Less radical surgery for early-stage cervical cancer: a systematic review

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OBJECTIVE: A systematic review was performed to examine the outcomes of simple hysterectomy for women with low-risk, early-stage cervical cancer.

DATA SOURCES: MEDLINE, Embase, Web of Science, and ClinicalTrials.gov were searched from inception until November 4, 2020.

STUDY ELIGIBILITY CRITERIA: Original research reporting recurrence or survival outcomes among women with early-stage cervical cancer (defined as stage IA2 to IB1 disease) who were treated with simple hysterectomy.

METHODS: Data regarding study characteristics, tumor characteristics, other treatment modalities, adjuvant therapy, recurrence, and survival outcomes were analyzed. Studies that reported both simple hysterectomy and radical hysterectomy outcomes were compared in a subgroup analysis. Summary statistics were reported and eligible studies were further analyzed to determine an estimated hazard ratio comparing simple hysterectomy with radical hysterectomy.

RESULTS: A total of 21 studies were included, of which 3 were randomized control trials, 14 retrospective studies, 2 prospective studies, and 2 population-level data sets. The cohort included 2662 women who underwent simple hysterectomy, of which 36.1% had stage IA2 disease and 61.0% stage IB1 disease. Most cases (96.8%) involved tumors of $\leq$2 cm in size, and 15.4% of cases were lymphovascular space invasion positive. Approximately 71.8% of women who underwent simple hysterectomy had a lymph node assessment, and 30.7% of women underwent adjuvant chemotherapy or radiation. The most common complications described were lymphedema (24%), lymphocysts (22%), and urinary incontinence (18.5%). The total death rate for studies that reported deaths was 5.5%. By stage, there was a 2.7% mortality rate among IA2 disease and a 7.3% mortality rate among IB1 disease. Of note, 18 studies reported outcomes for both simple and radical hysterectomy, with a 4.5% death rate in the radical hysterectomy group and a 5.8% death rate in the simple hysterectomy group. Estimated and reported hazard ratio demonstrated no significant association for mortality between radical and nonradical surgeries for IA2 disease but potentially increased risk of mortality among IB1 disease. All studies had a moderate to high risk of bias, including the 3 randomized control trials. Level of evidence was limited to III to IV.

CONCLUSION: The use of less radical surgery for women with stage IA2 and small volume IB1 cervical cancers appears favorable. However, there is concern that simple hysterectomy in women with stage IB1 tumors may adversely impact survival. Overall, the quality of studies available is modest, limiting the conclusions that can be drawn from the available literature.

Key words: cervical cancer, conservative surgery, early-stage, less radical surgery, simple hysterectomy

Introduction

For women with early-stage cervical cancer, radical hysterectomy with pelvic lymphadenectomy is the standard of care. This procedure involves resection of the uterus, cervix, and upper vagina and surrounding parametria. Although radical hysterectomy is curative for most women with early-stage cervical cancer, with 5-year overall survival rates ranging from 73% to 98%, the procedure is associated with significant morbidity and adversely impacts quality of life.[1,2] Radical hysterectomy is associated with a significant risk for intraoperative blood loss, postoperative lymphedema, bowel and bladder dysfunctions, fistula formation, and sexual dysfunction.[2–8] This morbidity can be largely attributed to the resection of the parametrial tissues adjacent to the cervix, which carry critical gastrointestinal and genitourinary autonomic fibers that may be damaged during surgery.[9]

The utility of parametrial resection in women with small, early cervical tumors has been controversial.[10] Several studies have demonstrated that in select patients

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AJOG at a Glance

Why was this study conducted?

Radical hysterectomy is the standard of care for early-stage cervical cancer yet is associated with significant morbidity because of resection of the parametria. Simple hysterectomy may be an alternative to radical hysterectomy in women with small, early-stage cervical cancers.

Key findings

The use of simple hysterectomy in stage IA2 to IB1 disease may have favorable outcomes; however, data are limited by the quality of current evidence. There was a 2.7% mortality for women with IA2 neoplasms compared with 7.3% risk of mortality for those with stage IB1 who underwent simple hysterectomy; the total death rate was 5.5%. Estimated and reported hazard ratios demonstrated no significant association for mortality between radical and nonradical surgeries for IA2 disease but potentially increased risk of mortality among IB1 disease.

What does this add to what is known?

Simple hysterectomy is associated with less morbidity and may be an appropriate alternative for select women with stage IA2 cervical cancer. Furthermore, there is concern that simple hysterectomy in women with stage IB1 tumors may adversely impact survival.

with cervical cancer, the risk of micrometastasis and parametrial invasion is low. Women with a tumor size of $\leq$2 cm in diameter, with the absence of lymphovascular space invasion (LVSI) and absence of pelvic lymph node metastasis, have been reported to have less than 1% risk of parametrial spread.[10–13] These results challenge the necessity of radical hysterectomy for women with select early-stage cervical cancers, in particular those with the International Federation of Gynecology and Obstetrics (FIGO) stage IA2 to small IB1 disease.

There has been a growing body of literature examining outcomes of less radical surgery, including conization, simple trachelectomy, and simple hysterectomy (SH) with or without lymph node assessment.[14] SH involves the resection of the uterus without the removal of the parametria. Coupled with pelvic lymphadenectomy, this procedure can be an alternative to radical hysterectomy in women with low-risk cervical cancer who do not wish to preserve fertility.

Objective

We performed a systematic review to examine the outcomes of SH for women with low-risk, early-stage cervical cancer (stage IA2 to IB1).

Method

Eligibility criteria

The inclusion criteria were original research reporting recurrence or survival outcomes among women with early-stage cervical cancer (defined as stage IA2 to IB1 disease) who were treated with SH. Articles that combined IA2 and IB1 results with other stages (eg, stage IA1 with LVSI, IB2, and IIA) were included and noted in the tables. Histologic subtypes included adenocarcinoma (AC), squamous cell carcinoma (SCC), and adenosquamous carcinoma (ASC). Studies were excluded if they (1) specifically examined stage IA1 or less or stage IB2 or greater unless these results were combined with IA2 to IB1 disease; (2) reported trials of neoadjuvant therapy, either chemotherapy (CT) or radiation; (3) focused on other histologic types, including clear cell, serous, and neuroendocrine; and (4) were case reports, letters of correspondence, conference abstracts, preprint articles, or written in a language other than English. Studies that examined the same cohort of patients were combined to determine different data elements from each study. We also combined studies that provided duplicate information.

