ORIGINAL ARTICLE

Simple versus Radical Hysterectomy in Women with Low-Risk Cervical Cancer

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ABSTRACT

BACKGROUND

Retrospective data suggest that the incidence of parametrial infiltration is low in patients with early-stage low-risk cervical cancer, which raises questions regarding the need for radical hysterectomy in these patients. However, data from large, randomized trials comparing outcomes of radical and simple hysterectomy are lacking.

METHODS

We conducted a multicenter, randomized, noninferiority trial comparing radical hysterectomy with simple hysterectomy including lymph-node assessment in patients with low-risk cervical cancer (lesions of ≤2 cm with limited stromal invasion). The primary outcome was cancer recurrence in the pelvic area (pelvic recurrence) at 3 years. The prespecified noninferiority margin for the between-group difference in pelvic recurrence at 3 years was 4 percentage points.

RESULTS

Among 700 patients who underwent randomization (350 in each group), the majority had tumors that were stage IB_1 according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) criteria (91.7%), that had squamous-cell histologic features (61.7%), and that were grade 1 or 2 (59.3%). With a median follow-up time of 4.5 years, the incidence of pelvic recurrence at 3 years was 2.17% in the radical hysterectomy group and 2.52% in the simple hysterectomy group (an absolute difference of 0.35 percentage points; 90% confidence interval, –1.62 to 2.32). Results were similar in a per-protocol analysis. The incidence of urinary incontinence was lower in the simple hysterectomy group than in the radical hysterectomy group within 4 weeks after surgery (2.4% vs. 5.5%; P=0.048) and beyond 4 weeks (4.7% vs. 11.0%; P=0.003). The incidence of urinary retention in the simple hysterectomy group was also lower than that in the radical hysterectomy group within 4 weeks after surgery (0.6% vs. 11.0%; P<0.001) and beyond 4 weeks (0.6% vs. 9.9%; P<0.001).

CONCLUSIONS

In patients with low-risk cervical cancer, simple hysterectomy was not inferior to radical hysterectomy with respect to the 3-year incidence of pelvic recurrence and was associated with a lower risk of urinary incontinence or retention. (Funded by the Canadian Cancer Society and others; ClinicalTrials.gov number, NCT01658930.)

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*A list of the CX.5 SHAPE investigators is provided in the Supplementary Appendix, available at NEJM.org.

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In 2020, more than 600,000 persons worldwide received a diagnosis of invasive cervical cancer, mostly in advanced stages of disease. In developed countries, owing to effective screening programs, a high proportion of cancers are diagnosed in early stages.[1]

A Quick Take is available at NEJM.org

Radical hysterectomy remains the standard of care for the treatment of early-stage cervical cancer. However, observational studies suggest no difference in overall survival between patients who undergo radical hysterectomy and those who undergo simple hysterectomy for cervical cancer that is stage IA_2 according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system.[2-4]

Several retrospective studies have indicated that the probability of parametrial infiltration is less than 1% in patients with FIGO 2009 stage IB_1 cervical cancer that meets criteria for low risk (i.e., lesions of ≤2 cm, with negative nodes, no invasion of the lymphovascular space, and a depth of stromal invasion of <10 mm), which suggests that less radical surgery might be a safe option for this population.[5-7] Although these data are retrospective, they have led many investigators to question the necessity of removing the parametrium and performing radical surgery in patients with low-risk disease.[8-13] In a recent systematic review of 21 studies, the authors concluded that simple hysterectomy compared favorably overall with radical hysterectomy for the treatment of FIGO 2009 stage IA_2 or IB_1 disease (lesions of ≤2 cm), but they raised concerns that simple hysterectomy for IB_1 disease may result in worse outcomes, with a death rate of 5.8% after simple hysterectomy as compared with 4.5% after radical hysterectomy. However, the quality of the studies was variable, which limited the conclusions that could be drawn.[13] Another population-based study showed that among patients with FIGO 2009 stage IB_1 lesions measuring no more than 2 cm, the 5-year survival was 2.9 percentage points lower among patients who underwent simple hysterectomy than among those who underwent radical hysterectomy; however, that study had several important limitations, including incomplete data for histopathological variables and the absence of lymph-node assessment in 19% of patients who underwent simple hysterectomy.[14,15] We designed the SHAPE (Simple Hysterectomy and Pelvic Node Assessment) trial to evaluate the safety of simple hysterectomy as compared with radical hysterectomy in patients with low-risk early-stage cervical cancer.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this phase 3, international, randomized trial according to a protocol developed by the Canadian Cancer Trials Group (CCTG) and approved by the institutional review board at each participating institution. CCTG was responsible for the collection, maintenance, and analysis of the data. International cooperative groups were responsible for regulatory submissions and for the conduct and monitoring of the trial within their own jurisdictions. The first author and the last two authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

