Sexual Health and Quality of Life in Patients With Low-Risk Early-Stage Cervical Cancer: Results From GCIG/CCTG CX.5/SHAPE Trial Comparing Simple Versus Radical Hysterectomy

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ABSTRACT

PURPOSE Simple hysterectomy and pelvic node assessment (SHAPE) is a phase III randomized trial (ClinicalTrials.gov identifier: NCT01658930) reporting noninferiority of simple compared with radical hysterectomy for oncologic outcomes in low-risk cervical cancer. This study presents secondary outcomes of sexual health and quality of life (QOL) of the SHAPE trial.

METHODS Participants were randomly assigned to receive either radical or simple hysterectomy. Sexual health was assessed up to 36 months postoperatively using the Female Sexual Function Index (FSFI) and Female Sexual Distress Scale-Revised and QOL using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Cervical Cancer-Specific Module (QLQ-CX24) questionnaires.

RESULTS Among participants with at least one QOL measure, clinical and pathologic characteristics were balanced and with no differences in preoperative baseline scores for sexual health or QOL between groups. FSFI total score met the cutoff for dysfunction up to 6 months ($P = .02$) in the radical hysterectomy group. Group differences favored simple hysterectomy for FSFI subscales: desire and arousal at 3 months ($P \leq .001$) and pain and lubrication up to 12 months ($P \leq .018$). Both groups met the cutoff for sexual distress but was higher in radical hysterectomy at 3 months ($P = .018$). For QLQ-CX24, symptom experience was significantly better up to 24 months ($P = .031$) and body image better at 3, 24, and 36 months ($P \leq .01$) for simple hysterectomy. Sexual-vaginal functioning was significantly better up to 24 months ($P \leq .022$) and more sexual activity up to 36 months ($P = .024$) in the simple hysterectomy arm. Global health status was significantly higher at 36 months for simple hysterectomy ($P = .025$).

CONCLUSION Simple hysterectomy was associated with lower rates of sexual dysfunction than radical hysterectomy, with a lower proportion of women having sustained sexual-vaginal dysfunction. These results further support the benefit of surgical de-escalation for low-risk cervical cancer.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Treatment of cervical cancer is associated with significant sexual morbidity secondary to the effects of various treatment modalities (surgery, radiation therapy, and chemotherapy) directly affecting sexual organs, autonomic nerves, and estrogen production.[1-3] These treatments cause vaginal stenosis and shortening, decreased vaginal lubrication and elasticity leading to dyspareunia, decreased sexual desire, and avoidance of sexual activity. These adverse changes in sexual health and the psychosocial impact are one of the most important causes of distress after cervical cancer.[1,4,5]

Early-stage cervical cancer is commonly diagnosed in young women and is managed surgically with radical hysterectomy and pelvic lymph node assessment that results in a cancer-specific survival of over 90%.[6] The impact of radical hysterectomy (and the associated parametrectomy, disruption

CONTEXT

Key Objective
Is simple hysterectomy associated with better sexual health outcomes compared with radical hysterectomy in patients with low-risk, early-stage cervical cancer?

Knowledge Generated
Sexual health outcomes were better in patients undergoing simple compared with radical hysterectomy. Specifically, sexual vaginal functioning was better up to 2 years after surgery resulting in more sexual activity.

Relevance *(G.F. Fleming)*
These results from the randomized simple hysterectomy and pelvic node assessment trial support consideration of less extensive surgery for early stage cervical cancer where appropriate.*

*Relevance section written by *JCO* Associate Editor Gini F. Fleming, MD, FASCO.

of autonomic nerves, and upper vaginectomy) on sexual health has been difficult to determine in patients with cervical cancer, since most studies are small, retrospective, and report on heterogeneous cohorts with varied stages and treatments.[4,7,8] There has been controversy over the impact of radical hysterectomy alone on sexual health, with some studies reporting no difference in sexual functioning and others reporting both short- and long-term negative effects of radical hysterectomy compared with healthy controls.[4,7,8] Considering the excellent oncologic outcomes for patients with surgically managed early-stage cervical cancer and the growing number of survivors, there is now a need for high-quality studies that aim to improve outcomes related to sexual health and quality of life (QOL).