Information sources and search strategy

This systematic review was performed and reported according to the reporting guidelines set forth by the Preferred Reporting Issues for Systematic Review and Meta-Analysis for systematic review of studies.[15] A patient intervention comparison and outcomes (PICO) (TT) model was defined to format and guide the initial search (Supplemental Table 1). A trained medical librarian (S.J.K.) composed a sensitive search utilizing keywords and subject headings to represent the concepts of cervical cancer, cervical cancer surgical treatments, cervical cancer stage, and outcomes. The databases MEDLINE, Embase, and Web of Science were searched from inception until December 13, 2019. An updated search was done on November 4, 2020, which included clinical trial registries. All results were compiled into EndNote (Clarivate Analytics) and then imported into Covidence (Melboure, Australia). All search strategies are available in Supplemental Table 2. The Covidence platform was utilized to ensure rigorous methodology and reporting.

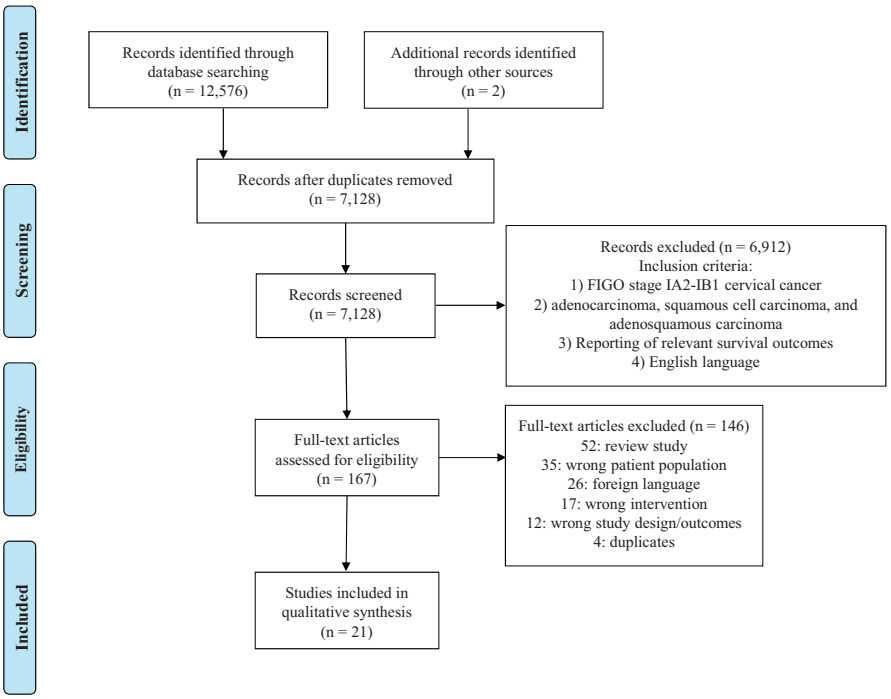
Study selection

Titles and abstracts of the searched articles were reviewed independently by 2 authors (J.W. and T.L.), and any disagreements were resolved by consensus or by third opinion of another author (J.D.W.). Studies that were included in the title and abstract screening were then retrieved for full-text screening and independent review by the same authors (J.W. and T.L.). Disagreements were resolved by consensus with a third author (J.D.W.). Review articles were initially included in the full-text screening to determine any articles that were not included in the original search. Ongoing clinical trials identified were also hand searched to identify any additional studies. References of included articles were checked to find other potential articles, and an independent search on PubMed was also conducted.

Data extraction and data synthesis

A standardized data abstraction form was used to extract data regarding study

FIGURE
PRISMA diagram



FIGO, International Federation of Gynecology and Obstetrics; *PRISMA*, Preferred Reporting Issues for Systematic Review and Meta-Analysis.

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characteristics; tumor characteristics, including FIGO stage; LVSI, positive lymph nodes; other treatments, including lymph node assessment and conization; adjuvant therapy; recurrence; and survival outcomes. Recurrence was defined as invasive recurrence and did not include intraepithelial neoplasia. Data extraction was done by 1 author (J.W.), and these data elements were then verified by a second author (T.L.). Articles that lacked specificity in stage or outcomes to adequately draw conclusions were further excluded. Differences were resolved by discussion and consensus.

Studies that reported both SH and radical hysterectomy outcomes were further analyzed and compared in a subgroup analysis. Summary statistics, including overall survival and disease-free survival in the SH group compared with the radical hysterectomy group, were extracted when reported. Eligible studies were further analyzed to determine an estimated hazard ratio (HR) based on the methods reported by Parmar et al.[16]

Assessment of quality and risk of bias

In this study, 3 quality assessment tools were used: the methodological index for nonrandomized studies (MINORS) criteria to determine the quality of each study, Cochrane Risk of Bias tool (RoB 2) to determine bias in studies deemed as randomized controlled trials, and the risk of bias in non-randomised studies of interventions (ROBINS-I) tool to determine bias in nonrandomized studies. Two authors (J.W. and T.L.) independently assessed each quality assessment item with discrepancies further resolved by discussion and consensus with a third author (J.D.W.) serving as a final arbitrator. The MINORS criteria included the evaluation of clearly stated aim, inclusion of patients, data collection and appropriate endpoints, follow-up period, and adequate control group.[17] Each study was given a quantitative score based on the MINORS criteria ranging from 0 to 24, with 24 representing a high-quality study. Because of the variability of the studies assessed, qualitative categorization of quality ("poor," "fair," or "good") based on the numeric score and authors' overall assessment was included. The RoB 2 tool utilizes signaling questions to determine the risk of bias in 5 domains, including the randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results. Bias was determined as low, high, or some concerns.[18] The ROBINS-I tool also utilizes signaling questions to determine the risk of bias in 7 domains, including the evaluation of confounding factors, selection bias, classification bias, deviation from the intended outcome, missing variables, outcome bias, and bias in results reporting. Bias was determined as low, moderate, and serious risks of bias.[19]

Results

Study selection and characteristics

Our search identified 7128 articles of which 167 records met initial screening criteria and were further assessed for eligibility (Figure). Here, 21 studies with 2662 women who underwent SH were included in the qualitative synthesis (Table 1).[20–40] Of note, 3 randomized control trials (RCTs) were identified, 14 studies were retrospective studies either at a single institution or multiple institutions, 2 studies were prospective institutional studies, and 2 studies utilized population-level data sets. Most studies also reported other surgical modalities, the most common being radical hysterectomy and conization. A total of 14 studies examined SH in patients with stage IA2 cervical cancer, whereas 9 studies analyzed patients with stage IB1 cervical cancer and 6 studies reported more than 1 stage.