PATIENTS

Patients were eligible for the trial if they had squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix; FIGO 2009 stage IA_2 or IB_1 tumors with lesions measuring no more than 2 cm; limited depth of cervical stromal invasion, as indicated by invasion of tumor tissue to a depth of less than 10 mm on the sample obtained by a diagnostic loop electrosurgical excision procedure (LEEP) or conization or by preoperative pelvic magnetic resonance imaging (MRI) showing invasion of less than 50% of cervical stromal tissue; a tumor of any histologic grade; and no evidence of lymph-node metastasis on preoperative imaging. Lymphovascular invasion was not an exclusion criterion. MRI was mandatory except for patients with stage IA_2 cancer who underwent preoperative LEEP or conization. Other histologic subtypes, lesions measuring more than 2 cm, and evidence of metastatic disease on preoperative imaging were criteria for exclusion. After providing written informed consent, eligible patients were randomly assigned in a 1:1 ratio to undergo simple hysterectomy or radical hysterectomy. Randomization was performed with the use of a minimization method after stratification according to participating

group, intended sentinel-node mapping, stage, histologic type, and grade.

TREATMENT PROCEDURES

The surgical treatment was specified in the surgery manual for the trial, included in the protocol. The uterus, cervix, medial one third of parametria, 2 cm of the uterosacral ligaments, and upper 1-to-2 cm of the vagina were removed en bloc in radical hysterectomy (type II). The uterine arteries were ligated laterally to the ureters, and the ureters were unroofed to the ureterovesical junction. Extrafascial simple hysterectomy involved removal of the uterus with the cervix, without adjacent parametria. The uterine arteries were transected medially to the ureters at the level of the isthmus, and the uterosacral ligaments were transected at the level of the cervix. A maximum of 0.5 cm of vaginal cuff could be removed to ensure the complete removal of the cervix. The choice of surgical approach (open or minimally invasive) was left to the discretion of the surgeons. Photographic images of the surgical specimen were requested for quality assurance purposes. Regardless of the treatment assignment, surgery included pelvic lymph-node dissection with optional sentinel lymph-node mapping. If sentinel lymph-node mapping was performed, the surgical approach was optional, but the laparoscopic approach was preferred. Preoperative diagnostic pathology reports from LEEP, conization, and cervical biopsy; imaging; and operative and postsurgery pathology reports were requested for quality assurance purposes and were reviewed by the trial chair and other trial team members. Adjuvant treatment was administered at the discretion of treating physicians in accordance with local practice.

TRIAL OUTCOMES AND ASSESSMENTS

The primary outcome was cancer recurrence in the pelvic area (pelvic recurrence) within 3 years after randomization. Pelvic recurrence was specified as disease recurrence below the pelvic brim and inferior to the L4–L5 vertebral level and included recurrence in the vaginal vault, parametrium, and pelvic lymph nodes. Secondary time-to-event outcomes included pelvic recurrence–free survival (the time from randomization to the date of the first documentation of pelvic recurrence), extrapelvic recurrence–free survival (the time from randomization to the date of the first documentation of extrapelvic recurrence), recurrence-free survival (the time from randomization to the date of the first documentation of pelvic or extrapelvic recurrence), and overall survival (the time from randomization to death from any cause). Data for patients who had not had disease recurrence or died by the time of analysis were censored at the last contact. Other secondary outcomes included sentinel-node detection, parametrial involvement, detection of disease at the margins of surgically removed tissue, and pelvic-node involvement; adverse events assessed with the use of the National Cancer Institute Common Toxicity Criteria, version 4.0; and patient-reported outcomes.

