2 cm was performed. Data about the type of recurrences (loco-regional vs distant) were collected.

*Conclusion.* LARVH does not appear to affect DFS and OS in ECC patients. The proposed results seem to be comparable with the open approach group of the LACC trial, which today represents the reference standard for the treatment of this pathology. More studies will be needed to test the safety and efficacy of LARVH in the ECC.



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**Contents**



## 1. Introduction

Radical hysterectomy and pelvic lymphadenectomy are considered the recommended standard treatment for early-stage cervical cancer [1,2]. In the last decades, minimally invasive surgery (MIS) has replaced the open approach of Abdominal Radical Hysterectomy (ARH) because of its benefits in postoperative outcomes [3]. Oncological safety of MIS came out from retrospective series and have never been tested by a Randomized Clinical Control Trial till publishing of Laparoscopic Approach to Cervical Cancer, LACC trial by P. Ramirez et al. in November 2018 [4]. This trial proved the oncological superiority of ARH to MIS, represented by Laparoscopic Radical Hysterectomy (LRH) or Robotic Radical Hysterectomy (RRH), both in terms of Disease-free survival (DFS) and Overall Survival (OS). However, the causes of those differences remain still an open issue. MIS techniques more often are associated with the use of uterine manipulators [5–7]. Moreover, the vaginal cuff is opened laparoscopically above the manipulator rim potentially exposing tumor cells to the abdominal cavity and leading to their spread by CO2 circulation [8]. In this scenario, Laparo-Assisted Vaginal Hysterectomy (LARVH), by creating a secure vaginal cuff around the tumor, represent a valid option to avoid those condition and preserve Basic principles of oncologic surgery such as avoidance of tumor spillage and careful tumor manipulation [9].

## 2. Material and methods

The methods for this study were specified a priori based on the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

### 2.1. Search method

A systematic search for articles about LARVH and Early-stage Cervical Cancer (ECC) in Pubmed Database and Scopus Database was performed in January 2022. No data limitation was performed. No restriction of the country was performed. Only English fully published studies were considered. Search imputes were ((“Minimally Invasive Surgical Procedures”[Mesh]) OR “Laparoscopy”[Mesh] OR “LARVH” [Text Word])) AND (“Uterine Cervical Neoplasms”[Mesh] OR “early cervical cancer” [Text Word]) for Pubmed Database; and (TITLE-ABS-KEY (minimal* AND invasive AND surgery) OR TITLE-ABS-KEY (laparoscopic*) OR TITLE-ABS KEY (larvh) AND TITLE-ABS- KEY (cervical AND cancer) OR TITLE-ABS- KEY (early AND cervical AND cancer)) AND (LIMIT- TO (PUBSTAGE, “final”)) AND (LIMIT-TO (DOCTYPE, “ar”)) AND (LIMIT- TO (LANGUAGE, “English”)) for Scopus Database.

### 2.2. Study selection

Study selection was done independently by CR and CK. In case of discrepancy NC decided for inclusion or exclusion. Inclusion criteria were: (1) studies that included patients with early cervical cancer FIGO 2009 stage IA1, IA2, IB1, IB2, IIA1; (2) studies that reported at least one outcome of interest (DFS and/or OS and/or Recurrence Rate); (3) peer-reviewed articles, published originally. Non-original studies, preclinical trials, animal trials, abstract-only publications, articles in a language other than English were excluded. If possible, the authors of studies that were only published as congress abstracts were tried to be contacted via email and asked to provide their data. The studies selected and all reasons for exclusion are mentioned in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Fig. 1).

All included studies were assessed regarding potential conflicts of interest.

### 2.3. Statistical analysis

Heterogeneity among the studies was tested using the Chi-square test and I-square tests [11]. The risk rate (RR) and 95% confidence intervals (CI) were used for dichotomous variables. Statistical analysis was conducted by fixed-effect models in the absence of significant heterogeneity ($I^2 < 50\%$), or random-effect models if $I^2 > 50\%$. DFS and OS were used as clinical outcomes. In each study, Disease-free survival was defined as the time elapsed between surgery and recurrence or the date of the last follow-up. Overall survival has been defined as the time elapsed between surgery and death for cervical cancer or the date of the last follow up. Chi-square tests were used to compare continuous variables. Subgroup analysis in patients with tumor size greater than 2 cm in maximum dimension was performed. Review Manager version 5.4.1 (REVman 5.4.1) and IBM Statistical Package for Social Science (IBM SPSS vers 25.0) for MAC were used for statistic calculation. For all performed analyses a $p$-value $<0.05$ was considered significant.