The results of the simple hysterectomy and pelvic node assessment (SHAPE) trial recently reported that simple hysterectomy is noninferior to radical hysterectomy for the treatment of women with low-risk early-stage cervical cancer, with a 3-year pelvic recurrence rate difference of only 0.35%.[9] In this population with very high recurrence-free (>96%) and overall survival rates (>99%), it is important to evaluate other outcomes such as sexual health that may be improved with surgical de-escalation. Here, we report on the secondary sexual health and QOL outcomes in patients with low-risk early-stage cervical cancer treated with simple compared with radical hysterectomy from the SHAPE trial.

METHODS

Trial Design and Patients

The design of the SHAPE trial has previously been described.[9] It is a prospective phase III, international, multicenter, randomized, noninferiority trial comparing outcomes in patients randomly assigned to simple versus radical hysterectomy for low-risk early-stage cervical cancer. The protocol was developed by the Canadian Cancer Trials Group (ClinicalTrials.gov identifier: NCT01658930) and approved by institutional review boards at each participating center. Patients were eligible and defined as having low-risk early-stage cervical cancer if they met the following inclusion criteria: squamous, adeno or adenosquamous carcinoma of the cervix; International Federation of Gynecology and Obstetrics 2009 stage IA2-IB1 tumors measuring ≤2 cm in size; depth of stromal invasion <10 mm as determined by loop electrosurgical excision procedure or cone; or <50% invasion on preoperative pelvic magnetic resonance imaging. As part of the inclusion criteria, all patients had to be willing to complete QOL questionnaires. Patients were randomly assigned to simple or radical hysterectomy in a 1:1 fashion. All patients underwent pelvic lymphadenectomy, and the surgical approach was determined by the treating physician. A separate consent form was signed by participants who opted to complete the sexual health measures.

Validated Measures

Patients completed validated questionnaires to assess sexual health and QOL at baseline (6 weeks before random assignment) and 3, 6, 12, 24, and 36 months after surgery or until recurrence. Sexual health was assessed using two questionnaires: the Female Sexual Functioning Index (FSFI) and Female Sexual Distress Scale-Revised (FSDS-R). These measures were administered in English, German, Dutch, and French. The FSFI is a 19-item assessment of six domains of sexual function that include desire (two items), arousal (four items), lubrication (four items), orgasm (three items), satisfaction (three items), and pain (three items), as well as a total score. This measure has been validated in cancer populations with psychometric properties similar to the original validation study with excellent internal consistency and test-retest reliability.[10,11] In addition, the FSFI is shown

to discriminate between patients with cervical cancer receiving chemotherapy versus radiation therapy.[11] A higher total score indicates better sexual function, and the clinical cutoff for sexual dysfunction is a total score of <26.55 (nonclinical range ≥26.55).[12] The FSDS-R[13,14] is a 13-item measure of sexually related distress scored on a five-point Likert scale. Scores range from 0 to 52, where higher scores represent higher levels of sexual distress, and a score >11 corresponds with clinically significant distress.[14] The FSDS-R has high validity in differentiating between sexually functional and dysfunctional women, with both strong consistency and test-retest reliability.[13,14]