Patients were assessed 4 to 6 weeks after surgery — or at the time when a decision was made not to undergo surgery — and again at 3 months after surgery. After this point, patients were followed up at 3-month intervals during year 1, at 4-month intervals during year 2, at 6-month intervals during year 3, and at 12-month intervals until death or trial completion for assessment of local pelvic disease, extrapelvic recurrence, treatment complications (including adverse effects of surgery), and receipt of any postprotocol anticancer treatment.

STATISTICAL ANALYSIS

The original sample-size calculation was based on pelvic recurrence–free survival as the primary outcome and on a total of 49 instances of pelvic recurrence among 700 patients enrolled at the time of the final analysis. Because of a lower-than-expected incidence of pelvic recurrence, we revised the primary outcome in June 2022 — with the approval of a CCTG data and safety monitoring committee and before the data were unblinded — to be pelvic recurrence at 3 years; the timing of the final analysis was changed to the point at which the last patients enrolled had been monitored for 3 years if they were not lost to follow-up. For this revised outcome, we calculated that a sample size of 700 patients would provide 85% power to show noninferiority on the basis of a margin of 4 percentage points at a significance level of 0.05, assuming an incidence of pelvic recurrence at 3 years of approximately 4% in both treatment groups.

The incidence of pelvic recurrence at 3 years was estimated by the Kaplan–Meier method from the pelvic recurrence–free survival. The upper limit of an asymptotic one-sided 95% confidence interval for the difference between treatment groups in the incidence of pelvic recurrence at 3 years was calculated on the basis of the Greenwood estimate of the variance. Noninferiority of simple hysterectomy to radical hysterectomy was specified as an upper limit of the 95% confidence interval for the difference between groups that was lower than or equal to 4 percentage points. The primary intention-to-treat analysis included all patients who underwent randomization, regardless of whether they received the assigned treatment. The per-protocol analysis excluded patients who did not meet eligibility criteria at the time of randomization, did not undergo surgery, were found to have more advanced stages of cervical cancer on sentinel-node mapping or pelvic-node dissection, or had other intraoperative findings consistent with pelvic disease.

Intention-to-treat comparisons of secondary time-to-event outcomes were conducted on the basis of stratified Cox proportional-hazards models, with adjustment for stratification factors at randomization except for participating groups. All patients who underwent hysterectomy were included in the analyses of surgical outcomes and complications according to the type of hysterectomy they actually underwent; Fisher's exact test was used to compare categorical outcomes. Methods for analyses of patient-reported outcomes, including the handling of missing data, are detailed in Section S3 in the Supplementary Appendix, available at NEJM.org.

No interim analysis of efficacy or futility was performed. Data regarding safety were reviewed by a CCTG data and safety monitoring committee every 6 months.

RESULTS

PATIENT CHARACTERISTICS

A total of 700 patients (350 in each group) were recruited at 130 centers in 12 countries from December 2012 through November 2019. Baseline characteristics of the patients were similar in the two trial groups (Table 1). Most patients had disease classified as stage IB_1 (91.7%), as squamous histologic type (61.7%), and as grade 1 or 2 (59.3%). Diagnostic LEEP or conization (with or without cervical biopsy) was performed in 80.2% of the patients.

