De-escalation of surgical radicality for non-fertility preserving management in patients with early-stage cervical cancer: a systematic review

David Viveros-Carreño, Rene Pareja, Marie Plante

ABSTRACT

Objective We sought to evaluate the oncologic outcomes of simple hysterectomy in patients with low-risk early-stage cervical cancer (tumors ≤2 cm with limited stromal invasion).

Methods This study was registered in PROSPERO (registration number CRD42023433840) following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist. MEDLINE (through Ovid), EmBase, and Cochrane Central Register of Controlled Trials were searched from inception until June 2023. Randomized controlled trials and observational studies with two arms of comparison (simple hysterectomy with lymph node assessment vs radical hysterectomy with lymph node assessment) in patients with low-risk early-stage cervical cancer were considered.

Results The search identified 1270 articles; eighteen studies were considered potentially eligible after removing duplicates, and four met the selection criteria. Three studies were randomized controlled trials, and the other was a retrospective cohort study. In total, 1813 patients were included. There were 485 (49.4%) and 496 (50.6%) patients in the simple hysterectomy and radical hysterectomy groups, respectively. Simple hysterectomy with lymph node assessment was not associated with a higher risk of death at 5 years (RR 0.98, 95% CI: 0.31 to 3.10; I²=0%), two randomized controlled trials, the risk of recurrence or death for simple hysterectomy in patients with low-risk cervical cancer was not inferior to the standard radical hysterectomy and this was associated with less morbidity.

Conclusion Simple hysterectomy with lymph node evaluation for low-risk early-stage cervical cancer is not associated with a detrimental effect on oncologic outcomes and has a better morbidity profile.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ According to guidelines, patients with early-stage cervical cancer who are not interested in future fertility undergo standard treatment with radical hysterectomy and lymph node evaluation. However, in such patients, retrospective and some prospective evidence shows that less radical surgery may achieve similar oncologic outcomes with less morbidity compared with radical surgery.

WHAT THIS STUDY ADDS

⇒ Based on this systematic review and meta-analysis, including three randomized controlled trials, the risk of recurrence or death for simple hysterectomy in patients with low-risk cervical cancer was not inferior to the standard radical hysterectomy and this was associated with less morbidity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given that the available evidence supports the de-escalation of surgical treatment in patients with low-risk early-stage cervical cancer (tumors ≤2 cm with limited stromal invasion) to simple hysterectomy and lymph node assessment, patients should be counseled regarding the best surgical treatment for their condition; guidelines likely will promote less radical surgery as the standard treatment or as a valid option in this patient population.

INTRODUCTION

Cervical cancer is the fourth most common malignancy in women worldwide. According to GLOBOCAN 2020, a total of 604,127 new cases and 341,831 deaths were estimated that year. The management for patients with early-stage cervical cancer (International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IA1+lymph vascular space invasion, IA2, IB1, and IB2) has been a radical hysterectomy with lymph node assessment (sentinel lymph node detection with or without pelvic lymph node dissection).

The surgical morbidity of radical hysterectomy is mainly due to the resection of the parametrium. The parametrectomy aims to identify and excise any micrometastatic disease that may have spread from the cervix in order to assure a safe resection margin. However, most patients undergoing radical hysterectomy have no parametrial disease, particularly patients with low-risk disease. The definition of low-risk disease is inconsistent, and includes a variable combination of prognostic factors such as tumor size ≤2 cm, limited stromal invasion (<10 mm depth
METHODS

For this review, we used a systematic approach following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist. This study was registered in PROSPERO (CRD42023433840). MEDLINE (through Ovid), Embase, and Cochrane Central Register of Controlled Trials databases were searched from inception until June 2023. The overall search strategy is included in the online supplemental file 1. We included articles published in the English language reporting randomized controlled trials and observational studies, with two arms of intervention comparing radical hysterectomy and lymph node assessment with simple hysterectomy and lymph node assessment. Single-arm studies, case reports, and commentaries were excluded. We contacted the authors for studies with available results but not yet published to get complete data for our review.

Studies included patients with confirmed FIGO 2018 stage IA1+lymph vascular space invasion, IA2, and IB1 cervical cancer, and histologic subtypes of squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. Criteria for excluding studies for this review were patients under 18 years of age, pregnancy, fertility-preserving surgery, and use of neoadjuvant chemotherapy or radiotherapy. Only the most complete manuscript was included in the review if two or more manuscripts were published by the same author/institution or using the same primary data source. The measured outcomes were overall survival (as defined by authors), progression-free survival (as defined by authors), and surgical short- and long-term morbidity (as reported by authors).

