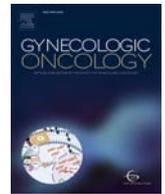




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Laparo-assisted vaginal radical hysterectomy as a safe option for minimal invasive surgery in early stage cervical cancer: A systematic review and meta-analysis

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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

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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. 18 studies fulfilled inclusion criteria. 8 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. 3033 patients were included. Meta-analysis highlighted a non-statistic significant difference between LAVRH and ARH (RR 0.82 [95% CI 0.55–1.23] $p = 0.34$; $I^2 = 0\%$; $p = 0.96$). OS was feasible only for 3 studies (RR 1.14 [95% CI 0.28–4.67] $p = 0.43$; $I^2 = 0$ $p = 0.86$). Data about the type of recurrences (loco-regional vs distant) were collected.

Conclusion. LAVRH 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 LAVRH in the ECC.

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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. In the case of studies published with analysis of the same population, only the earliest publications with the longest follow-up were considered. 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 >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 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 Appendix.

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

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, 18 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 8 were comparative studies between LARVH 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 [31] in 1987 with the name of Coelio-Schauta. Despite a few technical differences, all the studies reported crucial standardized procedures, such as vaginal creation of the vaginal cuff; closing of the vaginal cuff by suture or permanent tie; opening the Douglas pouch and vesico-vaginal space; parametrial-paracolpium resection only after transvaginal creation and closure of the vaginal cuff.

All steps of LARVH are performed intracorporeally except for the creation of the vaginal cuff plus or minus parametrial resection. At the time

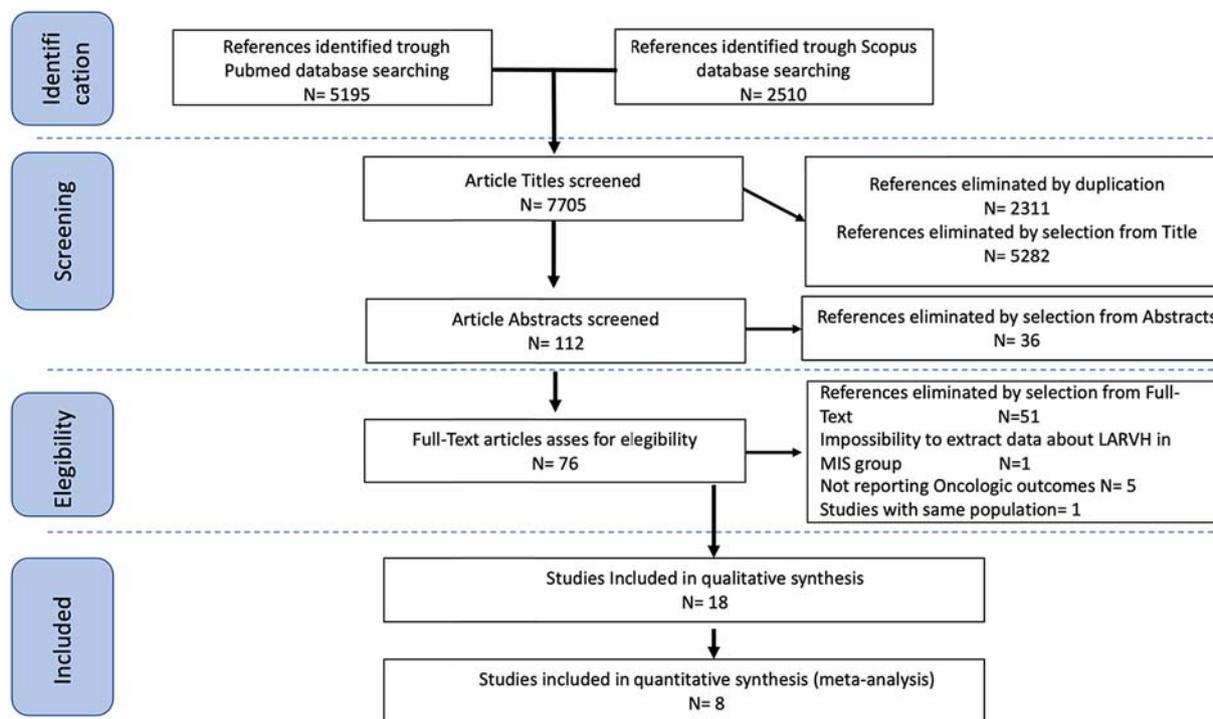


Fig. 1. PRISMA Flowchart.

of colpotomy, vaginal walls are cut just below vaginal cuff formation, to ensure no exposition of the tumor mass to the abdominal cavity.