Four ongoing or recently completed clinical trials were also identified by searching the clinical trial registries, of which 1 abstract was identified.[41] These trials are further elaborated in the "Ongoing trials" section.

Study characteristics

There were 960 simple hysterectomies with stage IA2 disease (36.1%) and 1623 with IB1 disease (61.0%) examined. Two

studies included 31 simple hysterectomies among women with IA1 neoplasms with LVSI or nonsquamous cell histology in the cohort.[25,32] In 2 other studies, IA1 and IA2 data were combined, and outcome results were reported together.[27,30] The most common histology examined was SCC, which consisted of 59.4% of the cohort, followed by AC in 35.7% and ASC in 4.9% of cases (Table 2). Most cases (96.8%) involved tumors of <2 cm in size. Approximately 15.4% of cases were LVSI positive; however, this is likely higher than the true LVSI positive number in this cohort as 79 cases (19.3%) were reported, combined with other surgical modalities.

Risk of bias of included studies

For the articles included in our study, MINORS scores ranged from 9 to 23 (Supplemental Table 3). Of note, 3 studies received an assessment of "good," 11 studies "fair," and 7 studies "poor." In general, studies that received a poor assessment did not report relevant outcomes and had research questions not specific to examining less radical surgery. All 3 RCTs assessed using RoB 2 demonstrated a "high" overall risk of bias owing to concern regarding randomization, measurement of outcomes, and reporting of results (Supplemental Table 4). Most nonrandomized studies received a "moderate" risk of bias based on the ROBINS-I because of the concern for confounding variables in all the studies (Supplemental Table 5). In addition, 3 articles received a score of "serious" risk of bias because of missing key variables.

Synthesis of results

Approximately 71.8% of women who underwent SH had a lymph node assessment, although some studies included in our review excluded patients with positive lymph nodes at the onset. Of all cases from studies with lymph node assessment, 3.2% exhibited positive lymph nodes (Table 3). A pilot study by Pluta et al[32] identified 60 women with stage IA1 with LVSI, IA2, and IB1 tumors <2 cm in size who underwent laparoscopic sentinel lymph node (SLN) assessment with a frozen section. Negative SLN patients then underwent an SH with completion pelvic lymphadenectomy, whereas patients with nodal metastases underwent radical hysterectomy, including low paraaortic lymphadenectomy.

Adjuvant therapy was utilized in 30.7% of patients undergoing SH. The most common adjuvant therapy utilized in the SH group was radiation therapy in 551 cases (20.7%) and CT in 289 subjects (10.9%). The 3 studies reported 26 women who received adjuvant chemoradiation.[25,26,40] It was not possible to assess the combination of chemoradiation adequately in 1 study, which reported CT and radiation separately.

TABLE 1
Summary of included studies

	Number			
Study characteristics				
Number of studies	21			
Randomized control trial	3			
Institutional retrospective	14			
Institutional prospective	2			
Population-based retrospective	2			
Total number of simple hysterectomies	2662			
Excluded patients	5219			
	Number	**%**	**Unknown**	**%**
Tumor characteristics				
Stage				
IA1	166	6.0	—	—
IA2	960	34.8	—	—
IB1	1623	58.8	—	—
IIA	9	0.3	—	—
Histology				
Squamous cell carcinoma	1628	59.4	—	—
Adenocarcinoma	977	35.7	—	—
Adenosquamous	134	4.9	—	—
Tumor size <2 cm	2577	96.8	27	1.0
LVSI positive	410	15.4	206	7.7
Lymphadenectomy				
Lymph node assessment	1913	71.8	56	2.1
Patients with positive lymph nodes	84	3.2	63	2.3
Additional therapy				
Radiation therapy	551	20.7	85	3.2
Chemotherapy	289	10.9	85	3.2
Oncologic outcomes				
Complications	At least 56	2.1	2371	89.1
Recurrences	At least 168	6.3	2187	82.2
Deaths	143	5.3	82	3.0

LVSI, lymphovascular space invasion.

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Furthermore, as this was a population-based data set comprising most adjuvant therapies reported, it was also not possible to assess the rationale for adjuvant therapy.[35] Of those that reported a rationale for adjuvant therapy, these included deep stromal invasion, positive lymph node metastasis, LVSI, margin involvement, grade 3 tumor, paracervical invasion. One case reported adjuvant radiation for the treatment of concurrent endometrial cancer.[39] The 12 studies reported no additional therapy after surgery for 421 of 591 cases (71.2%).

Only 7 studies described perioperative and postoperative complications of surgery with 56 complications described. Two studies reported no long-term complications.[25,31] Of the complications noted, the most commonly described were lymphedema (24%), lymphocysts (22%), and urinary incontinence (18.5%). Chen et al[26] reported an increased risk of morbidity in patients that received a radical hysterectomy compared with an SH ($P<.01$) without a substantial difference in mortality. Landoni et al[29] described grade 2 to 3 complications among 28 women, with 8 complications in the SH-only group and 20 in the additional radiation group. In comparison, 53 women in the radical hysterectomy group experienced grade 2 to 3 complications, with increased morbidity among women who received postoperative radiation.

Furthermore, 19 studies reported recurrence data, of which 6 studies reported recurrences, with 26 recurrences among 475 patients who received an SH.[26,27,29–31,40] A total of 12 studies reported no recurrences in 131 patients who received an SH.[20–22,24,25,28,30,32–34,37–39] Among patients with IA2 and less disease, 6 recurrences (3.7%) were reported, of which 2 recurrences were reported in a cohort with combined IA1 and IA2 diseases.[27] In IB1 and higher diseases, 15 recurrences (9.1%) were reported. Five recurrences (4.1%) were reported in 1 study among those that reported combined IA2 and IB1 diseases. The total recurrence rate for studies that reported recurrences was 5.4%. Of these, 9 were local recurrences within the pelvis, 8 were distal recurrences, and 9 recurrences were not further described. Most of these recurrences (53.8%) were reported by Landoni et al,[29] who compared SH with radical hysterectomy among stage IB and IIA diseases. Recurrences were noted to be higher in the SH group, with 14 recurrences (22.5%) reported compared with 8 recurrences (12.7%) reported in the radical hysterectomy group. Of note, Landoni et al[29] reported only 8 cases of tumor size of ≤2 cm (6.4%) with 44.8% with a tumor size between 2.1 and 3.0 cm and 48.8% with a tumor size between 3.1 and 4.0 cm. Furthermore, the SH group included substantially older patients ($P<.001$) and had more stage IIA cases ($P=.07$) compared with the radical hysterectomy group, which may have played a factor in the higher rates of recurrences reported. Two studies examining population data sets did not have data available for recurrence rates.[35,36]