Two authors (RP, DV-C) independently assessed all titles and abstracts of records retrieved from the search strategy for inclusion. The final selection of trials for inclusion was undertaken independently by three authors (RP, MP, DV-C), and any disagreement was resolved through discussion. Two authors (RP, DV-C) extracted the data independently, and disagreement about extracted data was resolved through discussion until a consensus was reached. The risk of bias was assessed using the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool for observational studies and the Rob-2 tool for randomized controlled trials according to our protocol.

The information was presented as the median or mean (according to its normal distribution) and percentages with absolute counts if it was a quantitative or qualitative variable, respectively. Two of the authors entered the data into RevMan Web (Nordic Cochrane Center, The Cochrane Collaboration), using the Mantel-Haenszel fixed-effect model for dichotomous data in which the trials were judged sufficiently homogeneous. Results are presented as a summary risk ratio (RR) and as risk difference with 95% confidence intervals (95% CI). Statistical heterogeneity was assessed using the I² statistic and χ² test values, and substantial heterogeneity was considered to exist when the I² statistic was >50% and when a low p value of <0.1 was found in the χ² test. The publication bias was not explored as there were no >10 randomized controlled trials or non-randomized studies in any meta-analysis. According to local regulations, no institutional review board agreement was required for this study.

RESULTS

The search identified 1270 articles; after duplicates were removed, 831 manuscripts were evaluated, and the title and abstract screening of these references identified 18 studies as potentially eligible for this review. The full-text screening excluded 14 studies. Eight studies were excluded because >10% of reported patients did not undergo lymph node assessment,10–16 six were excluded as they did not report outcomes specifically for the population of interest,17 and four studies finally met the selection criteria18–21 (Figure 1). Studies were published from 201720 to 202318 19, with inclusion periods from 2002 to 2019. Three of the included studies were randomized controlled trials,18 19 21 and the other study was a retrospective cohort study.20

In total, 981 patients were included: 485 (49.4%) and 496 (50.6%) patients in the simple hysterectomy and radical hysterectomy groups, respectively. All studies included patients with clinical tumors ≤2 cm, three included tumors stage IA2–IB1,18 19 21 and one included only IB1 tumors.20 Two studies included only tumors with stromal invasion <10 mm,19 20 and one study excluded tumors with lymph vascular space invasion.20 Two studies compared a Piver-Rutledge class I versus class III hysterectomy,20 21 one as Querleu-Morrow type A versus type B,19 and one as a simple hysterectomy versus radical hysterectomy.19 Age was reported as the median in three studies18 19 21 with a range from 37 to 50 years, and in one study as the mean (44.0±8.46 years and 43.0±8.59 years),20 Two studies used only laparoscopic surgery,20 21 one study included minimally invasive surgery and open surgery,19 and one included minimally invasive surgery, open surgery, and vaginal surgery.19 In total, 963 of 981 reported patients who underwent surgical management (18 randomized patients in the SHAPE trial did not have surgery), 753 patients (78.2%) underwent minimally invasive surgery (584 laparoscopic and 169 robotic surgery), 193 patients underwent open surgery (20.0%), only 15 patients underwent vaginal surgery (1.6%), and data were missing for two patients (0.2%). There were 473 (49.1%) and 490 (50.9%) patients in the simple hysterectomy and radical hysterectomy groups, respectively. In all studies, patients underwent pelvic lymph node dissection, in one study21 lymph node frozen section was used as lymph node metastases were an exclusion criteria, and in one randomized controlled trial19 some patients had sentinel lymph node detection and pelvic lymph node dissection (161 of 682 patients, 23.6%). Regarding the histology, 659 patients (67.2%) had a squamous cell carcinoma, 296 patients (30.2%) had adenocarcinoma, and 26 (2.6%) had adenosquamous carcinoma. In total, 861 patients (87.8%)
had IB1 stage tumors and 120 (12.2%) had IA2 tumors. Two studies reported final pathology tumor size, and 39 of 722 patients (5.4%) had a tumor >2 cm (22 and 17 patients in simple hysterectomy and radical hysterectomy groups, respectively). The lymph vascular space invasion was reported in all studies, 124 patients (12.9%) had positive lymph vascular space invasion (61 and 63 in simple hysterectomy and radical hysterectomy, respectively), and 14 of 473 patients (3.0%) in the simple hysterectomy and 19 of 490 patients (3.9%) in the radical hysterectomy group had lymph node metastases. Details are provided in Table 1.

