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Review Article

Simple hysterectomy versus radical hysterectomy in early-stage cervical cancer: A systematic review and meta-analysis

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ABSTRACT

Background: This systematic review (SR) and meta-analysis aims to compare the surgery-related results and oncological outcomes between SH and RH in patients with early-stage cervical cancer.
Method: We systematically searched databases including PubMed, Embase and Cochrane to collect studies that compared oncological and surgery-related outcomes between SH and RH groups in patients with stage IA2 and IB1 cervical cancer. A random-effect model calculated the weighted average difference of each primary outcome via Review Manager V.5.4.
Result: Seven studies comprising 6977 patients were included into our study. For oncological outcomes, we found no statistical difference in recurrence rate [OR = 0.88; 95% CI (0.50, 1.57); P = 0.68] and Overall Survival (OS) [OR = 1.23; 95% CI (0.69, 2.19), P = 0.48]. No difference was detected in the prevalence of positive LVSI and lymph nodes metastasis between the two groups. Concerning surgery-related outcomes, the comprehensive effects revealed that the bladder injury [OR = 0.28; 95% CI (0.08, 0.94), P = 0.04] and bladder disfunction [OR = 0.10; 95% CI (0.02, 0.53), P = 0.007] of the RH group were higher compared to the SH group.
Conclusion: This meta-analysis suggested there are no significant differences in terms of both recurrence rate and overall survival among patients with stage IA2-IB1 cervical cancer undergoing SH or RH, while the SH group has better surgery-related outcomes. These data confirm the need to narrow the indication for RH in early-stage cervical cancer.

1. Introduction

Cervical cancer is a major public health problem, with an estimated 604,000 new cases and 342,000 deaths in 2020, ranking as the fourth leading cause of cancer incidence and mortality in women worldwide [1]. Cervical cancer shows highest incidence in the 40–65 years old age group with an incidence rate of 16 per 100,000 women [2]. Because of the effective use of screening recommended by World Health Organization [3], an increasing number of women are being diagnosed with cervical cancer in an early stage of the disease with a 5-year Overall Survival (OS) of 60–90% [4]. According to the latest update of the European guidelines on cervical cancer treatment published in 2023 [5], simple hysterectomy (SH) with sentinel lymph node is adequate treatment for patients with stage IA2 disease and radical hysterectomy (RH) with pelvic lymphadenectomy is the primary surgical treatment for patients with stage IB1-IB2-IIA1 cervical cancer. The type of RH shall

Abbreviations: SH, simple hysterectomy; RH, radical hysterectomy; LVSI, lymphovascular space involvement; RCT, randomized controlled trial; FIGO, International Federation of Gynaecology and Obstetrics.

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depend on prognostic risk factors identified preoperatively. Prognosis depends mainly on staging, tumor size, lymph node and parametrial involvement, depth of stromal invasion and lymphovascular space involvement (LVSI) [6,7]. Regarding parametrial invasion, less than 1% of early-stage cervical cancer shows parametrial spread, in particular if tumor size is less than 2 cm and there is no LVSI or lymph node involvement [8–10]. Based on literature evidence, a trend has recently been established towards less radical surgical approach in patients with low-risk cervical cancer to reduce morbidity associated with parametrectomy while performing RH, thus ensuring oncological safety. One of the main and most promising clinical trials on this specific issue is the SHAPE Trial [11]. During the 2023 annual conference of the American Society of Clinical Oncology (ASCO), Plante et al. presented the study findings indicating the non-inferiority of SH to RH in terms of recurrence rate and overall survival in low-risk early-stages patients. In addition, Authors showed that RH is related to a higher rates of surgery related incidence of urinary incontinence and urinary retention having therefore an important impact on a patient's quality of life (QoL) [12–14].

The aim of present SR and meta-analysis is to summarize current evidence in literature regarding oncological safety of less radical surgery (SH versus RH) in patients with stage IA2-IB1 cervical cancer and to provide evidence supporting the role of surgical de-escalation in those patients.

2. Methods

1. Search strategy

A systematic search of PubMed (MEDLINE), Embase and CENTRAL (Cochrane Library) was conducted on October 13, 2023. The 1029 articles published from 2000 and November 2023 found in the different databases were uploaded onto the Rayyan platform. The review was promptly registered with the International Prospective Register of Systematic Reviews PROSPERO (Registration No CRD42023481056) and has been conducted in accordance with PRISMA Guidelines Statement 2020 [15].

2. Eligibility criteria and study selection

We included studies with the following inclusion criteria: (1) studies reporting the comparison of oncological outcomes between SH with RH in patients with cervical cancer; (2) studies enrolling patients with early-stage low risk cervical cancer (squamous, adenocarcinoma or adenosquamous cervical carcinoma), including stages IA2 and IB1 under the FIGO (International Federation of Gynaecology and Obstetrics) 2009 staging criteria (as stated in the SHAPE Trial); (3) studies reporting data about survival analysis (overall survival, recurrence rate, disease-free survival); (4) studies reporting data about intraoperative and postoperative complications. We excluded studies including patients with IA1 or > IB1 stages, studies including patients who underwent fertility-sparing treatment (conization alone or radical trachelectomy) as definitive surgery, studies not reporting duration of follow up. The main outcomes were OS and recurrence rate between the two groups. Secondary outcomes were intra- and postoperative complications. Published and unpublished material were subjected to the same rigorous methodological evaluation.