A total of 20 studies reported survival data, of which 5 studies reported 143 deaths in 2580 patients who underwent SH[26,29,35,36] and 15 studies reported no death in 235 patients. Only 1 study of 82 cases of SH did not report the number of deaths.[30] The total death rate for studies that reported deaths was 5.5%. By stage, there were approximately 27 deaths among 923 cases with IA2 stage disease, compromising a 2.7% mortality rate. Of those with IB1 stage disease, there were approximately 119 deaths among 1623 surgeries, compromising a 7.3% mortality rate. Most survival outcomes were determined by 1 population-based study examining 683 patients with stage IA2 disease and 1388 patients with stage IB1 disease. Sia et al[35] utilized the National Cancer Database and compared SH with radical hysterectomy for IA2 and IB1 diseases, reporting 22 deaths in the IA2 group (3.2%) and 98 deaths in the IB1 group (7.1%).

Of note, 18 studies reported outcomes for both SH and radical hysterectomy (Table 4).[20,21,24,26–40] There were 3863 radical hysterectomies (59.7%) examined and 2613 simple hysterectomies (40.3%) in this subanalysis. The use of adjuvant therapy, including radiation or CT, was reported for more simple hysterectomies (30.7%) than radical hysterectomies (16.7%). Of the 16 studies that reported recurrence data, 8 studies reported 30 recurrences (8.8%) in the radical hysterectomy group[26–31,33,40] and 6 studies reported 26 recurrences (6.1%) in the SH group.[26,27,29–31,40] Of the 17 studies that reported survival data, 7 studies reported a 4.5% death rate in the radical hysterectomy group, and 5 studies reported a 5.6% death rate in the SH group.[26,28,29,36,40] Of the 15 studies, 5 studies reported relevant summary statistics, including overall survival and disease-free survival.[26,29,35,36,40] Only 1 study reported an HR comparing SH with radical hysterectomy, and an estimated HR was analyzed for 3 studies.[26,29,36]

Compared with radical hysterectomy, Sia et al[35] reported an HR of 0.70 (95% confidence interval [CI], 0.41−1.20) for women with IA2 tumors who underwent SH and an HR of 1.55 (95% CI, 1.18−2.03) for those with IB1 disease, demonstrating no significant association for mortality between radical and nonradical surgeries for IA2 disease but an increased risk of mortality in IB1 disease. These findings are similar to those of Smith et al,[36] which analyzed 134 women with IA2 disease in the surveillance, epidemiology and end results database and demonstrated no substantial difference in survival between those who received radical hysterectomy and those who received SH (estimated HR, 0.31; 95% CI, 1.18−2.03). In IB1 and greater diseases, Landoni et al[29] noted a 5-year overall survival of 85% for SH and 95% for radical hysterectomy in patients with IB1 to IIA disease (estimated HR, 1.82; 95% CI, 0.89−3.73; $P=.11$). They noted no difference in survival in women with tumors of <3 cm ($P=.88$), but there is a substantial difference in survival for those with tumors 3.1 to 4.0 cm in size ($P=.03$). Chen et al[26] and Wang et al[40] randomized patients with IA2 to IB1 disease to SH or radical hysterectomy and noted no substantial difference in the overall survival in patients that received radical compared with less radical surgery. Chen et al[26] reported a

TABLE 2
Tumor characteristics of the studies included

Citation	Years assessed	Number of surgeries		Stage			Histology			Tumor size <2 cm	LVSI
		Total	SH	IA1	IA2	IB1	SCC	AC	ASC		
Al-Kalbani et al,[20] 2012	1990–2010	74	3	—	—	3	—	3	—	3	3[a]
Baalbergen et al,[21] 2011	1987–2006	59	6	—	6	—	—	6	—	6	4[a]
Biliatis et al,[22] 2012; Naik et al,[23] 2007	2000–2010	62	27	—	—	27	49[a]	11[a]	2[a]	NR	14[a]
Bisseling et al,[24] 2007	1987–2004	38	3	—	3	—	—	3	—	3	1
Bouchard-Fortier et al,[25] 2014	1991–2013	51	22	28[a,b]	10[a]	13[a]	26[a]	22[a]	3[a]	22	18[a]
Chen et al,[26] 2018	2006–2011	101	45	—	25	20	35	10	—	45	10
Gadducci et al,[27] 2003	1984–1998	166	82	113[a]	23[a]	—	82	—	—	82	NR
Kasamatsu et al,[28] 2002	1969–1997	79	3	—	—	3	—	3	—	3	0
Landoni et al,[29] 2012	1981–1986	125	62	—	—	53 (+9 IIA)	52	10	—	4	26
Marana et al,[30] 2001	1978–1998	59	49	22[a]	37[a]	—	51[a]	6[a]	2[a]	49	4[a]
Östör et al,[31] 1994	1967–1987	200	8	—	8	—	8	—	—	8	NR
Pluta et al,[32] 2009	2000–2007	60	57	3[a,b]	11[a]	46[a]	50[a]	10[a]		57	19[a]
Qian et al,[33] 2014	2003–2013	324	9	—	9	—	9	—	—	9	5[a]
Reynolds et al,[34] 2010	1983–2008	66	2	—	2	—	—	2	—	2	0
Sia et al,[35] 2019	2004–2015	5461	2071	—	683	1388	1187	782	102	2071	292
Smith et al,[36] 2002	1983–1997	560	116	—	116	—	—	91	25	116	NR
Smrkolj et al,[37] 2012	1973–2009	89	15	—	15	—	15	—	—	15	12[a]
Sopracordevole et al,[38] 2014	1993–2003	153	2	—	2	—	2	—	—	2	1
van Meurs et al,[39] 2009	1994–2006	14	10	—	10	—	9	1	—	10	1
Wang et al,[40] 2017	2002–2014	140	70	—	—	70	53	17	—	70	0
Total		7881	2662	166	960	1623	1628	977	134	2577	410

Most data presented are regarding characteristics of the simple hysterectomies in stage IA2 to IB1.

AC, adenocarcinoma; *ASC*, adenosquamous carcinoma; *LVSI*, lymphovascular space invasion; *SCC*, squamous cell carcinoma; *SH*, simple hysterectomy.