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 [26], all the other studies avoided the use of uterine manipulators. Moreover, Kanno [14], and Fugesì [24] explicitly declared that they systematically removed surgical specimens into a collection bag. No data about surgical specimen retrieval 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 [31] or Piver Classification [32] and principal international Guidelines [1,2].

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

3.3. Oncological outcomes

A total of 3033 patients were included in the review. 17 of the 18 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 [29] and Steed [30], the other 13 studies presented OS data.

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. Fugesì 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 \leq 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%). 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. [26], 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 retrieved 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. [27], 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. [28], 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

Table 1
Studies included.

Name	Country	Study design	Study Year	FIGO stage	N of participant	Mean FUP* months
Not Comparative Studies						
Hertel [13] 2003	Germany	Prospective Observational Monocentric study	1994–2002	IA1-IB1	110 [^]	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 [^]	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 [^]	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 [^]	59
Fugesí [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
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

[^] Sub-analysis of the entire cohort.

* Follow Up.

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. [29] 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. [30] 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.

Table 2
LARVH oncological outcome.

Name	3Y DFS* (%)	3Y OS° (%)	4.5Y DFS* (%)	4.5Y OS° (%)
Chiva 2021	-	-	93.0	-
Fugesí 2021	92.4	100	90.9	100
Hertel 2003	-	-	94.0	98.0
Jackson 2004	-	-	94.0	94.0
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

° Overall Survival.

* Disease Free Survival.

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 5 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%. No statistical difference was observed in those distributions (p 0.180) (Table 3).

3.4. Meta-analysis

The 8 studies comparing LARVH and ARH were enrolled in the meta-analysis. A total of 1825 patients were analyzed. 634 patients in the LARVH arm were compared with 1191 patients which underwent ARH, exploring DFS outcome. Because of low heterogeneity (I² = 0%; p = 0.98), fixed-effects model was applied.

LARVH group showed a non-significant better DFS than ARH (RR 0.82 [95% CI 0.55–1.23] p = 0.34) Fig. 2.

We aimed to performed a sub-analysis for the patients with a tumor's maximum diameter >2 cm. Unfortunately, only the study by Fugesí [24] documented direct comparison in this subgroup of patients, so no meta-analysis was feasible.

In the end, Fugesí, Jackson, and Morgan presented comparative data about OS and were included in a second meta-analysis. (RR 1.14 [95% CI 0.28–4.67] p = 0.43; I² = 0 p = 0.86) (Fig. 3).

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

Name	3Y DFS* (%)	3Y OS° (%)	4.5Y DFS* (%)	4.5Y OS° (%)
Fugesí 2021	85.0	-	85.0	-
Kanno 2019	-	-	94.0	96.0
Kwon 2020	-	-	79.1	81.5
Li 2022	-	-	91.2	94.1
Marchiole 2007	-	-	87.3	89.9

° Overall Survival.

* Disease Free Survival.

Table 3
Type of recurrence.

Name	Loco-regional Recurrence Rate (%)	Distant Recurrence Rate (%)	p
Fugesi 2021	2.7	2.7	
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	0.180

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. [34] 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. [35] 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 [36] since 1908 and Wertheim [37] 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 [8,37,38,39]. 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 [14,40–42]. Other studies proved the hypothesis that LARVH prevents tumor cells' spillage [43]. 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. [26], 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.

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 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. 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 [31–33]. In contrast, the same studies have shown unfavorable oncological outcomes for the MIS approach in cases of tumors >2 cm. For this reason, we supposed to perform 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 4 studies were feasible to obtain data about this population and meta-analysis wasn't able to be performed and obtain 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.