Finally, single case reports, meta-analysis, books chapters and editorial letters were excluded.

Two reviewers independently reviewed and screened title and abstracts according to the predefined strategy and criteria. Then full-text articles of selected studies were retrieved. The discrepancies in decisions regarding study inclusion were discussed by the authors until agreement was reached.

3. Data extraction

Microsoft Excel was utilized to collect and summarize the alternative data. The following data and information were extracted: type of study, sample size, mean age, tumor histotype, tumour size, FIGO stage, diagnostic method was performed (e.g. whether diagnostic conization was performed prior to surgery), follow up period, type of surgical approach, lymph node status, presence of LVSI, parametrial involvement and the duration of follow-up. Among the final parameters we considered OS, Disease Free Survival (DFS), mortality, recurrence rate. Then we considered surgery-related outcomes such as intraoperative complication (bladder injury, major vessel injury, ureteral injury) and postoperative complication (bladder disfunction, lymphedema, symptomatic lymphocist, ureterostenosis and deep vein thrombosis).

4. Quality assessment

The quality of the included studies was evaluated using the ROB1 for randomized studies. Two independent reviewers assessed the risk of bias including selection bias, performance bias, detection bias and attrition bias. The level of risk (low risk, unclear risk, and high risk) for each item was subsequently evaluated for bias. Observational studies were examined according to the scale of ROBINS 2.

5. Statistical analysis

We performed meta-analyses with the generic inverse-variance method with a random-effects model considering the heterogeneity between the studies. We used the Odds Ratio (OR) with 95 % two-sided confidence intervals (CI) as the principal summary measure for survival and surgery-related outcomes. Hazard Ratio (HR) with 95 % two-sided confidence intervals (CI) was also used as summary measure for OS. Heterogeneity within each subgroup was reported with the I-square statistics. If present ($P < 00.1$, $I2 > 50\%$), *sensitivity analysis* or subgroup analysis was used to find the source of the heterogeneity. We conducted meta-analyses with the Review Manager software, version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) and considered p-values below 0.05 statistically significant.

3. Results

3.1. Study selection

The initial searches identified a total of 1029 articles. Once duplicates were removed, 985 unique articles remained, we reviewed titles and abstracts to identify those that met the inclusion criteria. Full-text copies of the remaining 17 articles were obtained and analyzed again for eligibility. During the selection process, where consensus was initially reached between the two reviewers, the analysis of individual studies highlighted the need to exclude 10 additional studies. Smrkolj et al., in 2012, presented results exclusively for the microinvasive stage IA1, preventing us from extrapolating a subgroup of interest for our meta-analysis [16]. Similarly, Pluta et al. [17], Marana et al. [18], and Ostor et al. [19] were excluded since their results lacked differentiation by tumor stages of interest. Consequently, we were unable to extrapolate a subgroup pertinent to our endpoints. Then, we excluded three additional studies including patients treated solely with conization [20–22] and one study in which the type of surgery was not reported in detail [23].

Our final analysis incorporated a total of 7 studies, comprising 6977 enrolled patients. These studies were performed in Canada (1), Brasil (1), Italy (1), China (3) and USA (1). Of the total number of patients, 2779 underwent SH and 4197 underwent RH.

Four RCTs [11,24–26] and three observational studies [27–29] that evaluated the association between SH vs RH and oncological and surgery-related outcomes were included in the review (see Fig. 1).

3.2. Quality assessment

Regarding the randomization process, none of the four RCTs showed a "high" overall risk of bias assessed by the ROB 1 scale. Secondly, in terms of selection and attrition bias, all trials were concerned as low risk. Moreover, two RCTs were estimated as unclear risk in the detection bias, and two studies were at low risk. Regarding reporting bias, all trials were considered as low risk with the exception for one trial that was concerned as unclear risk (Fig. 2A). Most observational studies got an "unclear" bias rating based on ROBINS-I, because of concerns about confounding variables across all the studies (Fig. 2B).

3.3. Study characteristics

The characteristics of the included studies are summarized in Table 1.

Six studies assessed outcomes for both IA2 and IB1 FIGO stages. Data for only IB1 stage were available in 2 studies.

The predominant histotype was squamous cell carcinoma (SCC). Adenocarcinoma (ADC) and adenosquamous (ADSQ) histotypes followed in frequency. All the included studies excluded the more aggressive and less common histotypes from the eligibility criteria.

Preoperative staging was not commonly detailed in selected studies. Wang et al. and Carneiro et al. included conization in the preoperative assessment but do not specify the percentage of patients in whom it was performed.

Regarding the type of surgical approach, in two studies all procedures were performed laparoscopically, in one study 100% of the procedures were abdominal hysterectomy, two studies did not report data about minimally invasive surgery (MIS) or open approach, whereas the remaining studies included both MIS and open hysterectomies.