[a] The information could not be further characterized between simple hysterectomy subgroups and other surgical modalities; [b] Includes LVSI or nonsquamous cell histology.

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91% 5-year overall survival in the radical hysterectomy group compared with 93% 5-year survival in the SH group (estimated HR, 0.48; 95% CI, 0.11–2.15; $P>.05$). Wang et al[40] noted a 98.5% 5-year overall survival in the radical hysterectomy group compared with 100% 5-year overall survival in the SH group ($P=.32$).

Structured Discussion or Comment

Main findings

We noted a growing number of reports describing the use of less radical surgery for women with stage IA2 and small volume IB1 cervical cancers. Overall, the outcomes of women who underwent SH seem favorable. However, there is a concern from some reports that SH, especially in women with stage IB1 tumors, may adversely impact survival. These results may be limited as only 72% of patients undergoing SH underwent lymph node assessment, which can significantly impact recurrence and survival rates independent of stage. Current guidelines by the National Comprehensive Cancer Network and the European Society for Medical Oncology recommend lymph node assessment in all patients undergoing hysterectomy.[42,43] Overall, the quality of studies available is modest, limiting the conclusions that can be drawn from the available literature.

Reassuringly, survival rates are high for radical and less radical surgeries for both stage IA2 and IB1 diseases. Not surprisingly, tumor size is an important predictor of outcomes for women with early-stage cervical cancer. There was a 2.7% mortality rate for women with microscopic stage IA2 neoplasms compared with 7.3% risk of mortality for those with stage IB1 carcinomas. Importantly, the 3 randomized studies noted no difference in survival between SH and radical hysterectomy for small tumor sizes (<2–3 cm). Although a smaller percentage of

TABLE 3
Outcomes of the studies included

Citation	Number of SH	Stage analyzed	LN assessment	(+) LN	Additional therapy	Complications	Recurrences	Deaths	Follow-up in mo (range)
Al-Kalbani et al,[20] 2012	3	IB1	3	0	None	—	0	0	36.0 (1–120)
Baalbergen et al,[21] 2011	6	IA2	0	0	None	—	0	0	79.9 (10–131)
Biliatis et al,[22] 2012; Naik et al,[23] 2007	27	IB1	26	1	None	5	0	0	56.0 (13–132)
Bisseling et al,[24] 2007	3	IA2	2	0	None	—	0	0	72.0 (0–156)
Bouchard-Fortier et al,[25] 2014	22	IA1–IB1	22	1	2 CRT	No long term	0	0	21.0 (1–112)
Chen et al,[26] 2018	45	IA2–IB1	45	0	22 CRT	18	5	3	60.0
Gadducci et al,[27] 2003	82	IA1–IA2	13	0	NR	—	2	NR	45.0 (24–84)
Kasamatsu et al,[28] 2002	3	IB1	NR	NR	NR	—	0	0	118.0 (9–348)
Landoni et al,[29] 2012	62	IB–IIA	62	13	43 RT	Grade 2–3: 28	14	18	280.0
Marana et al,[30] 2001	49	IA2	NR	NR	None	—	3	1	50.0 (12–228)
Östör et al,[31] 1994	8	IA2	1	0	1 RT	No long term	1	0	(3–120)
Pluta et al,[32] 2009	57	IA1–IB1	57	2	1 RT	2 long term	0	0	47.0 (12–92)
Qian et al,[33] 2014	9	IA2	0	NR	None	—	0	0	32.3 (0–128)
Reynolds et al,[34] 2010	2	IA2	NR	0	None	—	0	0	71.0 (4–255)
Sia et al,[35] 2019	683 IA2	IA2–IB1	457 IA2	17 IA2 48 IB1	46 CT, 102 RT IA2	—	NR	22 IA2	56.0 (32–88)
	1388 IB1		1119 IB1		217 CT, 361 RT IB1			98 IB1	
Smith et al,[36] 2002	116	IA2	26	0	16 RT	—	NR	1	(1–119)
Smrkolj et al,[37] 2012	15	IA2	10	0	None	—	0	0	225.0
Sopracordevole et al,[38] 2014	2	IA2	NR	NR	None	—	0	0	184.5
van Meurs et al,[39] 2009	10	IA2	0	0	1 RT	—	0	0	69.0 (9–119)
Wang et al,[40] 2017	70	IB1	70	2	2 CRT	3 postop	1	0	75.0 (26–170)
Total	2662	IA1–IIA	1913	84	26 CRT, 263 CT, 525 RT	56	26	143	

CRT, chemoradiation; *CT*, chemotherapy; *LN*, lymph node; *NR*, not reported; *postop*, postoperative; *RT*, radiation; *SH*, simple hysterectomy.

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TABLE 4
Studies comparing radical hysterectomy to simple hysterectomy

Citation	Stage	Type of surgery		LVSI	(+) LN	Adjuvant therapy		Recurrences[a]		Deaths		Summary statistics
		RH	SH			RH	SH	RH	SH	RH	SH	
Al-Kalbani et al,[20] 2012	IB1	20	3	4	0	0	0	0	0	0	0	—
Baalbergen et al,[21] 2011	IA2	13	6	4	0	0	0	0	0	0	0	—
Bisseling et al,[24] 2007	IA2	4	3	2	0	0	0	0	0	0	0	—
Chen et al,[26] 2018	IA2–IB1	56	45	25	0	23	22	10	5	5	3	5-y OS: 91% RH, 93% SH ($P>.05$) HR[b]: 0.48 (95% CI, 0.11–2.15)
Gadducci et al,[27] 2003	IA1–IA2	54	82	NR	0	NR	NR	2	2	NR	NR	—
Kasamatsu et al,[28] 2002	IB1	48	3	6	1	5	0	4	0	4	0	—
Landoni et al,[29] 2012	IB–IIA	63	62	52	24	35	43	8	14	12	18	5-y OS: 95% RH, 85% SH ($P=.11$) DFS: 86% in RH and 70% in SH HR[b]: 1.82 (95% CI, 0.89–3.73)
Marana et al,[30] 2001	IA1–IA2	3	49	4	NR	NR	NR	2	3	1	1	—
Östör et al,[31] 1994	IA1–IA2	22	8	NR	0	1	1	1	1	0	0	—
Pluta et al,[32] 2009	IA2–IB1	3	57	19	5	3	1	0	0	0	0	—
Qian et al,[33] 2014	IA2	32	9	5	1	0	0	1	0	0	0	—
Reynolds et al,[34] 2010	IA2	9	2	0	0	0	0	0	0	0	0	—
Sia et al,[35] 2019	IA2–IB1	3390	2071	758	186	575	716	NR	NR	149	120	IA2 HR: 0.70 (95% CI, 0.41–1.20) IB1 HR: 1.55 (95% CI, 1.18–2.03)
Smith et al,[36] 2002	IA2	134	116	NR	1	3	16	NR	NR	2	1	OS: 98.57% RH, 98.88% SH ($P=.31$) HR[b]: 0.31 (95% CI, 0.03–2.99)
Smrkolj et al,[37] 2012	IA2	8	15	12	0	0	0	0	0	0	0	—
Sopracordevole et al,[38] 2014	IA2	7	2	3	NR	0	0	0	0	0	0	—
van Meurs et al,[39] 2009	IA2	4	10	3	0	0	1	0	0	0	0	—
Wang et al,[40] 2017	IB1	70	70	0	4	2	2	2	1	1	0	5-y DFS: 97.1% RH, 98.6% SH ($P=.56$) 5-y OS: 98.5% RH, 100% SH ($P=.32$)
Total		3863	2613	897	222	647	802	30	26	174	143	