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 [44,45].

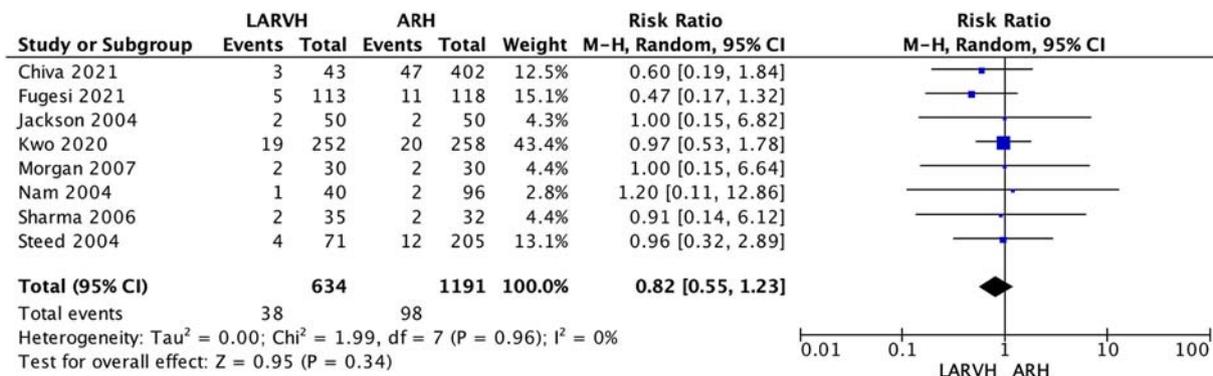


Fig. 2. DFS forest plot.

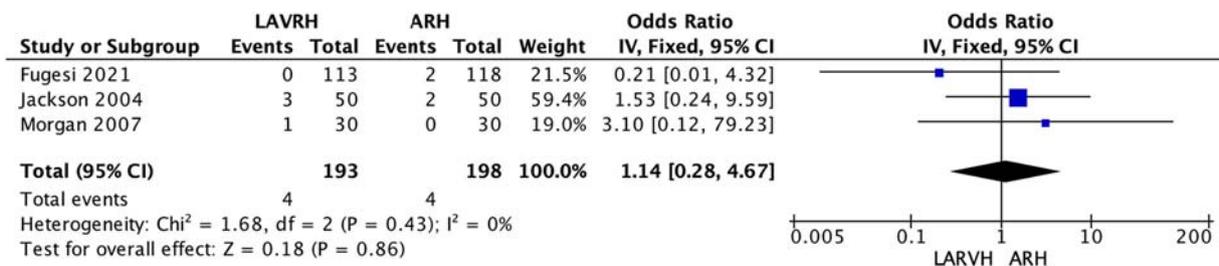


Fig. 3. OS Forest Plot.

These studies have shown very heterogeneous results. Only Kwon, Li, Renaud and Turné showed a higher distant Recurrence rate. On the other hand, some series showed no distant recurrence (Nam, Querleu and Sharma). This difference, which has not shown any 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]. 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 [46]. The lack of uni- and multivariate analyzes with other risk factors for distant diffusion, such as Grading [47] or LVSI [48], 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 LAVRH approach.

The strength of this study can be found in the rigor of the research, which included everything that has been published regarding LAVRH. Similarly, the statistical evidence in all oncological outcome studies comparable to ARH respects the objective of the study to prove the non-inferiority of one technique over the other. On the contrary, weaknesses are represented by the great prevalence of retrospective studies and with the presence of only 8 comparative studies between LAVRH and ARH and really few data about OS.

Currently, the issue of the feasibility of MIS in the ECC is of crucial importance and under investigation. Several international RCTs [49,50] 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.

Author contribution

C. R.: Conceptualization, Methodology, Data curation, Writing - original draft. C. K.: Review & Editing. P. D. F.: Data curation. M. L. V.: Formal analysis. L. M.: Data Curation. M. C. S.: Formal Analysis. N. C.: Review & Editing, Validation.

Declaration of Competing Interest

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