1. LVSI positive

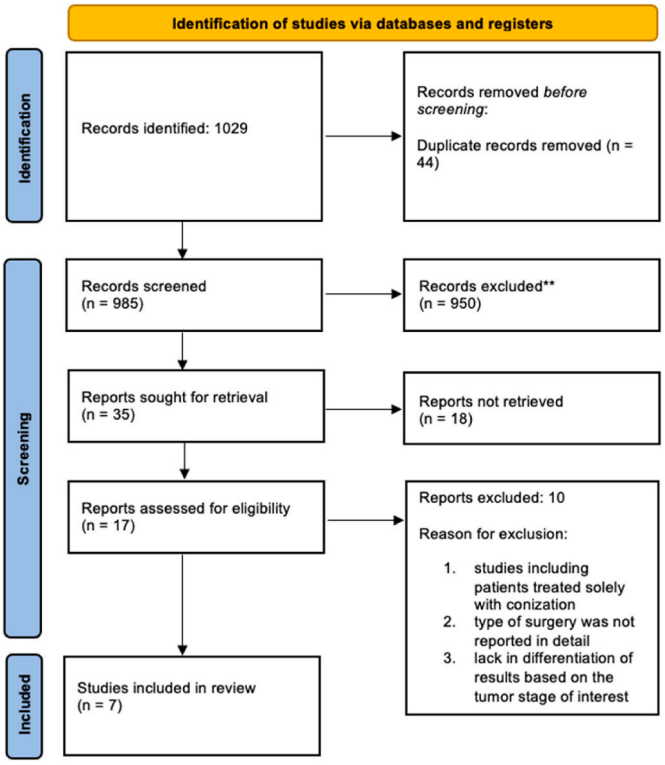

Fig. 1. PRISMA flowchart.
** we reviewed titles and abstracts to identify those that met the inclusion criteria.

Six of the seven studies reported data related to LVSI. A total of 383 (17.5%) patients with presence of LVSI were reported among SH, and 566 (12.10%) among RH. No difference in terms of LVSI were observed in the SHAPE trial between SH and RH (p value = 1.00). Our pooled analysis showed that there was no difference in positive LVSI [OR = 1.31; 95% CI (0.92, 1.86); P = 0.13] between the SH group and the RH group in patients with IA2-IB1 cervical cancer (Fig. 3A).

2. Lymph nodes metastasis

Six of the seven studies reported data related to lymph nodes metastasis. In the study performed by Carneiro et al. all patients underwent pelvic lymph node dissection without sentinel lymph node biopsy in association with SH or modified RH. Similarly, both SH and RH included bilateral pelvic lymphadenectomy in the study performed by Plante et al., Landoni et al., Wang et al., Chen et al. In another study (Liu et al.) RH or SH were performed with or without pelvic lymphadenectomy.

Our pooled analysis showed that there was no difference in lymph nodes metastasis [OR = 1.27; 95% CI (0.97, 1.67); P = 0.07] between the SH group and the RH group in patients with 1A2-1B1 cervical cancer (Fig. 3B).

3.4. Primary outcome

3.4.1. Survival and recurrence data

Among the 17 studies, 7 studies reported relevant summary statistics, including overall survival and disease-free survival. Carneiro et al. and Liu et al. reported both OS and DFS, whereas other studies reported only 3-year or 5-year OS (Table 2).

Six studies reported no significative difference in the OS in patients that received RH compared with SH. 5 studies reported a total of 120 deaths in 2512 patients (4.7%) who underwent SH and 155 deaths in 3882 patients (3.9%) who underwent RH.

3.4.1.1. Recurrence rate. Five studies reporting the results of recurrence included 1403 patients. The pooled analysis showed that there was no difference in recurrence [OR = 0.88; 95% CI (0.50, 1.57); P = 0.68] between the SH group and the RH group, with low heterogeneity (I2 = 0%). (Fig. 3C). The publication bias of recurrence was assessed in Egger's test, which showed no publication bias.

SHAPE trial reported distinct results for pelvic and extra-pelvic recurrence. Both SHAPE and LESSER trial reported recurrence at 3 years, Chen et al. 5 years, Wang et al. and Liu. et al. reported recurrence with a mean follow-up respectively of 29 months (2.5 years) and 45 months. Considering only the studies that considered a 3-year risk of recurrence, the results did not vary significantly [OR = 0.95; 95% CI (0.43, 2.11); P = 0.91].

Finally, we performed a subgroup analysis only including studies where both SH and RH were performed laparoscopically only (Wang et al. and Chen et al.). However, the difference in recurrence rate remains statistically insignificant between the two groups [OR = 0.56; 95% CI (0.20, 1.58); P = 0.27].

3.4.1.2. 5-Years overall survival. Seven studies reported results on OS and included 6977 patients. In a random effects meta-analysis, the pooled results showed that there was no difference in the overall survival [OR = 1.23; 95% CI (0.69, 2.19); P = 0.48] between the SH group and the RH group, with moderate heterogeneity (I2 = 40%) (Fig. 3D). The publication bias of the overall survival was assessed in Egger's test, which showed no publication bias.

After the exclusion of SHAPE trial which calculated the OS at 3 years compared to the 5 years of the other studies, the results did not change substantially [OR = 1.30; 95% CI (0.71, 2.39); P = 0.40].