DFS, disease-free survival; *HR*, hazard ratio; *LN*, lymph node; *LVSI*, lymphovascular space invasion; *NR*, not reported; *OS*, overall survival; *RH*, radical hysterectomy; *SH*, simple hysterectomy.

[a] Recurrences are defined as invasive recurrence; we did not consider intraepithelial neoplasia; [b] Estimated hazard ratio.

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studies reported recurrence risk, there were less recurrences in patients with stage IA2 disease compared with patients with IB1 disease; however, most recurrences in the IB1 group were largely reported in 1 study. Landoni et al[29] included stage IIA disease and a very small proportion of <2-cm tumors (3%) with almost half of the cases with tumor sizes between 3.1 and 4.0 cm. Patients with larger tumors are at greater risk of occult disease, which may in part have driven the increased mortality seen in some reports of women with stage IB1 tumor who underwent SH.

We noted that approximately 30% of patients undergoing SH and 17% of patients undergoing radical hysterectomy received adjuvant CT or radiation. The receipt of adjuvant therapy is relatively high in this low-risk cohort with a low rate of positive lymph nodes (3%). Radiation with or without CT for patients with stage IA2, IB1, or IIA1 disease who have negative nodes is recommended for those with intermediate-risk factors (Sedlis criteria), including LVSI, large tumor size, and deep stromal invasion.[44] Unfortunately, it was difficult to assess the rationale for adjuvant therapy use in most cases reported here.

The driving factor to perform less radical surgery for early-stage cervical cancer is the desire to reduce the morbidity associated with radical hysterectomy.[4,5] The increased risk of complications and long-term sequelae associated with radical hysterectomy is largely due to resection of the parametrium. Despite the potential benefits of SH, we found few studies that compared long-term outcomes of the 2 procedures. Based on the studies that reported perioperative and long-term complications, there does seem to be an increased risk of morbidity with radical hysterectomy compared with SH, which may be further compounded by the receipt of adjuvant radiation therapy.

Strengths and limitations

We recognize a number of important limitations in this systematic review. First, data from prospective RCTs that examine outcomes in stage IA2 to IB1 cervical cancer were limited. Most of the studies included were retrospective case series, with only 3 prospective trials. All 3 RCTs received a high risk of bias score, and all of the nonrandomized studies received a moderate or severe risk of bias score. The inclusion and exclusion criteria varied widely across studies. The significant variability in selection criteria for SH limits the ability to draw conclusions regarding specific criteria and risk factors that would influence modality of surgery. Second, most of the findings are driven by population-based registry studies with large cohorts. Importantly, these studies do not capture recurrence rates or report cause of death. Owing to the overall favorable prognosis for stage IA2 cancers, most studies are underpowered to detect differences in survival, and recurrence rates may be a more important prognostic factor. Third, few studies reported perioperative and long-term complications with less radical surgery, which is the most important impetus in examining alternatives to radical hysterectomy. These limitations can be addressed in the ongoing larger, prospective studies.

Ongoing trials

A total of 4 ongoing prospective trials examining the use of SH for early-stage cervical cancer were identified in this systematic review, with the results of the ConCerv trial recently published. Led by Schmeler et al,[41] the multicenter trial evaluated the safety of conservative surgery for 100 eligible women with stage IA2 to IB1 disease, with 44 women desiring fertility receiving conization and lymph node assessment and 56 women not desiring fertility receiving SH with lymph node assessment. Positive lymph nodes were noted in 5% of cases with 1 case demonstrating evidence of residual disease in the hysterectomy specimen. After a median follow-up of 25 months, there were 3 recurrences reported (3%). These results are reassuring regarding the safety of conservative surgery in early-stage, low-risk cervical cancer.

Compared with modified radical hysterectomy with pelvic lymph node dissection in stage IA2 to IB1 cervical cancer (≤2 cm), the Less Surgical Radicality for Early Stage Cervical Cancer trial (NCT02613286) is a multicenter, randomized, phase II noninferiority trial, evaluating the safety of extrafascial hysterectomy with pelvic lymph node dissection. Primary outcomes include disease-free survival in 3 years with secondary outcomes, including quality of life, adverse events, and rates of adjuvant therapy.[45] The Radical versus Simple Hysterectomy and Pelvic Node Dissection with Low-Risk Early-Stage Cervical Cancer (SHAPE) trial (NCT01658930) is a noninferiority randomized phase III trial comparing SH with pelvic lymph node dissection to radical hysterectomy with pelvic lymph node dissection in patients with stage IA2 to IB1 cervical cancer (≤2 cm). Primary outcomes include safety and whether pelvic relapse free survival is substantially different between the 2 arms.[46] Finally, compared with historic data on radical surgery, the Gynecologic Oncology Group protocol 278 trial (NCT01649089) is assessing the impact of nonradical surgery (SH or cone biopsy with pelvic lymphadenectomy) on functional outcomes of lymphedema, bladder, bowel, and sexual function in patients with stage IA1 disease with LVSI and IA2 to IB1 (≤2 cm) disease. Secondary outcomes include quality-of-life measures, recurrence, and survival.[47] These ongoing studies share similar parameters that have been variable in the studies reported in this review, notably eligibility requirements, including squamous or AC histology, ≤2 cm tumor size, ≤10 mm stromal invasion, and nodal assessment in all cases. The results of these trials will be instrumental in furthering the current understanding of potential complications, recurrence, and survival outcomes of less radical surgery.