### 2.4. Quality assessment

Assessment of the quality of the included studies was conducted by using the Newcastle– Ottawa scale (NOS) [12]. This assessment scale

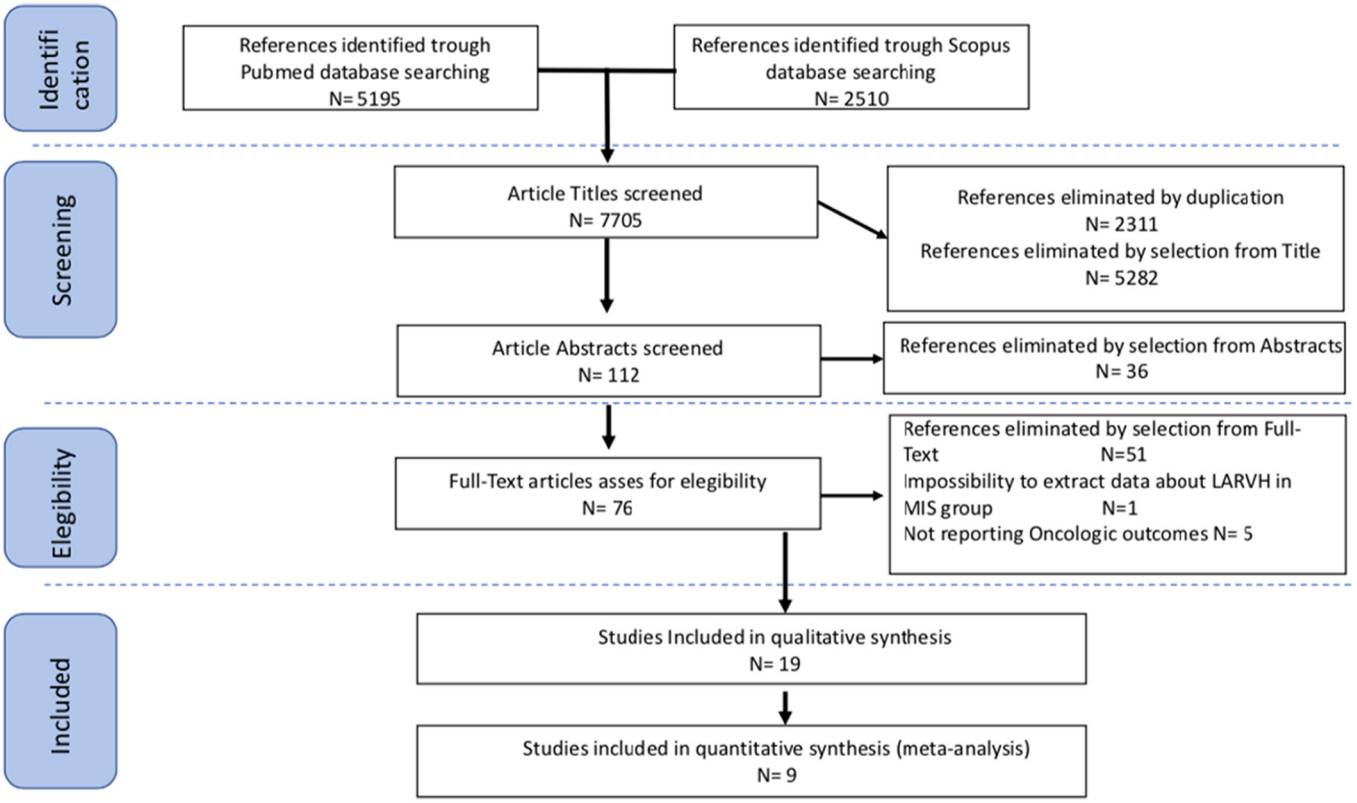


**Fig. 1.** PRISMA flowchart.

uses three broad factors (selection, comparability, and exposure), with the scores ranging from 0 (lowest quality) to 8 (best quality). Two authors (CR and CK) independently rated the study's quality. Any disagreement was subsequently resolved by discussion or consultation with NC. NOS Scale is reported in Supplementary.

A funnel plot analysis was used to assess publication bias. Egger's regression test was used to determine the asymmetry of funnel plots (Supplementary).

## 3. Results

### 3.1. Studies' characteristics

After the databases search, a total of 7705 articles was matching the searching criteria. After removing records with no full-text, duplicates and wrong study designs (e.g. reviews), 76 were suitable for eligibility. Of those, 19 matched inclusion criteria and were included in the systematic review. 9 of them were non-comparative, single-armed studies evaluating only LARVH. 1 was a comparative study between LARVH and Laparo-Assisted Vaginal Trachelectomy. The other 9 were comparative studies between LAVRH and ARH and were included in quantitative analysis (Fig. 1). The countries where the studies were conducted, the publication year range, the studies' design, FIGO stage of cervical cancer and number of participants are summarized in Table 1.