Similar results were found when we considered only studies

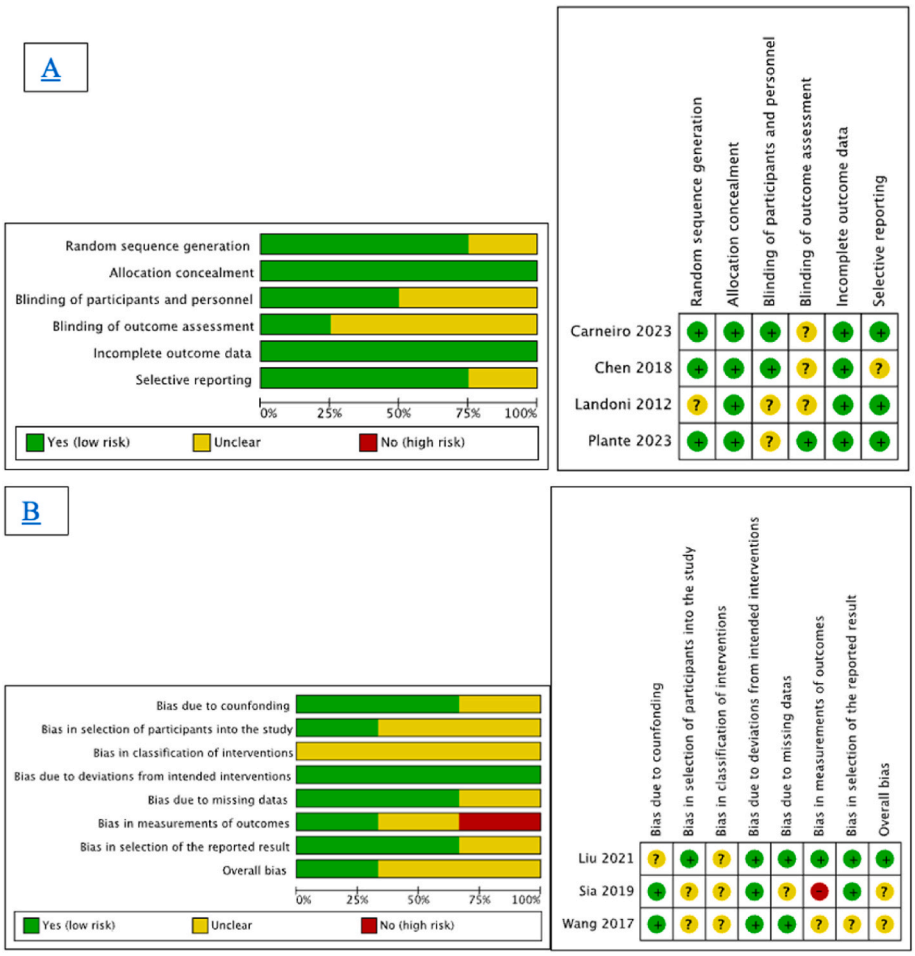

Fig. 2. A) ROB1 for RCTs summary and graph: review authors' judgements about each risk of bias item for each included study B) ROBINS 2 for observational studies summary and graph: review authors' judgements about each risk of bias item for each included study.

including only FIGO stage 1B1 [OR = 0.59; 95% CI (0.07, 4.83); P = 0.63]. In addition, we performed a sub-group analysis removing the studies in which both SH and RH were performed with a minimally invasive approach. However, the results did not vary significantly [HR = 1.08; 95% CI (0.52, 2.26); P = 0.84]. Additionally, since the meta-analysis is dominated by data from the study performed by Sia et al., which is a retrospective analysis of a national cancer database, we performed a sensitive analysis after the exclusion of this study. We found that results did not vary substantially [OR = 0.92; 95% CI (0.51, 1.66); P = 0.78]. with low heterogeneity (I2 = 0%)

Three studies reported the results of the overall survival with HRs using Cox regression proportional hazards model. The pooled analysis considering only HRs showed that there was no difference in the 5 years OS [HR = 0.79; 95% CI (0.50, 1.25); P = 0.31], with low heterogeneity (I2 = 0%) (Table 3).

3.4.2. *Intraoperative complications*

A total of 4 studies described intraoperative and/or postoperative complications.

Intraoperative complications were described only by 2 studies. They reported a total of 3 intraoperative bladder injury (0.7%), 4 major vessel injury (0.9%) and 3 intraoperative ureteral injury (0.7%) among 407 patients who underwent SH and 12 intraoperative bladder injury (2.8%), 2 major vessel injury (0.4%) and 6 intraoperative ureteral injury (1.4%) among 414 patients who underwent RH (**Supplemental Material 1**).

In a random effects meta-analysis, the overall risk of intraoperative complication in terms of bladder injury was statistically significant higher in RH group [OR = 0.28; 95% CI (0.08, 0.94); P = 0.04] with low heterogeneity (I2 = 0%). No significant differences were found in terms of major vessel injury [OR = 1.54; 95% CI (0.14, 17.22); P = 0.04, I2 = 38%] and ureteral injury [OR = 0.55; 95% CI (0.15, 2.04); P = 0.37, I2 = 0%] between the two groups. Due to lack of data no sensitivity analysis was performed (**Supplemental Material 2**)

3.4.3. *Post-operative complications*

A total of 4 studies reported post-operative complications. Of the post-operative complications noted, the most described was bladder dysfunction (23.1%) which was reported in 29 patients out of 453 patients who underwent SH (6.4%) and in 185 patients out of 470 patients who underwent RH (39.3%). Carneiro et al. reported a cumulative incidence rate of post-operative complications with a total of 8 complications, 3 in the SH group (15%) and 5 (25%) in the RH group (p value 0.69) (**Supplemental Material 3**)

In a random effects meta-analysis, the overall risk of bladder disfunction was significantly higher in the RH group compared to SH group [OR = 0.10; 95% CI (0.02, 0.53); P = 0.007], consistent with the report results in most literature.