Conclusions and implications

As cervical cancer screening programs lead to earlier detection of low-risk tumors, more women are being diagnosed at the earlier stage of the disease with a favorable long-term prognosis. The low risk of parametrial spread and long-term morbidity of radical hysterectomy prompt further investigation into the necessity of parametrial resection. This review suggests that the use of SH for

small volume, early-stage cervical cancer may be an appropriate alternative to radical hysterectomy. Future trials will continue to shed light on the role of less radical surgery in low-risk patients with cervical cancer. ■

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SUPPLEMENTAL TABLE 1

Patient intervention comparison and outcomes (TT) model for defining search

Variable	Key concepts	Inclusion criteria	Exclusion criteria
Population	Patients with early-stage cervical cancer	IA2	CIN
		IB1	IA1
		IA1 with LVSI	IB2
			IIA–IV
Intervention	Simple hysterectomy	Simple hysterectomy	Conization
		Type I hysterectomy	Simple trachelectomy
			Radical trachelectomy
Comparison	Radical hysterectomy	Type II radical hysterectomy	
		Type III radical hysterectomy	
Outcome	Survival, recurrence, morbidity	Deaths	
		Recurrences	
		Overall survival, hazard ratio, disease-free survival	
		Complications (short term or long term)	
Type of question	Therapy is simple hysterectomy an appropriate alternative to radical hysterectomy in patients with low-risk, early-stage cervical cancer?		
Type of study	Randomized control trials, retrospective observational studies, prospective observational studies, population-level studies		

CIN, cervical intraepithelial neoplasia; *LVSI*, lymphovascular space invasion.

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SUPPLEMENTAL TABLE 2

Search strategy

Topic: Low-risk cervical cancer surgeries

Searcher: S.J.K

Date: December 13, 2019

Database (including vendor and platform): Legacy PubMed (NLM)

Set number	Terms	Results
1 cervical cancer	"Uterine cervical neoplasms"[mesh] or (((cervical[tiab] or cervix[tiab]) and (neoplasm[tiab] or neoplasms[tiab] or cancer[tiab] or cancers[tiab] or cancerous[tiab] or carcinoma[tiab] or carcinomas[tiab] or adenocarcinoma[tiab] or adenocarcinomas[tiab]))	115,814
2 treatment	"Conization"[mesh] or "hysterectomy"[mesh] or "lymph node excision"[mesh] or "conservative treatment"[mesh] or "minimally invasive surgical procedures"[mesh] or "surgery"[sh] or conization[tiab] or conizations[tiab] or conization[tiab] or "cone resection"[tiab] or hysterectomy[tiab] or hysterectomies[tiab] or trachelectomy[tiab] or trachelectomies[tiab] or lymphadenectomy[tiab] or lymphadenectomies[tiab] or cervicectomy[tiab] or cervicectomies[tiab]	2,315,422
3 stage	"Neoplasm staging"[mesh] or ((stage[tiab] or stages [tiab]) and (early[tiab] or IA[tiab] or IA1[tiab] or IA2[tiab] or IB[tiab] or IB1[tiab] or IB2[tiab]))	423,340
4 outcomes	"Pregnancy outcome"[mesh] or "treatment outcome"[mesh] or "fertility preservation"[mesh] or "survival rate"[mesh] or "survival analysis"[mesh] or "statistics and numeric data"[sh] or "mortality"[sh] or outcome[tiab] or outcomes[tiab] or mortality[tiab] or mortalities[tiab] or death[tiab] or deaths[tiab] or dying [tiab] or fertility[tiab] or survival[tiab] or surviving[tiab] or survivals[tiab] or survived[tiab] or survivor[tiab] or survivors[tiab] or safety[tiab] or safer[tiab] or safe[tiab]	6,141,075
5	1 and 2 and 3 and 4	4552
6	5 not (animals[mh] not humans[mh])	4551
7	6 not (Editorial[ptyp] or Comment[ptyp])	4527

Database (including vendor and platform): Embase (Elsevier)

Set number		Results
1 cervical cancer	"uterine cervix cancer"/exp or (((cervical:ab,ti or cervix:ab,ti) and (neoplasm:ab,ti or neoplasms:ab,ti or cancer:ab,ti or cancers:ab,ti or cancerous:ab,ti or carcinoma:ab,ti or carcinomas:ab,ti or adenocarcinoma:ab,ti or adenocarcinomas:ab,ti)))	161,674
2 treatment	"uterine cervix conization"/exp or "hysterectomy"/exp or "lymph node dissection"/exp or "conservative treatment"/exp or "minimally invasive procedure"/exp or "cervicectomy"/exp or conization:ab,ti or conizations:ab,ti or conisation:ab,ti or "cone resection":ab,ti or hysterectomy:ab,ti or hysterectomies:ab,ti or trachelectomy:ab,ti or trachelectomies:ab,ti or lymphadenectomy:ab,ti or lymphadenectomies:ab,ti or cervicectomy:ab,ti or cervicectomies:ab,ti	798,368

Wu. Less radical surgery for early-stage cervical cancer. Am J Obstet Gynecol 2021. *(continued)*

SUPPLEMENTAL TABLE 2
Search strategy *(continued)*

Database (including vendor and platform): Embase (Elsevier)

Set number		Results
3 stage	"cancer staging"/exp or ((stage:ab,ti or stages:ab,ti) and (early:ab,ti or IA:ab,ti or IA1:ab,ti or IA2:ab,ti or IB:ab,ti or IB1:ab,ti or IB2:ab,ti))	660,473
4 outcomes	"pregnancy outcome"/exp or "treatment outcome"/exp or "fertility preservation"/exp or "survival rate"/exp or "survival analysis"/exp or "statistics and numerical data"/exp or "cancer mortality"/exp or outcome:ab,ti or outcomes:ab,ti or mortality:ab,ti or mortalities:ab,ti or death:ab,ti or deaths:ab,ti or dying:ab,ti or fertility:ab,ti or survival:ab,ti or surviving:ab,ti or survivals:ab,ti or survived:ab,ti or survivor:ab,ti or survivors:ab,ti or safety:ab,ti or safer:ab,ti or safe:ab,ti	6,445,913
5	1 and 2 and 3 and 4	5296
6	5 and [humans]/lim	4985
7	6 and [humans]/lim and ([article]/lim or [article in press]/lim or [conference paper]/lim or [letter]/lim or [review]/lim)	3748

Database (including vendor and platform): Web of Science (Clarivate)