The quality of all studies was assessed by NOS [12] (Supplementaries). Overall, the publication years ranged from 1986 to 2019. In total, 3196 patients with surgical treatment for early cervical carcinoma were included. Follow up period ranged from 21 to 113 months on average.

### 3.2. Surgical technique

The included studies examined the use of laparoscopic-assisted radical vaginal hysterectomy LARVH for combined laparoscopic staging and vaginal radical resection of parametria, as firstly described by D. Dargent [32] in 1987 with the name of Coelio-Schauta. Despite a lack of standardization, all studies were based on the principle of preventing direct exposure of tumor tissue to the abdominal cavity. This was possible either by the creation of a vaginal cuff or closing of the vaginal cuff by suture or permanent tie. Although preparation of the surgical spaces, depending on the authors, may precede or follow this step, the opening of the vesicovaginal septa or the Douglas, as well as the parametrial resection occurs only after the incarceration of the tumor tissue by the vaginal cuff.

The creation of the vaginal cuff can precede or follow trocar placement, pneumoperitoneum induction, or all laparoscopic steps, depending on the study population.

Li et al. [15] represent the only substantial variation to this technique. A cuppy uterine manipulator was placed around the tumor ensuring that the entire tumor was enclosed in the cup. By laparoscopy, a tie was tightened about 4 cm from the external cervix, then the uterus was resected along the underside of the tie.

Even if this technique is different from the one described by Dargent, it was considered eligible for the review, because it preserves the oncological principle of safety, such as avoidance of tumor spillage and careful tumor manipulation.

Except for Li [16], Park [17] and Kwon [27], all the other studies avoided the use of uterine manipulators. Moreover, Kanno [14], Fugesi [24] and Kanao [26] explixity declared that they systematically removed surgical specimens into a collection bag. No data about surgical speciment retrival were reported in the other studies.

In all the studies, the ovaries were either resected or left in situ according to the stage, the guidelines indications [1,2] and the patient's desire to preserve ovarian function. The radicality of parametrectomy was modulated on tumor's risk factors such as dimension, stromal invasion, LVSI and FIGO staging, according to Querleu-Morrow Classification [32] or Piver Classification [33] and principal international Guidelines [1,2].

Laparoscopic systematic pelvic lymphadenectomy and pelvic space creation were described as steps in all the series.

**Table 1**
Studies included.

| Not comparative studies | | | | | | |
|---|---|---|---|---|---|---|
| Name | Country | Study design | Study Year | FIGO stage | N of partecipant | Mean FUP[a] months |
| Hertel [13] 2003 | Germany | Prospective Observational Monocentric study | 1994–2002 | IA1-IB1 | 110[b] | 40 |
| Kanno [14] 2019 | Japan | Retrospective Observational Monocentric study | 2006–2015 | IA1-IB1 | 109 | 73 |
| Köhler [15] 2019 | Germany | Retrospective Observational Monocentric study | 1994–2018 | IA1-IIA1 | 389 | 99 |
| Li [16] 2022 | China | Retrospective Observational Monocentric study | 2012–2017 | IA1-IB1 | 137 | 53 |
| Marchiole [17] 2007 | France | Retrospective Case-Control Monocentric study | 1986–2003 | IA1-IIA | 139[b] | 113 |
| Park [18] 2002 | Rep of Korea | Case Series Report Monocentric | Lac of data-2002 | IB1 < 3 cm | 52 | 45 |
| Querleu [19] 1993 | France | Case Series Report Monocentric | 1990–1992 | IA2-IIB | 8 | 24 |
| Renaud [20] 2000 | France | Retrospective Observational Monocentric study | 1993–1999 | IA1-IIA | 102 | 36 |
| Sardi [21] 1999 | Argentina | Prospective Observational Monocentric study | 1993–1997 | IA2-IIB | 47[b] | 48 |
| Torné [22] 2021 | Spain | Retrospective Observational Multicentric study | 2001–2018 | IA1-IIA1 | 115 | 88 |
| Comparative Studies, Included for meta-analysis | | | | | | |
| Chiva [23] 2021 | European | Retrospective Case-Control Multicentric study | 2013–2014 | IB1 | 445[b] | 59 |
| Fugesi [24] 2021 | Japan | Retrospective Case-Control Multicentric study | 2014–2019 | IA2-IIA1 | 231 | 39 |
| Jackson [25] 2004 | United Kingdom | Prospective matched Control Monocentric study | 1996–2003 | IA2-IB2 | 100 | 50 |
| Kanao [26] 2019 | Japan | Retrospective Case-Control Monocentric study | 2014–2017 | IB1 | 163 | 31 |
| Kwon [27] 2020 | Rep of Korea | Retrospective Case-Control Multicentric study | 2008–2017 | IA2-IB2 | 510 | 82 |
| Morgan [28] 2007 | Ireland | Retrospective Case-Control Monocentric study | 2000–2005 | IA1-IIB | 60 | 31 |
| Nam [29] 2004 | Rep of Korea | Retrospective Case-Control Monocentric study | 1997–2002 | IA1-IB1 | 136 | 39 |
| Sharma [30] 2006 | United Kingdom | Retrospective Case-Control Monocentric study | 1999–2005 | IA2-IIB | 67 | 34 |
| Steed [31] 2004 | Canada | Retrospective Case-Control Monocentric study | 1996–2003 | IA1- IB2 | 276 | 21 |