SURGICAL FINDINGS

Among patients who underwent randomization, 18 (7 assigned to undergo simple hysterectomy and 11 assigned to undergo radical hysterectomy) did not undergo surgery because they were found to have disease that had advanced beyond the prespecified limits for the trial, because they decided not to undergo surgery, or because of other reasons (i.e., suspected allergic reaction to an anesthetic agent or previous total lymphadenectomy). Among those who underwent surgery, 7 patients assigned to simple hysterectomy and 2 assigned to radical hysterectomy did not receive the assigned treatment (Fig. S1). Surgical outcomes among patients who underwent the assigned procedure (336 patients assigned to simple hysterectomy and 337 assigned to radical hysterectomy) are listed in Table 2.

Patients who underwent simple hysterectomy were less likely than those who underwent radical hysterectomy to undergo abdominal surgery (16.9% vs. 28.8%) and were more likely to undergo laparoscopic surgery (55.6% vs. 44.2%); the percentage of patients who underwent robotic surgery was similar in the two groups (24.3% and 25.3%, respectively). Among patients who underwent a preoperative LEEP or conization and had data available on residual disease, 114 of 285 (40.0%) who underwent simple hysterectomy and 98 of 265 (37.0%) who underwent radical hysterectomy had residual disease in the hysterectomy specimen; among those who underwent cervical biopsy only and had data available on residual disease, residual disease was present in 39 of 50 patients (78.0%) who underwent simple hysterectomy and in 61 of 73 (83.6%) who underwent radical hysterectomy.

Sentinel lymph-node mapping was performed in 37.3% of the patients who underwent simple hysterectomy and in 38.2% of the patients who underwent radical hysterectomy, and the procedure was successful (i.e., at least one sentinel node on each side of the body was identified) in 61.9% and 63.4% of these patients, respectively. The incidence of and indications for postsurgical adjuvant treatment are shown in Table S2.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Simple Hysterectomy (N=350)	Radical Hysterectomy (N=350)
Race or ethnic group — no. (%)†		
White	264 (75.4)	261 (74.6)
Asian	22 (6.3)	19 (5.4)
Black	3 (0.9)	5 (1.4)
American Indian or Alaska Native	2 (0.6)	1 (0.3)
Not reported	46 (13.1)	50 (14.3)
Unknown	13 (3.7)	14 (4.0)
Age		
Median (range) — yr	42 (26–77)	45 (24–80)
Distribution — no. (%)		
≤50 yr	271 (77.4)	246 (70.3)
>50 yr	79 (22.6)	104 (29.7)
ECOG performance status — no. (%)‡		
0	336 (96.0)	335 (95.7)
1	14 (4.0)	13 (3.7)
3	0	1 (0.3)
Data missing	0	1 (0.3)
Median body-mass index (range)§	25.0 (16.4–53.3)	24.8 (16.1–57.6)
Tumor histologic type — no. (%)		
Squamous-cell carcinoma	218 (62.3)	214 (61.1)
Adenocarcinoma	114 (32.6)	131 (37.4)
Adenosquamous carcinoma	18 (5.1)	5 (1.4)
Tumor FIGO stage — no. (%)		
IA_2	30 (8.6)	28 (8.0)
IB_1	320 (91.4)	322 (92.0)
Tumor histologic grade — no. (%)		
1	76 (21.7)	87 (24.9)
2	129 (36.9)	123 (35.1)
3	49 (14.0)	49 (14.0)
Not assessable	96 (27.4)	91 (26.0)
Diagnostic procedure — no. (%)		
LEEP or conization with or without cervical biopsy	294 (84.0)	267 (76.3)
Cervical biopsy only	52 (14.9)	77 (22.0)
Missing	4 (1.1)	6 (1.7)

* FIGO denotes International Federation of Gynecology and Obstetrics, and LEEP loop electrosurgical excision procedure.
† Race or ethnic group was reported by the patients in a multiple-choice format, with "unknown" as one of the options. "Not reported" includes patients who did not select any answer choice.
‡ Scores on the Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with 0 indicating no restrictions on activities and higher scores indicating greater disability.
§ Body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Secondary Surgical Outcomes among Patients Who Underwent Surgery as Randomly Assigned.