Set number		Results
1 cervical cancer	TS=((cervical or cervix) and (neoplasm or neoplasms or cancer or cancers or cancerous or carcinoma or carcinomas or adenocarcinoma or adenocarcinomas))	103,343
2 treatment	ts=(conization or conizations or conisation or "cone resection" or hysterectomy or hysterectomies or trachelectomy or trachelectomies or lymphadenectomy or lymphadenectomies or cervicectomy or cervicectomies or ((minimal or minimally or conservative) and (treatment or treatments or procedure or procedures or surgery or surgeries)))	266,277
3 stage	TS=((stage or stages) and (early or IA or IA1 or IA2 or IB or IB1 or IB2))	405,198
4 outcomes	TS=(outcome or outcomes or mortality or mortalities or death or deaths or dying or fertility or survival or surviving or survivals or survived or survivor or survivors or safety or safer or safe)	5,743,402
5	1 and 2 and 3 and 4	2601
6	5 and document types: (article or letter or proceedings paper or review)	

NLM, National Library of Medicine.

Wu. Less radical surgery for early-stage cervical cancer. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 3

MINORS quality assessment for included studies

Citation	Aim	Pt	Data	Outcome	Bias	Time	Loss	Size	Control	Contemp	Equiv.	Analysis	Total	Grade
Al-Kalbani et al,[20] 2012	2	2	0	2	0	1	2	0	1	2	0	1	13	Fair
Baalbergen et al,[21] 2011	2	2	0	2	0	2	2	0	1	2	0	1	14	Fair
Biliatis et al,[22] 2012	2	2	0	2	0	2	2	0	0	0	0	1	11	Fair
Naik et al,[23] 2007	2	2	0	2	0	2	2	0	0	0	0	1	11	Fair
Bisseling et al,[24] 2007	1	2	0	2	0	1	2	0	1	2	0	1	12	Fair
Bouchard-Fortier et al,[25] 2014	2	2	0	2	0	1	2	0	0	0	0	1	10	Fair
Chen et al,[26] 2018	2	2	2	2	1	2	2	0	2	2	1	2	20	Fair
Gadducci et al,[27] 2003	1	1	0	1	0	1	1	0	1	2	0	1	9	Poor
Kasamatsu et al,[28] 2002	2	2	0	2	0	2	2	0	1	2	0	1	14	Poor
Landoni et al,[29] 2012	2	2	2	2	2	2	2	2	2	2	1	2	23	Good
Marana et al,[30] 2001	1	1	0	1	0	1	1	0	1	2	0	1	9	Poor
Östör et al,[31] 1994	2	2	0	2	0	2	2	0	0	0	0	1	11	Fair
Pluta et al,[32] 2009	1	2	0	2	0	2	1	0	1	2	0	1	12	Poor
Qian et al,[33] 2014	2	2	2	2	1	1	2	0	1	2	0	1	16	Fair
Reynolds et al,[34] 2010	1	2	0	2	0	1	1	0	1	2	0	2	12	Poor
Sia et al,[35] 2019	1	2	0	2	0	2	1	0	1	2	0	1	12	Poor
Smith et al,[36] 2002	2	2	0	2	0	2	2	0	2	2	1	2	17	Good
Smrkolj et al,[37] 2012	1	2	0	2	0	2	2	0	2	2	0	2	15	Good
Sopracordevole et al,[38] 2014	1	2	0	2	0	2	2	0	1	1	0	1	12	Fair
van Meurs et al,[39] 2009	2	2	0	2	0	2	2	0	1	2	0	1	14	Poor
Wang et al,[40] 2017	1	2	0	2	0	2	2	0	1	2	0	1	13	Fair
	2	2	2	2	1	2	2	0	2	1	1	2	19	Fair

Aim: a clearly stated aim; pt: inclusion of consecutive patients; data: prospective collection of data; outcome: endpoints appropriate to the aim of the study; bias: unbiased assessment of the study endpoint; time: follow-up period appropriate to the aim of the study; loss: loss to follow-up less than 5%; size: prospective calculation of the study size; control: an adequate control group; contemp: contemporary groups; eqiuv.: baseline equivalence of groups; stat: adequate statistical analyses. Items are scored 0 (not reported), 1 (reported but not adequate), or 2 (reported and adequate).

MINORS, methodological index for nonrandomized studies.

Wu. Less radical surgery for early-stage cervical cancer. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 4

Cochrane revised risk of bias tool for randomized control trials

Citation	Randomization	Deviation	Missing	Outcomes	Results	Overall bias
Chen et al,[26] 2018	Some concern	Low	Low	Some concern	High	High
Landoni et al,[29] 2012	High	Some concern	Low	Low	Some concern	High
Wang et al,[40] 2017	Some concern	Low	Low	Some concern	High	High

Randomization: bias arising from the randomization process; deviation: bias owing to deviations from intended interventions; missing: bias because of missing outcome data; outcomes: bias in measurement of the outcome; results: bias in selection of the reported result.

Wu. Less radical surgery for early-stage cervical cancer. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 5

ROBINS-I bias assessment for nonrandomized studies

Citation	Confounding	Selection	Classification	Deviation	Missing	Outcomes	Results	Overall
Al-Kalbani et al,[20] 2012	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Baalbergen et al,[21] 2011	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Biliatis et al,[22] 2012	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Naik et al,[23] 2007	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Bisseling et al,[24] 2007	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Bouchard-Fortier et al,[25] 2014	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Gadducci et al,[27] 2003	Moderate	Low	Moderate	Low	Serious	Low	Low	Serious
Kasamatsu et al,[28] 2002	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Marana et al,[30] 2001	Moderate	Low	Moderate	Low	Serious	Low	Low	Serious
Östör et al,[31] 1994	Moderate	Low	Moderate	Low	Serious	Low	Low	Serious
Pluta et al,[32] 2009	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Qian et al,[33] 2014	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Reynolds et al,[34] 2010	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Sia et al,[35] 2019	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Smith et al,[36] 2002	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Smrkolj et al,[37] 2012	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Sopracordevole et al,[38] 2014	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
van Meurs et al,[39] 2009	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate

Confounding: bias owing to confounding; selection: bias in the selection of participants in the study; classification: bias in the classification of interventions; deviation: bias owing to deviations from intended interventions; missing: bias owing to missing data; outcomes: bias in the measurement of outcomes; results: bias in the selection of reported results.

ROBINS-I, risk of bias in non-randomised studies of interventions.

Wu. Less radical surgery for early-stage cervical cancer. Am J Obstet Gynecol 2021.