Lymphedema was reported in 0.6% of SH group and in 2.3% of RH group. Only one study found a statistical significative differences between the two groups regarding incidence rate of lymphedema and symptomatic lymphocyst whereas other studies did not highlight such difference reporting similar rates between SH and RH group. The pooled analysis showed that the prevalence of lymphedema was higher in RH group, with low heterogeneity (I2 = 0%). However, this difference was not statistically significant [OR = 0.30; 95% CI (0.08, 1.10); P = 0.07].

Table 1
Characteristics of the included studies.

Study	Country	Study design	Patients	Mean age	Histotype	Tumor dimension	Stage	LVSI positive	Parametrial involvement	Lymph node metastasis	Preoperative assessment	Operative time	Blood loss	MIS/Open/ Robot	Hospital stay (days)	Adiuvant Therapy
Plante 2023	Canada	RCT	Total: 700 (but 18 patients never received surgery) SH = 338 RH = 344	44	SCC, ADC, ADSQ	<2 cm	FIGO IA2/ IB1	SH = 45/ 338 (13.3%) RH = 45/ 344 (13.1%) p value 1.00	SH = 0/338 RH = 6/344 (1.7%) p value 0.03	SH = 11/ 338 (3.3%) RH = 15/ 344 (4.4%) p value 0.55	PE, RVE, colposcopy, Chest x-ray or CT scan of chest and pelvic MRI conization/ cervical biopsy	–	–	−50% MIS (56% SH vs. 44% RH), -25% robot (24% vs. 25%) −23% open (17% vs. 29%)	–	SH = 31/338 (9.2%) RH = 29/344 (8.4%) pvalue 0.79 ++ chemoradiation
Carneiro 2023	Brasil	RCT	Tot = 40 SH = 20 RH = 20	37	SCC, ADC	<2 cm	FIGO IA2/ IB1	Tot = 15/ 36 SH = 6/17 RH = 3/17	Tot = 2 (5%) SH = 1/20 RH = 1/20	Tot = 2 (5%) SH = 1/20 RH = 2/20 p value ns	PE, conization/ cervical biopsy	SH = 150 min (IQR 137.5–180) RH = 199.5 min (IQR 140–230) p value = 0.003	–	−92,5% Open (n = 37/40)	SH = 2 days (IQR 1–5) RH = 2 days (IQR 2–4) p = 0.51	SH = 6/20 (30%) RH = 4/20 (20%) p = 0.48
Wang 2017	China	Retrospective, matched cohort	tot = 140 SH = 70 RH = 70	43.5	SCC, ADC, ADSQ	<2 cm	FIGO IB1	0	0	Tot = 4/ 140 SH = 2/68 (2.8%) RH = 2/68 (2.8%)	Pelvic MRI or CT scan conization/ cervical biopsy	SH = 131.21 ± 37.88 RH = 226.43 ± 44.21 pvalue = 0	SH = 100.57 ± 46.59 RH = 224.29 ± 124.45 pvalue = 0	−100% LPS	SH = 2.96 ± 0.77 RH = 9.30 ± 4.99 pvalue = 0	SH = 2/70 RH = 2/ 70 chemoradiation
Chen 2018	China	RCT	tot = 101 SH = 45 RH = 56	48.5	SCC, ADC	<2 cm	FIGO IA2/ IB1	Tot = 25/ 101 SH = 10/45 RH = 15/56 pvalue ns	tot = 2 SH = 0 RH = 2/56	0	Chest RX and intravenous pyelography, pelvic MRI or PET-CT scan cervical biopsy	–	–	−100% LPS	–	Tot = 45/101 SH = 22/45 RH = 23/56 chemoradiation
Landoni 2012*	Italy	RCT	tot = 113 SH = 53 RH = 60	–	SCC, ADC	<3 cm	FIGO IB1	–	–	SH = 13, RH = 11	PE, measurement of the cervical diameter by an alginate mold, Chest RX, intravenous pielography, CT scan	–	–	−100% Open (laparotomy through a midline incision)	–	–
Sia 2019	USA	Retrospective	Tot = 5461 RH = 3390; SH = 2071	IA2: <40 (38.8), 40–49 (45.9), 50–59 (47.9)	SCC, ADC, ADSQ	<2 cm	IA2, IB1	76 RH vs 67 SH IA2; 390 RH vs 225 SH in IB1	–	IA2: 20 RH vs 17 SH IB1: 101 RH vs 48 SH	–	–	–	NA	–	IA2: external beam RH 38 vs SH 50; brachitherapy in 17 SH IB1: external beam RH 202 vs SH184; brachitherapy in 38 RH vs 51 SH
Liu 2021	China	Retrospective	Tot = 440 SH = 182 RH = 258	RH: 44.3 (SD 12.3); SH: 44.5 (SD 12.8)	SCC, ADC, ADSQ	<2 cm	IA2	SH = 30 RH = 37	3 (group not specified)	0*	Preoperative imaging (not specified)	–	–	- MIS in the RH cohort: 159 (61.6%) -MIS in the SH cohort: 131 (72%).	–	P < 0.001. RT: 10 RH vs 21SH; CHT: 13RH vs 27SH

Legend: SCC: squamocellular carcinoma, ADC: adenocarcinoma, ADSQ: adenosquamous, SH: simple hysterectomy, RH: radical hysterectomy, -; not available, pt: patient, cone: conization, RT: radiotherapy, CHT: chemotherapy, DIV: depth of invasion, MIC: microinvasive, CKC: cold knife conization, LEEP: Loop electrosurgical excision procedure, p: p value, SD: standard deviation, PE: pelvic examination, RVE: recto-vaginal examination, MIS: Minimally-invasive surgery.
*Patients with lymph node metastasis were considered ineligible for this study.