Outcome	Simple Hysterectomy (N=336)	Radical Hysterectomy (N=337)	Difference (95% CI)*
	number (percent)		*percentage points*
Invasion of lymphovascular space	45 (13.4)	42 (12.5)	0.9 (–4.1 to 6.0)
Margins positive for disease on final pathology specimen	8 (2.4)	9 (2.7)	–0.3 (–2.7 to 2.1)
Positive nodes on final pathology specimen	11 (3.3)	14 (4.2)	–0.9 (–3.7 to 2.0)
Residual disease in hysterectomy specimen	154 (45.8)	159 (47.2)	–1.3 (–8.9 to 6.2)
Lesions >2 cm on final pathology specimen	14 (4.2)	14 (4.2)	0.0 (–3.0 to 3.0)
Parametrial involvement	0	6 (1.8)	–1.8 (–3.2 to –0.4)
Parametrial involvement and lesions >2 cm on final pathology specimen	0	2 (0.6)	

* The 95% confidence intervals (CIs) were not adjusted for multiplicity and should not be used in place of hypothesis testing.

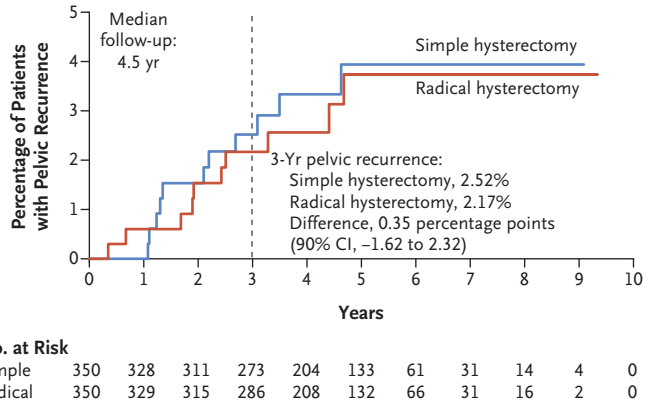

Figure 1. Kaplan–Meier Curves for Pelvic Recurrence.

PRIMARY AND SECONDARY OUTCOMES

Among 700 patients included in the intention-to-treat analysis, 11 pelvic recurrences occurred in the simple hysterectomy group and 10 in the radical hysterectomy group after median follow-up times of 4.5 and 4.6 years, respectively. The incidence of pelvic recurrence at 3 years was 2.52% in the simple hysterectomy group and 2.17% in the radical hysterectomy group (Fig. 1). The difference was 0.35 percentage points (90% confidence interval, –1.62 to 2.32); the upper limit of the confidence interval (2.32) was consistent with noninferiority of simple hysterectomy. Table 3 lists sites of recurrence in both groups. The results of a prespecified per-protocol analysis including 317 patients in the simple hysterectomy group and 312 in the radical hysterectomy group were similar to those of the intention-to-treat analysis. Results in subgroups are listed in Figure S2. Recurrences outside the pelvis occurred in 7 patients in the simple hysterectomy group and 2 in the radical hysterectomy group (Table 3).

Among patients who underwent simple hysterectomy, pelvic recurrence occurred in 9 of 281 patients (3.2%) who underwent minimally invasive surgery as compared with 2 of 57 patients (3.5%) who underwent open surgery; among patients who underwent radical hysterectomy, pelvic recurrence occurred in 7 of 243 patients (2.9%) who underwent minimally invasive surgery as compared with 3 of 99 (3.0%) who underwent open surgery. A total of 14 patients died (7 in each group); 4 deaths in the simple hysterectomy group and 1 in the radical hysterectomy group were attributed to cervical cancer. There was no apparent association between treatment group and pelvic recurrence–free survival, extrapelvic recurrence–free survival, recurrence-free survival, or overall survival (Table 3).