[a] Follow up.
[b] Sub-analysis of the entire cohort.

### 3.3. Oncological outcomes

A total of 3196 patients were included in the review. 18 of the 19 selected studies presented DFS data. One other by Querleu [19] showed only data about recurrence rate. Except for Chiva [23], Nam [29], Park [18], Sharma [30] and Steed [31], the other 13 studies presented OS data. In addition, the study by Hartel et al [13] and the study by Koheler et al [15] show a potential overlap of part of patients, as they are studies conducted by the same teams at the same institution at different time.

By alphabetic, Chiva et al. [23] performed a retrospective comparison between MIS and ARH. Data about LARVH sub-analysis were shown with a total of 445 patients (43 for LARVH and 402 for ARH). It highlighted a 4.5 DFS of 93%, with a mean Follow-Up (FUP) of 59 months. Fugesi et al. [24] showed a population of 113 ECC undergone to LARVH with 3 years and 5 years DFS of 92.4% and 90.9% respectively, and 3 years and 4.5 years OS of 100% and 100% with 39 months FUP in average. Hertel et al. [13] published in 2002 a prospective observational study with a recruitment of 8 years (from 1994 to 2002) and a mean FUP of 40 months. All stages of cervical cancer were enrolled with a cumulative OS of 83%. But, a sub-analysis about 110 patients with stage ≤IB1 reported a 4.5 years DFS and OS of 94% and 98% respectively. Jackson et al. [25] published a direct comparison between LARVH and ARH with a match controlled study. The 50 patients of each arm presented a non-statistically significant identical rate of RcR, DFS and OS (Respectively 4%; 96% and 94%). Kanao et al. [26] proposed a 3 years DFS and OS of 94.4% and 100% in a population of 80 patients with a mean FUP of 31 months. Kanno et al. [14] examined a population of 109 with a 5 years DFS of 96.3% and a 5 years OS of 97.2% after 77 months mean FUP. Köhler et al. [15] proposed the largest series with 389 patients undergone to LARVH and the longest mean FUP of 99 months (3 years DFS 96.8%; 3 years OS 98.5%; 4.5 years DFS 95.7%; 4.5 years DFS 97.6%). Kwon et al. [27], vice versa, reported the largest comparative study, with the arm of LARVH composed of 252 patients, which presented a 5 years DFS and OS of 86.6% and 88% during a mean of 82 months FUP. Li et al. [16] is the latest article published, with 137 patients and 53 months of FUP, showing a 5 years DFS of 96.4% and 5 years OS of 96.8%. Marchiole et al. [17] focused on difference between LARVH and Laparo-Assisted Vaginal Radical Trachelectomy. Data about LARVH arm were retrived with a 4.5 years DFS of 94.7% and 4.5 OS of 95% in 139 patients followed up with a mean of 113 months. Morgan et al. [28], between 2000 and 2005, treated 30 patients with LARVH approach and 30 with ARH and compared them in a retrospective analysis. Even if ECC was an inclusion criterion, parametrial involvement was proved in 3 patients of ARH arm, which were upstaged to IIB FIGO stage. LARVH group presented a 3 years DFS and a 3 years OS 92.3% and 96.7%, respectively. Nam et al. [29], as well, compared 47 LARVH operation for ECC with 96 ARH. With a mean FUP of 39 months, a 3 years DFS of 97.1% was observed in LARVH group and 98.9% in ARH ($p = 0.63$). Park et al. [18] in 2002 published a case series of 52 IB1 ECC treated with LARVH in them institution, with a 4.5 years DFS of 96.2% and a mean FUP of 45 months. Querleu [19] presented the really first case series of LARVH for ECC, presenting data about 8 patients in 1993. This study focused on feasibility of the technique, but 2 recurrence were reported (25%) in the 24 months of FUP. Renaud et al. [20], conversely, proved a RcR of 4% in 102 patients, with a 3 years DFS of 96% and OS of 98% after 36 months of FUP. Sardi et al. [21] conducted an observational study about learning curve of LARVH technique. Of the 56 patients eligible for the procedure, 47 completed it, with a 4.5 years DFS and OS both of 91.5%. Sharma et al. [30] compared 35 consecutive patients treated undergone to LARVH in the period between 1999 and 2005 with 32 patients which received an Open approach. In a mean of 34 months of FUP, RcR was respectively 5.7% and 6.2% in LARVH and ARH groups ($p$ = NS). Steed et al. [31] enrolled 276 patients with ECC. Of them, 71 were treated by LARVH and 205 with ARH. No randomization was performed, and the choice of which technique to use was demanded to the surgeon. After a mean FUP of only 21 months, both arms presented a DFS of 94% ($p$ = NS). Lastly, Torné et al. [22] exposed data about 3 years DFS and 3 years OS of 96.7% and 97.8%, as well 4.5 years DFS 93.5% and 4.5 years OS 94.8% in 115 patients with ECC followed for a mean of 88 months.