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the cervical cancer-specific module (EORTC QLQ-CX24) were used to assess QOL.[15] The EORTC QLQ-C30 has been validated in multiple cancers and consists of 30 questions that have eight symptom subscales (fatigue, nausea and vomiting, insomnia, appetite loss, constipation, diarrhea, dyspnea), five functional subscales (physical, role, emotional, social, and cognitive), one financial toxicity subscale, and one global health status.[16] The EORTC QLQ-CX24 is a 24-item cervical cancer-specific questionnaire to assess disease-specific concerns and symptoms that can adversely affect QOL[17] and was used to supplement the general QLQ-C30. It consists of three multi-item subscales: symptom experience, body image, and sexual-vaginal functioning and five single items: lymphedema, peripheral neuropathy, vasomotor symptoms, sexual worry, sexual activity, and sexual enjoyment. This QLQ-CX24 has excellent psychometric properties and can differentiate between clinical subgroups[17] and has been validated in patients with surgically treated cervical cancer.[18] For each subscale, scoring was completed according to the EORTC manual with all scores standardized to a value between 0 and 100.[17,19] A higher score for EORTC QLQ-C30 functional subscale and global health status indicates good functioning, whereas higher scores for the symptom subscales indicate worse outcomes. Higher scores of QLQ-CX24 indicate worse symptoms and functioning except for sexual activity and satisfaction.

Statistics Analyses

The compliance rate at each time point was calculated by the proportion of patients who answered at least one question on a questionnaire of those who were required to complete the assessment. For each subscale and domain, cross-section analysis including all patients with nonmissing scores was performed at each postbaseline time point, which compares the scores between two treatment groups using the approach of rank analysis of covariance with adjustment of baseline scores.[20] Cohen *d* was calculated for those scales and time points with statistically significant differences to assess effect sizes.[21] There was no imputation for missing data. The sample size was determined by the main SHAPE trial design with no specific sample size calculation for the sexual health and QOL analyses. All *P* values are nominal because no adjustment was made for multiple comparisons.

RESULTS

Participant Demographics

A total of 700 patients (350 in each group) were recruited from 130 centers in 12 countries between December 2012 and November 2019 (Fig 1). Of them, a total of 207 (84.8%) patients in the radical hysterectomy group and 198 (88.0%) in the simple hysterectomy group completed sexual health measures before random assignment (Table 1). For QOL measures, pre-random assignment data were provided by 254 (73.2%) patients in the simple and 254 (72.8%) in the radical hysterectomy groups. The completion rate after baseline was 63%-79% for sexual health assessments and 56%-69% for EORTC QOL assessments (Table 1). Table 2 depicts the baseline characteristics of participants who completed at least one sexual health measure at any time point and Appendix Table A1 (online only) shows the baseline clinical and demographic characteristics of those who completed at least one EORTC QOL measure at any time point. The characteristics were similar between treatment arms for those with at least one sexual health assessment. There was no significant difference in the rate of oophorectomy (32% *v* 41%; *P* = .08) and adjuvant radiation therapy (9% *v* 8%; *P* = .62) and rate of minimally invasive surgery (81% *v* 75%; *P* = .12) between patients with simple and radical hysterectomy. The characteristics were also similar between all enrolled patients and patients who completed at least one sexual health assessment.

Sexual Function and Sexual Distress

At baseline, the FSFI revealed no significant group differences in overall sexual function or FSFI subscales (Appendix Table A2), and total FSFI scores were in the nonclinical range for both surgical groups. Desire showed significant group differences favoring simple hysterectomy at 3 months only (*P* = .001), and the same was found for the arousal subscale at 3 months (*P* < .0001) and 12 months (*P* = .034; Fig 2; Appendix Table A3). Lubrication scores were significantly higher in the simple compared with radical hysterectomy at 3 (*P* = .018), 6 (*P* = 0016), and 12 months (*P* = .003; Fig 2; Appendix Table A3). Sexual pain was significantly higher in the radical hysterectomy group at 3 (*P* < .0001), 6 (*P* = .01), and 12 months (*P* = .001; Fig 2; Appendix Table A3). Orgasm and sexual satisfaction subscales did not differ at any time point. Overall sexual function was higher in the simple compared with the radical hysterectomy group at month 3 (*P* < .0001) and month 6 (*P* = .02) but was only in the clinical range (FSFI total scores <26.55) for the radical hysterectomy group at the first two assessment points (Fig 2; Appendix Table A3). The effect sizes for significant group differences were within the small to moderate range (Cohen *d* from 0.09 to 0.37).