ADVERSE EVENTS

Intraoperative surgical complications occurred in 7.1% of the patients (24 of 338) who underwent simple hysterectomy as compared with 6.4% (22 of 344) who underwent radical hysterectomy. Bladder injuries occurred in 0.9% of the patients (3 of 338) who underwent simple hysterectomy as

Table 3. Sites of Disease Recurrence and Causes of Death.*

Event	Intention-to-Treat Analysis			Per-Protocol Analysis		
	Simple Hysterectomy (N=350)	Radical Hysterectomy (N=350)	Hazard Ratio (95% CI)	Simple Hysterectomy (N=317)	Radical Hysterectomy (N=312)	Hazard Ratio (95% CI)
	number (percent)			*number (percent)*		
Disease recurrence†	15 (4.3)	10 (2.9)	1.54 (0.69–3.45)	12 (3.8)	10 (3.2)	1.19 (0.51–2.77)
Pelvic recurrence	11 (3.1)	10 (2.9)	1.12 (0.47–2.67)	10 (3.2)	10 (3.2)	1.01 (0.42–2.44)
Vaginal vault	9 (2.6)	8 (2.3)		9 (2.8)	8 (2.6)	
Parametrium	1 (0.3)	0		1 (0.3)	0	
Lower paraaortic and common iliac lymph nodes	1 (0.3)	0		0	0	
Central pelvis	0	1 (0.3)		0	1 (0.3)	
Pelvic sidewall	0	1 (0.3)		0	1 (0.3)	
Extrapelvic recurrence	7 (2.0)	2 (0.6)	3.82 (0.79–18.4)	4 (1.3)	2 (0.6)	2.03 (0.37–11.2)
Abdomen	2 (0.6)	0		0	0	
Paraaortic lymph nodes	2 (0.6)	2 (0.6)		1 (0.3)	2 (0.6)	
Supraclavicular lymph nodes	1 (0.3)	0		1 (0.3)	0	
Interaortocaval and obturator lymph nodes and vaginal vault	1 (0.3)	0		1 (0.3)	0	
Vaginal introitus	1 (0.3)	0		1 (0.3)	0	
Death	7 (2.0)	7 (2.0)	1.09 (0.38–3.14)	3 (0.9)	4 (1.3)	0.71 (0.16–3.21)
Cervical cancer	4 (1.1)	1 (0.3)		2 (0.6)	1 (0.3)	
Other primary cancer	1 (0.3)	3 (0.9)		0	2 (0.6)	
Other medical condition	2 (0.6)	3 (0.9)		1 (0.3)	1 (0.3)	

* Hazard ratios are from stratified proportional-hazards models for secondary time-to-event outcomes (tests for superiority). The 95% CIs were not adjusted for multiplicity and should not be used in place of hypothesis testing. The intention-to-treat analysis included all patients who underwent randomization; the per-protocol analysis included all patients who met the eligibility criteria at the time of randomization, underwent randomization, underwent surgery, and had postsurgical findings that did not meet criteria for exclusion on the basis of disease severity.

† Patients may have both pelvic and extrapelvic recurrences.

compared with 2.6% (9 of 344) who underwent radical hysterectomy, and ureteral injuries occurred in 0.9% of the patients (3 of 338) as compared with 1.5% (5 of 344). The incidence of surgery-related adverse events was lower in the simple hysterectomy group than in the radical hysterectomy group within 4 weeks after surgery (42.6% vs. 50.6%; P=0.04). The incidence of urinary incontinence was 2.4% in the simple hysterectomy group as compared with 5.5% in the radical hysterectomy group within 4 weeks after surgery (P=0.048) and 4.7% as compared with 11.0% beyond 4 weeks (P=0.003). The incidence of urinary retention was lower in the simple hysterectomy group than in the radical hysterectomy group within 4 weeks after surgery (0.6% vs. 11.0%; P<0.001) and beyond 4 weeks (0.6% vs. 9.9%; P<0.001) (Table 4).