In total, 61 of 473 patients (12.9%) and 58 of 490 patients (11.8%) received adjuvant treatment in the simple and radical hysterectomy groups, respectively. Details regarding the type of adjuvant treatment were provided in 109 patients (91.6%) included in three studies. In total, of all patients who underwent adjuvant treatment, 39 of 55 patients (70.1%) and 43 of 54 patients (79.6%) received chemo-radiotherapy in the simple hysterectomy and the radical groups, respectively. All studies followed patients every 3 months for the first 2 years, every 6 months for the next 3 years, and annually after that.

**Risk of Bias Evaluation**

The three randomized controlled trials were judged with some concern of risk of bias according to the Rob-2 tool. The risk domain with some concern score was the randomization for allocation concealment in two trials, the measurement of the outcome in one trial, and the selection of the reported result in two trials. The non-randomized study was judged at some concerns according to ROBINS-I. The risk domains with some concern scores were confounding bias and selection of the study-reported result. Details are provided in online supplemental file 2.

**Oncologic Outcomes**

Three studies reported disease-free survival and overall survival, and one study reported pelvic recurrence-free survival. However, not all reported the outcomes at the same...
follow-up time. Overall survival at 5 years was not significantly different in the two groups, with deaths reported in five of 65 patients (7.7%) in the simple hysterectomy and six of 76 patients (7.9%) in the radical hysterectomy group, with a relative risk in the simple hysterectomy group of 0.98 (95% CI 0.31 to 3.10, p=0.97, two randomized controlled trials and 141 participants) with no change in the absolute risk (risk difference of zero percentage points, 95% CI −9.0 to 9.0) (Figure 2).

As recurrence outcomes were not reported at the same follow-up time, and one study reported pelvic recurrence-free survival and not disease-free survival, it was not possible to perform a meta-analysis. The observational study reported non-significant differences with one recurrence (1.4%) in the simple hysterectomy and two recurrences (2.8%) in the radical hysterectomy group (p=0.56). One randomized controlled trial with a minimum follow-up of 60 months reported 10 recurrences (17.8%) in patients in the radical hysterectomy group, and five recurrences (11.1%) in the simple hysterectomy group. The differences were not statistically significant (p>0.05). The second randomized controlled trial reported, with a median follow-up of 52.1 months, a 3-year disease-free survival of 95% and 100% for simple hysterectomy and radical hysterectomy, respectively (p=0.30). Finally, the last randomized controlled trial reported a pelvic recurrence-free survival at 3 years with a median follow-up of 4.5 years of 97.5% and 97.8% for simple hysterectomy and radical hysterectomy, respectively (p=0.79).

Morbiditity was reported differently in all studies. In the retrospective study, complications were defined as any event during and after surgery that required further management. No intra-operative complications were reported in the simple hysterectomy group, and six patients (8.5%) had a major complication in the radical hysterectomy group (p=0.014). The rate of bladder dysfunction (74.3% vs 0%) was significantly higher in the radical hysterectomy group. One randomized controlled trial reported no significant differences in post-operative complications, and one randomized controlled trial reported no significant differences in intra-operative injuries (7.1% vs 6.4%, p=0.77), but a higher proportion of adverse events within the first 4 weeks of surgery (50.6% vs 42.6%, p=0.04) in patients undergoing radical hysterectomy. Urinary incontinence (11.0% vs 4.7%, p=0.003) and urinary retention (9.9% vs 0.6%, p<0.0001) were statistically significantly higher in the radical hysterectomy group after the first 4 weeks of surgery.

**DISCUSSION**

**Summary of Main Results**

In this systematic review, simple hysterectomy with lymph node assessment for patients with low-risk early-stage cervical cancer was not associated with a higher risk of recurrence at 3 years or death at 5 years compared with radical hysterectomy and lymph node assessment. The morbidity profile favored the non-radical surgical approach.