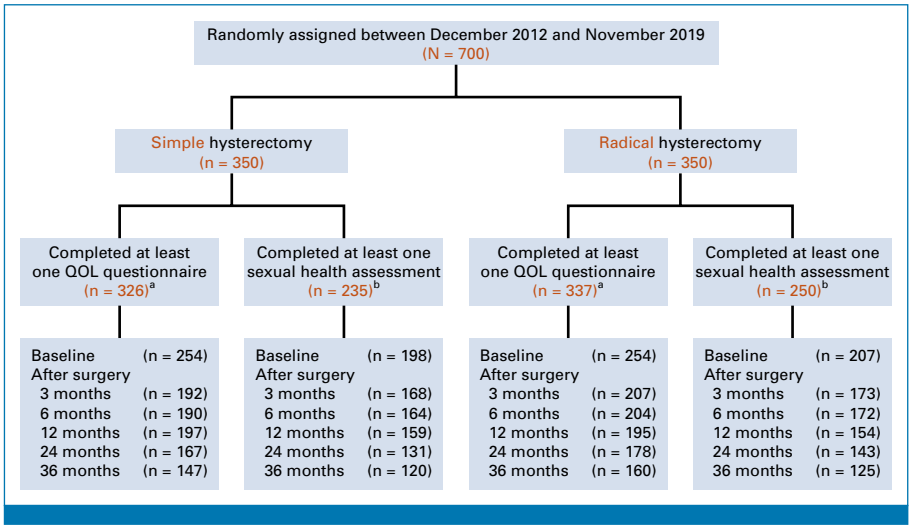

FIG 1. Flow diagram. Have completed at least one questionnaire at any time point. EORTC CX24, European Organization for Research and Treatment of Cancer cervical cancer-specific module; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QOL, quality of life. [a]QOL questionnaire include EORTC QLQ-C30 and EORTC CX24 cancer-specific module. [b]Sexual health assessment includes Female Sexual Functioning Index and Female Sexual Distress Scale-Revised.

In both groups, sex-related distress was in the nonclinical range at baseline (FSDS-R <11; Appendix Table A2). The radical hysterectomy group had significantly more sex-related distress than the simple hysterectomy group at 3 months only ($P = .018$; Fig 2), and there was a significantly higher proportion of patients in the radical hysterectomy group who were in the clinical range of distress (52%) compared with the simple hysterectomy group (44%; $P = .043$). Group differences had a small magnitude of effect (Cohen $d = 0.21$; Appendix Table A3).

The EORTC QLQ-CX24 has two multi-item subscales (sexual-vaginal functioning) and three single items (sexual activity, sexual enjoyment, and sexual worry) which address sexual health and are represented in Table 3 and Figure 3. Sexual-vaginal functioning was significantly

TABLE 1. Completion Rate of Patient-Reported Outcomes Assessments by Treatment Arms

	Simple Hysterectomy		Radical Hysterectomy	
Questionnaire	Expected	Received (%)	Expected	Received (%)
EORTC QOL Questionnaire				
Before random assignment	349	254 (72.8)	347	254 (73.2)
After surgery before recurrence				
3 months	311	192 (61.7)	312	207 (66.3)
6 months	302	190 (62.9)	310	204 (65.8)
12 months	286	197 (68.9)	295	195 (66.1)
24 months	273	167 (61.2)	281	178 (66.3)
36 months	261	147 (56.3)	268	160 (59.7)
Sexual Health Questionnaire				
Before random assignment	225	198 (88.0)	244	207 (84.8)
After surgery before recurrence				
3 months	219	168 (76.7)	227	173 (76.2)
6 months	216	164 (75.9)	217	172 (79.3)
12 months	204	159 (77.9)	214	154 (72.0)
24 months	199	131 (65.8)	207	143 (69.1)
36 months	191	120 (62.8)	193	125 (64.8)

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; QOL, quality of life.