Overall, LARVH approach presented a 3 years DFS ranged between 92.4% and 97.1% and a 4.5 years DFS between 86.6% and 96.4%. As well, 3 years OS was enclosed in 96.7% and 100%, and 4.5 years in 88% and 100%. Those results are summarized in Table 2.

In 6 studies, we also evaluated data about DFS in ECC with tumor's maximum diameter > 2 cm. In 3 of them was also feasible to extract data about OS, as shown in Table 2.1.

To consolidate the conceptualization of LARVH as a technique with no tumor spillage, we also analyzed data about local recurrence rate, which oscillated from 0.7% to 25% in the different studies. As well distant recurrence rate was recorded from 0% to 9.5%.

**Table 2**
LARVH oncological outcome.

| Name | 3Y DFS[a] (%) | 3Y OS[b] (%) | 4.5Y DFS[a] (%) | 4.5Y OS[b] (%) |
|---|---|---|---|---|
| Chiva 2021 | – | – | 93.0 | – |
| Fugesi 2021 | 92.4 | 100 | 90.9 | 100 |
| Hertel 2003 | – | – | 94.0 | 98.0 |
| Jackson 2004 | – | – | 94.0 | 94.0 |
| Kanao 2019 | 94.4 | 100 | – | – |
| Kanno 2019 | – | – | 96.3 | 97.2 |
| Köhler 2019 | 96.8 | 98.5 | 95.7 | 97.6 |
| Kwon 2020 | – | – | 86.6 | 88.0 |
| Li 2022 | – | – | 96.4 | 96.8 |
| Marchiole 2007 | – | – | 94.7 | 95.0 |
| Morgan 2007 | 92.3 | 96.7 | – | – |
| Nam 2004 | 97.1 | – | – | – |
| Park 2002 | – | – | 96.2 | – |
| Renaud 2000 | 96.0 | 98.0 | – | – |
| Sardi 1999 | – | – | 91.5 | 91.5 |
| Sharma 2006 | 94.3 | – | – | – |
| Steed 2004 | 94.0 | – | – | – |
| Torné 2021 | 96.7 | 97.8 | 93.5 | 94.8 |

[a] Disease free survival.
[b] Overall survival.

**Table 2.1**
LARVH oncological outcome. Tumor >2 cm sub-analysis.

| Name | 3Y DFS[a] (%) | 3Y OS[b] (%) | 4.5Y DFS[a] (%) | 4.5Y OS[b] (%) |
|---|---|---|---|---|
| Fugesi 2021 | 85.0 | – | 85.0 | – |
| Kanao 2019 | 89.9 | – | – | – |
| Kanno 2019 | – | – | 94.0 | 96.0 |
| Kwon 2020 | – | – | 79.1 | 81.5 |
| Li 2022 | – | – | 91.2 | 94.1 |
| Marchiole 2007 | – | – | 87.3 | 89.9 |

[a] Disease free survival.
[b] Overall survival.

No statistical difference was observed in those distributions ($p$ 0.220) (Table 3).