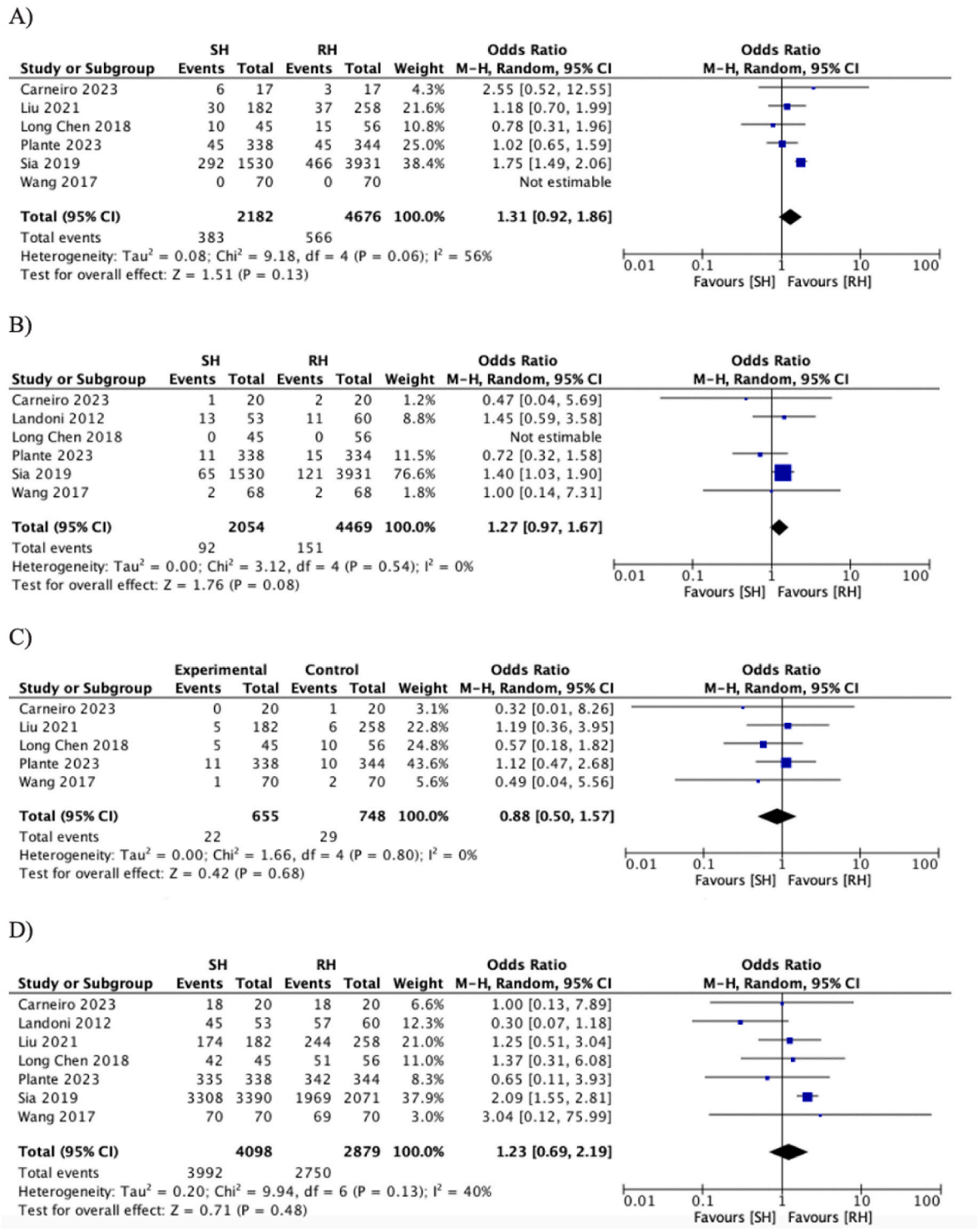

Fig. 3. A) Forest plot of positive LSVI; B) Forest plot of lymph nodes metastasis; C) Forest plot of recurrence rate; D) Forest plot of overall survival.

Finally, we found no statistically significant difference in other postoperative complication rate such as symptomatic lymphocist [OR = 0.41; 95% CI (0.12, 1.45); P = 0.17], ureterostenosis [OR = 0.32; 95% CI (0.03, 3.19); P = 0.33] and deep vein thrombosis [OR = 0.66; 95% CI (0.13, 3.23); P = 0.60] between SH group and RH group (**Supplemental Material 4**).

4. Discussion

In this review we examined the oncological outcomes of studies comparing SH versus RH for the treatment of FIGO stage IA2 and IB1 cervical cancer.

Historically, the rationale for performing radical parametrial resection was to remove the occult disease at the time of extirpation of the primary cervical lesion in order to improve survival and reduce the need for adjuvant radiation therapy [30]. Nevertheless, in the literature, numerous retrospective studies cast doubt on the necessity of parametrial resection in early-stage cervical cancer [31–34]. Two primary concerns have emerged: firstly, the low incidence of parametrial tumor involvement in a specific subset of patients with early cervical cancer

Table 2
Survival analysis.