PATIENT-REPORTED OUTCOMES

European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life assessments were completed by 73.0% of the patients at baseline and by 56.3 to 68.9% after baseline. Sexual health assessments were completed by 86.4% of the patients at baseline and by 62.8 to 79.3% after baseline. Quality-of-life and sexual-function measures appeared overall to favor simple hysterectomy over radical hysterectomy (Table S3).

Table 4. Safety Outcomes.*

Outcome	Simple Hysterectomy (N=338)	Radical Hysterectomy (N=344)	P Value
	number (percent)		
Intraoperative injury			
Any intraoperative injury	24 (7.1)	22 (6.4)	0.77
Bladder	3 (0.9)	9 (2.6)	0.14
Ureter	3 (0.9)	5 (1.5)	0.73
Nerve	5 (1.5)	2 (0.6)	0.28
Bowel	2 (0.6)	2 (0.6)	1.00
Vein	4 (1.2)	1 (0.3)	0.21
Other	7 (2.1)	3 (0.9)	0.22
Surgery-related adverse event ≤4 wk after surgery†			
Any adverse event	144 (42.6)	174 (50.6)	0.04
Abdominal pain	33 (9.8)	42 (12.2)	0.33
Constipation	16 (4.7)	22 (6.4)	0.40
Fatigue	19 (5.6)	23 (6.7)	0.63
Paresthesia	14 (4.1)	22 (6.4)	0.23
Urinary incontinence	8 (2.4)	19 (5.5)	0.05
Urinary retention	2 (0.6)	38 (11.0)	<0.001
Pelvic pain	19 (5.6)	9 (2.6)	0.05
Surgery-related adverse event >4 wk after surgery†			
Any adverse event	181 (53.6)	208 (60.5)	0.08
Abdominal pain	36 (10.7)	47 (13.7)	0.24
Constipation	13 (3.8)	19 (5.5)	0.37
Fatigue	19 (5.6)	28 (8.1)	0.23
Paresthesia	17 (5.0)	22 (6.4)	0.51
Peripheral sensory neuropathy	21 (6.2)	13 (3.8)	0.16
Urinary incontinence	16 (4.7)	38 (11.0)	0.003
Urinary retention	2 (0.6)	34 (9.9)	<0.001
Dyspareunia	21 (6.2)	19 (5.5)	0.75
Pelvic pain	23 (6.8)	17 (4.9)	0.33
Lymphedema	35 (10.4)	36 (10.5)	1.00
Hot flashes	14 (4.1)	20 (5.8)	0.38

* Safety outcomes are reported for the treated population. A total of 700 patients underwent randomization, with 350 assigned to each treatment group. The total of 338 patients who underwent simple hysterectomy includes 2 patients originally assigned to undergo radical hysterectomy who underwent simple hysterectomy instead and excludes 7 patients who did not undergo surgery and 7 who underwent radical hysterectomy instead. The total of 344 patients who underwent radical hysterectomy includes 7 patients originally assigned to undergo simple hysterectomy who underwent radical hysterectomy instead and excludes 11 patients who did not undergo surgery and 2 who underwent simple hysterectomy instead.

† Data include adverse events of grade 1 or higher that occurred in at least 5% in either group. Grading was performed according to the Common Toxicity Criteria of the National Cancer Institute, version 4.0.

DISCUSSION

In this multicenter, randomized trial involving women with early-stage, low-risk cervical cancer, simple hysterectomy was noninferior to radical hysterectomy with respect to pelvic recurrence at 3 years. Simple hysterectomy was also associated with fewer urologic complications.