### 3.4. Meta-analysis

The 9 studies comparing LAVRH and ARH were enrolled in the meta-analysis. A total of 1988 patients were analyzed. 714 patients in the LARVH arm were compared with 1274 patients which underwent ARH, exploring DFS outcome. Because of low heterogeneity ($I^2 = 0\%$; $p = 0.98$), fixed-effects model was applied.

LARVH group showed a non-significant better DFS than ARH (RR 0.80 [95% CI 0.55–1.16] $p = 0.24$). Fig. 2.

**Table 3**
Type of recurrence.

| Name | Loco-regional recurrence rate (%) | Distant recurrence rate (%) | $p$ |
|---|---|---|---|
| Fugesi 2021 | 2.7 | 2.7 | |
| Kanao 2019 | 5.0 | 2.5 | |
| Kanno 2019 | 3.7 | 0.9 | |
| Köhler 2019 | 2.5 | 2.5 | |
| Kwon 2020 | 5.9 | 9.5 | |
| Li 2022 | 0.7 | 3.7 | |
| Marchiole 2007 | 3.7 | 2.9 | |
| Morgan 2007 | 3.3 | 3.3 | |
| Nam 2004 | 2.5 | 0 | |
| Park 2002 | 1.9 | 1.9 | |
| Querleu 1993 | 25.0 | 0 | |
| Renaud 2000 | 1.0 | 3.0 | |
| Sardi 1999 | 4.3 | 4.3 | |
| Sharma 2006 | 5.7 | 0 | |
| Torné 2021 | 1.7 | 4.4 | 0.220 |

We performed a sub-analysis for the patients with a tumor's maximum diameter greater than 2 cm. Unfortunately, only 2 of the 9 comparative studies were reporting useful data. 145 patients for the LARVH group and 158 for the ARH group. As well, in this analysis LARVH documented a non-significant better DFS than ARH (554 patients, 273 LARVH and 281 ARH; RR 0.57 [95% CI 0.27–1.23] $p = 0.18$; $I^2 = 0$ $p = 0.44$). (Fig. 2.1).

In the end, Fugesi, Jackson, Kanao and Morgan presented comparative data about OS and were included in a second meta-analysis. (RR 0.79 [95% CI 0.23–3.02] $p = 0.79$; $I^2 = 0$ $p = 1.00$). (Fig. 3).

## 4. Discussion

LACC trial [4] was a cornerstone in the treatment of ECC. After its publication, a trend reversal was observed in clinical practice with a progressive return to open surgery. Chiva et al. [35] demonstrated how after LACC publication 57% of members of the European Society of Gynaecological Oncology moved from MIS to an open approach in ECC. But scientific evidence is not to be accepted as dogma and should be deeply investigated in their reasons. In 1992 Nezhat et al. [36] firstly described Laparoscopic Radical Hysterectomy. This technique in decades evolved and proved better post-operative outcomes with comparable oncological ones [3,5–7]. MIS approach was also contemplated in guidelines as a valid alternative to ARH [1,2]. But LRH departed from the surgical principles envisioned by Shauta [37] since 1908 and Wertheim [38] since 1911. The clamp of vaginal vault previous colpotomy was a crucial step in the open technique, which can't be routinely replicated in LRH. Moreover, the use of uterine manipulators is a sort of trauma on tumor tissue [23]. As well, at the time of colpotomy, during LRH there is direct communication between tumor and abdominal cavity, and an exposition to CO2 circulation. This was seen in "in vivo" and "in vitro" how could favor tumor spread and its implantation [8,38,39,40]. In this scenario, LARVH represents a MIS technique that avoids this LRH's flaws. The laparoscopic staging, integrated with the vaginal creation of a tumor-adapted covering cuff, combine the advantages of MIS and open approaches. Following this principle, it has been declined in different variations [14,41–43]. Other studies proved the hypothesis that LARVH prevents tumor cells' spillage [44]. For these reasons, we found it useful for clinical practice to investigate its oncological outcomes. As shown in the results, different centers found a DFS and OS comparable with ones of the open arm in the LACC trial [4], which nowadays set the standards, and it represented an unexpectedly favorable prognosis group, superior to survival rates previously published in the scientific literature. With a 3 years DFS of 97.1% and 4.5 years DFS of 96.5%, it remains the highest reported percentage in literature after a randomized controlled trial. But, the results of LARVH studies are more similar to this arm than the MIS arm (3 years DFS of 87.1% and 4.5 years DFS of 86%). The only exception is represented by Kwon et al. [27], which presented a 4.5 years DFS overlapping LACC's MIS group. However, in this comparative study, no difference was seen with ARH's outcomes (5 years DFS 84.4% (95% confidence interval [CI] 79.7–89.1) in the ARH group, and 86.6% (95% CI 82.1–91.1) in the LARVH group; $p = 0.467$). Moreover, LARVH was shown to be significantly non-inferior to ARH with the noninferiority margin of −7.2 in PFS. This suggests that these results must be attributed to different risk factors than surgical approaches such as routine use of uterine manipulators in this population.