Study	Lenght of follow up	Overall Survival	Recurrence rate	Disease Free Survival	Recurrence free survival	Mortality for CC
Plante et al., 2023	54 months	3 years-OS: SH = 99.1% RH = 99.4% (HR 1.09, p-value 0.89)	SH = 11 (3.1%) RH = 10 (2.9%)	3 year-DFS: SH = 96.3% RH = 97.8% (HR1.54, p value 0.30)	Pelvic RFS: SH = 97.5% RH = 97.8% (HR 1.12, p value 0.79) Extrapelvic RFS: SH = 98.1% RH = 99.7% (HR 3.82, p value 0.10)	SH = 4/350 (1.1%) RH = 1/350 (0.35%)
Carneiro et al., 2023	52 months	5 year-OS: SH = 90% (95% CI 64%–97%) RH = 91% (95% CI 50%–98%) (log-rank p = 0.46)	Tot = 1/40 (2.5%)	3 year-DFS: SH = 95% (95% CI 68%–99%) RH = 100% (95% CI 100%–100%) (log-rank p = 0.30).	–	SH = 1/20 RH = 0/20
Wang et al., 2021	75 months	5-years OS SH = 100% RH = 98.5 % p value 0.32	SH = 1/70 (1.4%) RH = 2/70 (2.8%)	–	5years-RFS: SH = 98.6% RH = 97.1% p value 0.56	SH = 0/70 RH = 1/70 (due to recurrence) pvalue ns
Chen et al., 2018	60 months (minimum)	5year-OS: SH = 93% RH = 91% p value ns	SH = 5/45 (11%) RH = 10/56 (18%)	–	–	0
Landoni et al., 2012	280 months (minimum)	5 years OS: SH 85% RH 95% p value = 0.11	–	–	–	–
Sia et al., 2019	56 months for IA2, 53 months for IB1	IA2 (HR 0.70, 95% CI 0.41–1.20, 5-years OS SH 97.6% RH 95.1%	–	–	–	IB1, SH 55% increased risk of death (HR 1.55, 95% CI 1.18–2.03)
Liu et al., 2021	45 mo in RH vs 39 mo in SH. p < 0.001	5year-OS: SH 95.71% RH 94.76%, p = 0.482 (aHR, 1.122; 95% CI, 0.319–3.493; P = 0.858)	RH = 6 (2.33%) SH = 5 (2.75%)	5-year-DFS SH 89.25% RH 91.14%, P = 0.562 aHR, 1.608; 95% CI, 0.640–4.041; P = 0.312	–	–

Legend: mo: months, CI: confidence interval, MA: multivariate analysis.

Table 3
Meta-analysis of oncological and surgery-related outcomes.

Outcome	Number of included studies	Meta-analytic effect (random-effect model)	P value
LVSI positive	6	[OR = 1.31; 95% CI (0.92, 1.86)]	P = 0.13
Lymph nodes metastasis	7	[OR = 1.27; 95% CI (0.97, 1.67)]	P = 0.07
Recurrence rate	6	[OR = 0.88; 95% CI (0.50, 1.57)]	P = 0.68
Overall survival	7	[OR = 1.23; 95% CI (0.69, 2.19)]	P = 0.48
Complications			
Bladder injury	3	[OR = 0.28; 95% CI (0.08, 0.94)]	P = 0.04
Major vessel injury	3	[OR = 1.54; 95% CI (0.14, 17.22)]	P = 0.04
Ureteral injury	3	[OR = 0.55; 95% CI (0.15, 2.04)]	P = 0.37
Bladder disfunction	3	[OR = 0.10; 95% CI (0.02, 0.53)]	P = 0.007
Lymphedema	2	[OR = 0.30; 95% CI (0.08, 1.10)]	P = 0.07
Symptomatic lymphocist	2	[OR = 0.41; 95% CI (0.12, 1.45)]	P = 0.17
Uretero stenosis	2	[OR = 0.32; 95% CI (0.03, 3.19)]	P = 0.33
Deep vein thrombosis	2	[OR = 0.66; 95% CI (0.13, 3.23)]	P = 0.60

(tumor size <2 cm, invasion depth <10 mm, and negative pelvic nodes) is less than 1%, making a radical approach seemingly unjustifiable [35]. Secondly, the excision of the parametrium, which contains autonomic nerve fibers, is linked to considerable morbidity in up to 38% of patients, including bladder dysfunction, sexual issues, and rectal dysmotility [30]. Given these factors, RH could represent an overtreatment.

The publication of the SHAPE trial results in *The New England Journal of Medicine* in 2024 marked a pivotal moment, providing new insight into the treatment of early-stage cervical cancer [11]. This randomized controlled trial (RCT), involving 700 patients, compared the pelvic recurrence rate at 3-years and surgery-related outcomes of SH versus RH in patients with FIGO stage IA2-IB1. The robustness of the trial design and the substantial sample size contribute to its strength. The LESSER trial shares a similar methodology and results with the SHAPE trial but is notably limited by a smaller sample size, with only 20 patients in both the SH and RH arms [24].

In a previous SR, Wu et al. included 21 studies reporting recurrence or survival outcomes among women with early-stage cervical cancer [36]. Despite the more stringent inclusion criteria in our SR (e.g., we excluded studies where even a small proportion of patients had undergone fertility-sparing treatments), our findings are consistent with Wu et al., suggesting that opting for less invasive surgery in women with stage IA2 and small IB1 cervical cancer is not inferior in terms of survival outcomes. Moreover, as shown in our pooled analysis, there is a significant difference in bladder injury and postoperative bladder disfunction in the RH compared to the SH group (respectively p = 0.04 and p = 0.007).