Results from our trial are in line with those from ConCerv, a phase 2, single-group feasibility study of simple hysterectomy in 100 patients.[16] With a median follow-up time of 36.3 months, the ConCerv study showed a disease recurrence of 3.5%, but the criteria for inclusion (e.g., having a conization specimen that was negative for disease at the margins) and exclusion (e.g., adenocarcinoma grade 3 and invasion of the lymphovascular space) were different from those in the present trial. Recently updated National Comprehensive Cancer Network guidelines indicate that only patients meeting all ConCerv criteria are eligible for alternatives to radical hysterectomy.[17] However, the SHAPE trial included patients with adenocarcinoma grade 3 (2.7%), invasion of the lymphovascular space (13.4%), and residual disease in the hysterectomy specimen (45.8%). Whereas the similarity in the overall incidence of recurrence in the SHAPE and ConCerv trials (3.6% and 3.5%, respectively) suggests that patients with these features could potentially be offered conservative surgery, the percentages of patients with invasion of the lymphovascular space and with adenocarcinoma grade 3 in the SHAPE trial were small, and therefore more data are needed.

The results from a small, phase 2, proof-of-concept, randomized trial comparing simple with radical hysterectomy among 40 patients with lesions measuring no more than 2 cm were recently reported.[18] With a median follow-up time of 52.1 months, the 3-year disease-free survival was 95% after simple hysterectomy and 100% after radical hysterectomy. However, the trial did not have sufficient power to assess noninferiority for efficacy outcomes.[19] A nonrandomized trial assessing physical function and quality of life in patients undergoing either simple hysterectomy or conization for disease at stage IA_2 or IB_1 with lesions of less than 2 cm is ongoing.[20]

In the present trial, the percentage of patients who had surgically removed tissue that was found to have cancer cells at the tissue margins (positive surgical margins) was 2.5%. A previous retrospective study showed that the surgical approach used in radical hysterectomy was not associated with positive surgical margins or the presence of cancer cells close to the margins of the surgical specimen.[21] As expected, ureteral and bladder injuries were more common in the radical hysterectomy group than in the simple hysterectomy group, as were urinary incontinence and urinary retention. Fewer perioperative complications and earlier recovery with simple hysterectomy than with radical hysterectomy have been reported by others.[22]

The SHAPE trial was not designed to address the safety of minimally invasive surgery in patients with low-risk cervical cancer. In the Laparoscopic Approach to Cervical Cancer (LACC) trial, patients with lesions measuring up to 4 cm who were randomly assigned to undergo minimally invasive radical hysterectomy had less favorable outcomes than those assigned to undergo open radical hysterectomy, but the trial did not have sufficient power to evaluate patients with lesions measuring less than 2 cm. In that subgroup, disease recurred in 1 of 147 patients (0.6%) who underwent open surgery as compared with 5 of 150 (3.3%) who underwent minimally invasive surgery.[23] In contrast, a retrospective observational study involving patients with low-risk disease and using propensity matching showed that the 10-year disease-free survival after laparoscopic radical hysterectomy was similar to that after open radical hysterectomy.[24] In our trial, 9 extrapelvic recurrences occurred (7 in the simple hysterectomy group and 2 in radical hysterectomy group). Recent studies have indicated that preoperative conization and the presence of residual disease in the hysterectomy specimen may influence the risk of recurrence — including the risk of peritoneal carcinomatosis — after minimally invasive surgery.[25-29]

Limitations of the present trial include the small number of events (disease recurrence or death) that occurred during the follow-up period, which resulted in wide confidence intervals around hazard ratios for time-to-event outcomes. The median follow-up time was 4.5 years (range, 3 to 10 years); disease recurrence beyond this time frame is possible. The surgical approach (minimally invasive or open) was chosen by trial surgeons after randomization and was not a stratification factor. Results cannot be generalized to patients who do not meet the criteria for low-risk

disease that we used in our trial (lesions measuring ≤2 cm and invasion of <50% of stromal tissue or to a depth of <10 mm or both). The trial was conducted largely in Western Europe, South Korea, and Canada. Black women and Native Americans were underrepresented in our trial, and therefore, results cannot be generalized to these populations or to populations in developing nations (Table S1).

In this trial, we found that among patients with low-risk cervical cancer, simple hysterectomy was noninferior to radical hysterectomy with respect to pelvic recurrence at 3 years and was associated with fewer urologic complications.

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APPENDIX

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