The same consideration may be applied in OS outcome, with a percentage closer to LACC's Abdominal Arm than MIS one (3 years OS 99% and 93.8%, respectively).

Furthermore, direct comparison studies did not show a statistically significant difference between LARVH and ARH, probably due to the very small number of studies. Similarly, however, the data show a trend that does not portend inferiority of the LARVH approach compared to the ARH one.

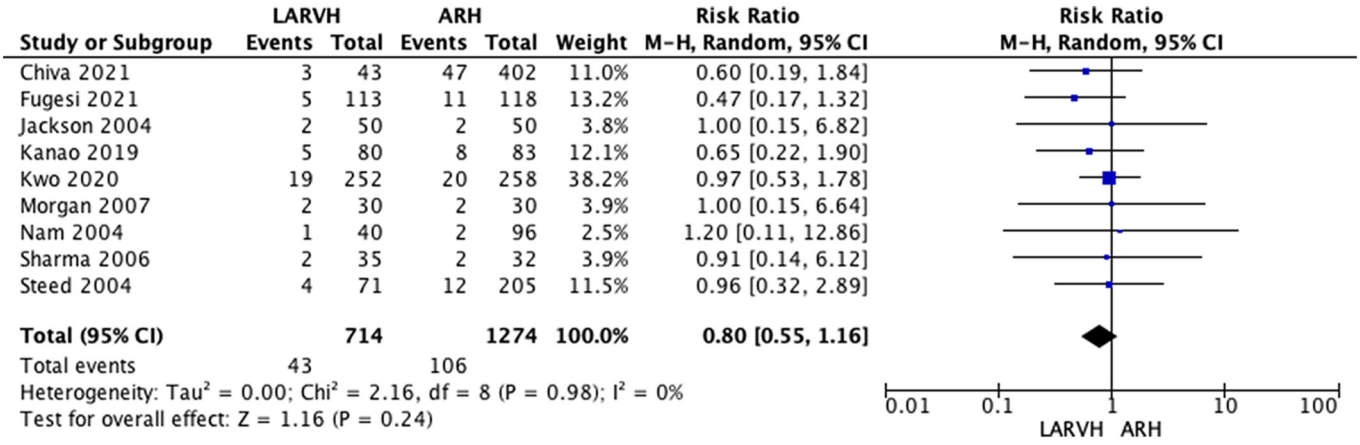


**Fig. 2.** DFS forest plot.


**Fig. 2.1.** DFS >2 cm forest plot.

This would support the hypothesis that the LARVH technique could represent a safe alternative to ARH precisely because it lacks all those vulnerabilities highlighted for LRH.

Similarly, a "hot topic" is the treatability of tumors <2 cm [45,46] by the MIS approach Sub-analysis of the LACC Trial proved a different Relative Risk for MIS and Open group (1.6% vs 0.3%, respectively, $p = 0.9$) and is the only known randomized clinical trial. Anyway, it is necessary to point out that LACC tiral was not powered to confirm the observed results in this subgroup of patients. But numerous retrospective series highlighted a comparable 5 years DFS and risk of death between LRH and ARH, even if in the absence of statistical significance [32–34]. In contrast, the same studies have shown unfavorable oncological outcomes for the MIS approach in cases of tumors >2 cm. For this reason, a sub-analysis of our study was dedicated to patients with tumors >2 cm.

As shown in the results, the studies showed a different range of DFS and OS in this type of patient, which can be difficult compared with ARH expected ones.

Only 5 studies were feasible to obtain data about this population and meta-analysis wasn't able to establish a comparison between LARVH and ARH. Moreover, the bigger the tumor is, the more vaginal tissue is demanded to form the vaginal cuff. Even in the absence of data, tumor size may continue to be a limitation to the MIS approach. This limitation, however, could be bypassed by conization preparatory to surgery. This method has been described in the literature and could also show an improved DFS and lower probability of receiving adjuvant treatment of ECC with higher tumor burden [47].

A final consideration is necessary regarding the pattern of relapses. If one leading hypothesis about MIS' worse outcomes come from tumor spillage at the time of colpotomy, we do not expect to see a higher local recurrence rate in a patient treated with LARVH.