Furthermore, we also conducted a subgroup analysis considering the open or minimally invasive approach. In two studies, all SH and RH procedures were performed laparoscopically, in one study all procedures were abdominal hysterectomies, and in the remaining studies, both open and minimally invasive approaches were used. For early-stage cervical tumors, we did not observe statistically significant differences in the SH and RH groups in the subgroup analysis.

Despite the apparent discrepancy with the findings of the LACC trial

which reported improved disease-free survival, OS, and reduced recurrence rates in patients undergoing open surgery, the data in our subgroup analysis were insufficient to draw meaningful conclusions on this matter [37].

In two previous studies, Pareja et al. and Lu et al. evaluated outcomes related to radical parametrectomy after SH with incidental histologic diagnosis of early-stage cervical cancer [38,39]. Despite the differences in methodology, results in both studies demonstrated the non-inferiority of a less radical surgery in terms of survival. Both studies find only one recurrence. Pareja et al. reported the recurrence after 99 months of follow-up and Lu et al. after an average follow-up of 66 months. Lu reported an intraoperative complication during radical parametrectomy, specifically an ileal anastomosis due to intestinal damage. Additionally, postoperatively, a vesicovaginal fistula was noted. Conversely, Pareja et al. reported 3 intraoperative bladder complications and 5 postoperative complications, which were not further specified.

The feasibility of conservative surgery –SH or conization alone-in women with early-stage, low-risk cervical cancer was evaluated in the ConCerv Trial. In this prospective, single-arm, multicenter study, Schmeler et al. found that conservative surgery was associated with a 3.5% recurrence rate in women with low-risk cervical cancer [40].

Furthermore, recent results were published by Bizzarri et al. in the subanalysis of SCCAn Trial [41]. The primary objective of this substudy was to assess whether the extent of radical hysterectomy had an impact on 5 years free survival in patient with early-stage cervical cancer. Non-nerve-sparing RH was associated with an improvement of 5-years free survival compared to nerve-sparing RH and representing an independent protective factor for risk of recurrence. After stratifying patients according to the tumor diameter, Authors showed that non-nerve-sparing RH was associated with with improved 5-year disease-free survival only in patients with tumor between 21 and 40 mm and not in patients below 20 mm. Even if it is not possible to draw any conclusions about SH from this study, it confirms that less radical hysterectomy is oncologically safe in small volume low risk tumors, narrowing the indication for RH in early-stage cervical cancer.

Following the revised FIGO 2018 staging system, imaging methods are integrated into cervical cancer staging assignment. Recent evidence shows that both expert transvaginal/transrectal ultrasound (TRS/TVS) and magnetic resonance imaging (MRI) provide accurate preoperative information for tumor detection and assessment of local tumor extension, playing a fundamental role in identifying the population for whom a less radical procedure is safe and beneficial [42]. However, the decision to reduce radicality should be also take into accounts diagnostic accuracy and intrinsic pitfalls of imaging modalities, as well as the possibility of inter-observer variation [43].

Novel imaging technologies, such as fusion images that combine different modalities (e.g., MRI and PET, or MRI and ultrasound), along with the integration of radiomics and algorithms, including artificial intelligence (AI), are emerging as tools that can contribute to improve the precision of tumor characterization and aid in the selection of the most appropriate treatment strategies.

5. Limitations

The strength of our meta-analysis was to apply strict inclusion and exclusion criteria by selecting those studies methodologically similar to the SHAPE Trial. This resulted in the exclusion of several studies that included conization or radical trachelectomy as definitive treatment. In addition, to determine the robustness of the observed outcomes, we performed sensitivity analyses. We addressed sources of heterogeneity by assessing the meta-analytic effect before and after excluding studies that included only the laparoscopic approach or studies with large retrospective cohorts (Sia et al.). However, we observed that the results did not change substantially.

Nevertheless, this meta-analysis shows several limitations such as the retrospective nature of some included studies and the presence of others unmeasured confounders such as surgeon experience and the extent of radicality (according to various classifications) that may also play a role in influencing survival and surgery-related outcomes. Similarly, some data, including grade, number of complications, surgical approach (MIS/open), strategy of adjuvant treatment were not available for all patients.

In addition, as highlighted in the 'Statement of the Uterus Commission of the Gynecological Oncology Working Group (AGO) on Surgical Therapy for Patients with Stage IA2-IIB1 Cervical Cancer', reporting the SHAPE trial's bias, the percentage of patients who underwent preoperative conization was higher in the SH arm (84%) compared to the RH arm (76.3%). Since there is evidence that demonstrated that conization prior to carrying out RH appears to be associated with a better outcome, this difference might have contributed to a positive impact on survival analyses of the SH group [44].

6. Conclusion

Our pooled analysis suggested that there was no statistically significant difference in the recurrence rate and in 5 years OS between the SH group and RH group in patients with early-stage low risk cervical cancer. The prevalence of positive LVSI and lymph nodes metastasis was similar between the two groups. Moreover, our study found that the RH group has a higher rate of intraoperative bladder injury and postoperative bladder disfunction compared to SH group. Therefore, this SR and the meta-analysis of available evidence confirm the potential non-inferiority of SH compared to RH in patients with low-risk early-stage cervical cancer.

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Credit author statement

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Appendix A. Supplementary data

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