**Results in the Context of Published Literature**

Less radical surgery for patients with early-stage cervical cancer has been assessed through retrospective cohort studies, including some population-based studies for more than 20 years, initially only for patients with microinvasive disease, but then also for patients with stage IB disease. The populations included in those studies varied regarding the low-risk definition, and included histologies, stages (IA vs IB), type of hysterectomies, lymph node assessment, and the inclusion of tumors >2 cm, making comparisons difficult. However, invariably a better morbidity profile with no differences in oncologic outcomes was reported when comparing simple with radical surgery hysterectomy. Prospective evidence is limited in this context. In the previously published ConCerv prospective study, 40 patients with a previous cervical conization confirming good prognosis characteristics (squamous cell or adenocarcinoma (grade 1 or 2) only) histology, tumor size <2 cm, no lymph vascular space invasion, depth of stromal invasion <10 mm, and conization margins and endocervical curettage negative for malignancy and high-grade dysplasia underwent a simple hysterectomy and lymph node assessment. Three of 40 patients had lymph node metastases, one had residual disease in the hysterectomy specimen, and no recurrences were reported among 36 patients with low-risk characteristics. The median follow-up for the entire cohort was 36.3 months (range 0.0–68.3). Unfortunately, no arm with comparison undergoing radical hysterectomy was included in this study.
Patients undergoing radical hysterectomy for cervical cancer treatment face high adverse event rates. In the LACC trial, the overall incidence of post-operative grade 2+ adverse events were 54% (152/279 patients) in the minimally invasive group versus 48% (124/257) in the open group. Other randomized controlled trials, including patients with larger tumors than those included in this systematic review, reported complications more commonly in the radical hysterectomy group (84%) compared with the simple hysterectomy group (45%). In this study 69% of patients received radiotherapy in the simple hysterectomy group, and 55% in the radical hysterectomy. In our review, even when morbidity profiles were not consistently reported using the same scales, patients undergoing less radical surgery had fewer treatment-related complications in all studies.

Previous systematic and non-systematic reviews have been published comparing less radical surgical treatment with radical surgery in patients with early-stage cervical cancer. These reviews are different from our review as we excluded all studies without an arm for comparison receiving standard radical treatment, and we also excluded studies without lymph node assessment, that is considered part of standard treatment. Those are the main reasons for including only four studies (one retrospective two-arm study and three randomized controlled trials) compared with the previous reviews. We had an updated search strategy, and the inclusion of recent studies was possible. Both qualitative and quantitative analysis through the creation of meta-analysis for some oncologic outcomes was carried out.

The results from the GOG-0278 study (NCT01649089), a prospective single arm study, are still awaited. This study is assessing the impact of non-radical surgery (simple hysterectomy or cone biopsy with pelvic lymphadectomy) on functional outcomes such as lymphedema, bladder, bowel, and sexual function in patients with FIGO stage IA1 disease with lymph vascular space invasion, IA2, and IB1. Secondary outcomes include quality-of-life measures, recurrence, and survival. The results will be limited given the absence of a comparison arm.

**Strengths and Weaknesses**

The main strength of this review is the rigorous methodology applied. It has a registered protocol and was conducted following the guidelines for reporting systematic reviews. Strict selection criteria focused only on the population with low-risk early-stage cervical cancer, and an adequate reference standard with radical surgery and lymph node assessment for all included patients.
Finally, published tools to assess methodological quality and risk of bias were considered for analyses.

We recognize several limitations of our review, such as the inclusion of retrospective and prospective studies, the limited sample size for most of the included studies, the inclusion of different radical hysterectomy types, and the reporting of different oncologic outcomes among studies. There was no consistent standard criteria for adjuvant treatment, and use of imaging modalities for routine surveillance, and there was no central pathology review.

Implications for Practice and Future Research

The good oncologic outcomes and favorable morbidity profile reported with simple hysterectomy in available prospective randomized controlled trials prompt a practice change for this population for the standard of care. However, we must always be reminded that cervical cancer is a completely preventable disease. The WHO for cervical cancer eradication initiative—to vaccinate 90% of girls before the age of 15 years, to screen with a highly sensitive test (human papillomavirus-based) 70% of women at 35 and 45 years of age, and to provide proper treatment by trained personnel to 90% of women diagnosed with either cervical dysplasia or invasive cervical cancer—is expected to lead to earlier detection of low-risk tumors, and achieve cervical cancer eradication. More women should be diagnosed at the earlier stage of the disease with a favorable long-term prognosis.

CONCLUSIONS

Simple hysterectomy with lymph node evaluation for low-risk early-stage cervical cancer is not associated with a detrimental effect on oncologic outcomes and has a better morbidity profile. Available evidence should prompt a change in clinical practice for this specific population.

Author affiliations
1Gynecologic Oncology, Instituto Nacional de Cancerología, Bogota, Colombia
2Gynecologic Oncology, Clínica Universitaria Colombia And Clínica Los Nogales, Bogotá, Colombia
3Gynecologic Oncology, Clínica ASTORGA, Medellín, and Instituto Nacional de Cancerología, Bogotá, Colombia
4Obstetrics and Gynecology, Centre Hospitalier Universitaire de Quebec, Quebec, Canada

Twitter Rene Pareja @RParejaGineOnc

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ORCID iDs
David Viveros-Carreño http://orcid.org/0000-0001-9395-0627
Rene Pareja http://orcid.org/0000-0003-0093-0438

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