These studies have shown very heterogeneous results. Only Kwon, Li, Renaud and Turné showed a higher distance Recurrence rate. On the other hand, some series showed no distant recurrence (Nam, Querleu and Sharma). This difference, which has not shown any

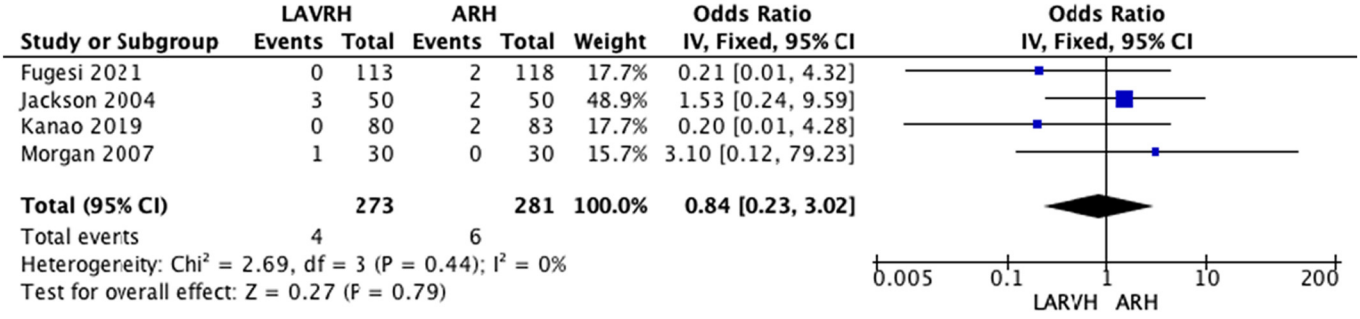


**Fig. 3.** OS forest plot.

statistical significance, can have its roots in multiple factors. For example, Li's and Kwon's studies, one more, involves the use of a uterine manipulator, which in itself is a manipulation of the tumor mass and can favor its spread [23]. Moreover, the technique described by Li requires the sacrifice of a substantial part of the vagina (placement of a ligature closure at 4 cm from the tumor margin), forcing the operator to an almost total colpotomy and potentially exposing the patient to unnecessary morbidity. As well, the highest Loco-regional RcR was reported in the eldest study with the fewest population (Querleu 1993 25%, 8 patients), and may have suffered from the low diffusion of the technique at that time. Even the most recent review of the literature did not show a significant difference among a pattern of recurrence between MIS and open approach [48]. The lack of uni- and multivariate analyzes with other risk factors for distant diffusion, such as Grading [49] or LVSI [50], makes this data difficult to interpret. Moreover, direct data from the ARH approach in comparative studies would also be needed to testify the effectiveness of the LARVH approach.

The strength of this study can be found in the rigor of the research, which included everything that has been published regarding LARVH or its declinations. Similarly, the statistical evidence in all oncological outcome studies comparable to ARH respects the objective of the study to prove the non-inferiority of techniques involving non-exposure of the tumor to the abdominal cavity compared with the open approach. On the contrary, weaknesses are represented by the great prevalence of retrospective studies and with the presence of only 9 comparative studies between vaginal cuff creation techniques and ARH and really few data about OS. As well, the high heterogeneity of the studies and the large time range during which they were conducted may limit their clinical impact.

Currently, the issue of the feasibility of MIS in the ECC is of crucial importance and under investigation. Several international RCTs [51,52] are underway to refine our knowledge on the risk mechanisms exercised by this approach.

## 5. Conclusion

Ultimately, LRVH represents a variation of the much more widespread LRH. It has a long learning curve that has prevented its spread worldwide. Consequently, few surgical schools, often concentrated in specific regions of the world, have published data relating to this technique. This limits the current scientific evidence regarding the technique and undermines this study. Similarly, however, it can be a good starting point to deepen our knowledge of the MIS approach in ECC. Moreover, the trend is shown by our results it can lay the foundation for controlled clinical trials.

## Conflict of interest disclosure

The authors made no disclosures. No specific funding was disclosed.

## CRediT authorship contribution statement

**Carlo Ronsini:** Conceptualization, Methodology, Data curation, Writing – original draft. **Christhardt Köhler**: Validation. **Pasquale D.E. Franciscis:** Data curation. **Marco La Verde**: Formal analysis. **Lavinia Mosca:** Data curation. **Maria Cristina Solazzo**: Statistic Analysis. **Nicola Colacurci:** Validation.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.04.010.

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