TABLE 2. Clinical and Demographic Characteristics of All Patients Enrolled and Those Who Completed At Least One Sexual Health Assessment

		Patients Who Completed At Least One Sexual Health Assessment		
No. of Patients	All Patients (N = 700)	Simple Hysterectomy (n = 235)	Radical Hysterectomy (n = 250)	Total (n = 485)
Race, No. (%)				
White	525 (75.0)	190 (80.9)	191 (76.4)	381 (78.6)
Asian	41 (5.9)	5 (2.1)	7 (2.8)	12 (2.5)
Black or African American	8 (1.1)	3 (1.3)	2 (0.8)	5 (1.0)
American Indian or Alaska Native	3 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)
Not reported (or refused)	96 (13.7)	27 (11.5)	38 (15.2)	65 (13.4)
Unknown	27 (3.9)	9 (3.8)	11 (4.4)	20 (4.1)
Age, years[a]				
Median (range)	44 (24-80)	40 (26-72)	43 (24-76)	42 (24-76)
≤50, No. (%)	517 (73.9)	200 (85.1)	186 (74.4)	386 (79.6)
>50, No. (%)	183 (26.1)	35 (14.9)	64 (25.6)	99 (20.4)
ECOG performance status, No. (%)				
0	671 (95.9)	228 (97.0)	237 (94.8)	465 (95.9)
1	27 (3.9)	7 (3.0)	12 (4.8)	19 (3.9)
Missing	2 (0.2)	0	1 (0.4)	1 (0.2)
BMI				
Median (range)	24.8 (16.1-57.6)	24.8 (16.4-51.2)	25.4 (16.1-57.6)	25.1 (16.1-57.6)
Histological type, No. (%)				
Squamous	432 (61.7)	142 (60.4)	156 (62.4)	298 (61.4)
Adeno	245 (35.0)	80 (34.0)	90 (36.0)	170 (35.1)
Adenosquamous	23 (3.3)	13 (5.5)	4 (1.6)	17 (3.5)
FIGO stage, No. (%)				
IA2	58 (8.3)	20 (8.5)	18 (7.2)	38 (7.8)
IB1	642 (91.7)	215 (91.5)	232 (92.8)	447 (92.2)
Histologic grade, No. (%)				
1	163 (23.2)	49 (20.9)	67 (26.8)	116 (23.9)
2	252 (36.0)	88 (37.4)	89 (35.6)	177 (36.5)
3	98 (14.0)	35 (14.9)	35 (14.0)	70 (14.4)
Not assessable	187 (26.7)	63 (26.8)	59 (23.6)	122 (25.2)
Diagnostic procedure, No. (%)				
LEEP/cone ± cervical biopsy	561 (80.1)	200 (85.1)	199 (79.6)	399 (82.3)
Cervical biopsy only	129 (18.4)	34 (14.5)	46 (18.4)	80 (16.5)
Missing	10 (1.4)	1 (0.4)	5 (2.0)	6 (1.2)
Unilateral/bilateral oophorectomy, No. (%)				
Yes	289 (41.3)	75 (31.9)	102 (40.8)	177 (36.5)
No	377 (53.9)	156 (66.4)	142 (56.8)	298 (61.4)
Missing	34 (4.9)	4 (1.7)	6 (2.4)	10 (2.1)
Surgical approach, No. (%)				
Minimally invasive (laparoscopic/robotic/vaginal)	524 (74.9)	191 (81.3)	188 (75.2)	379 (78.1)
Open (abdominal)	156 (22.2)	44 (18.7)	62 (24.8)	106 (21.9)
Missing	20 (2.9)	0	0	0
Adjuvant radiotherapy, No. (%)				
Yes	59 (8.4)	21 (8.9)	19 (7.6)	40 (8.3)
No	641 (91.6)	214 (91.1)	231 (92.4)	445 (91.7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; LEEP, loop electrosurgical excision procedure.

[a]$P < .05$ for the comparison between two treatment groups.

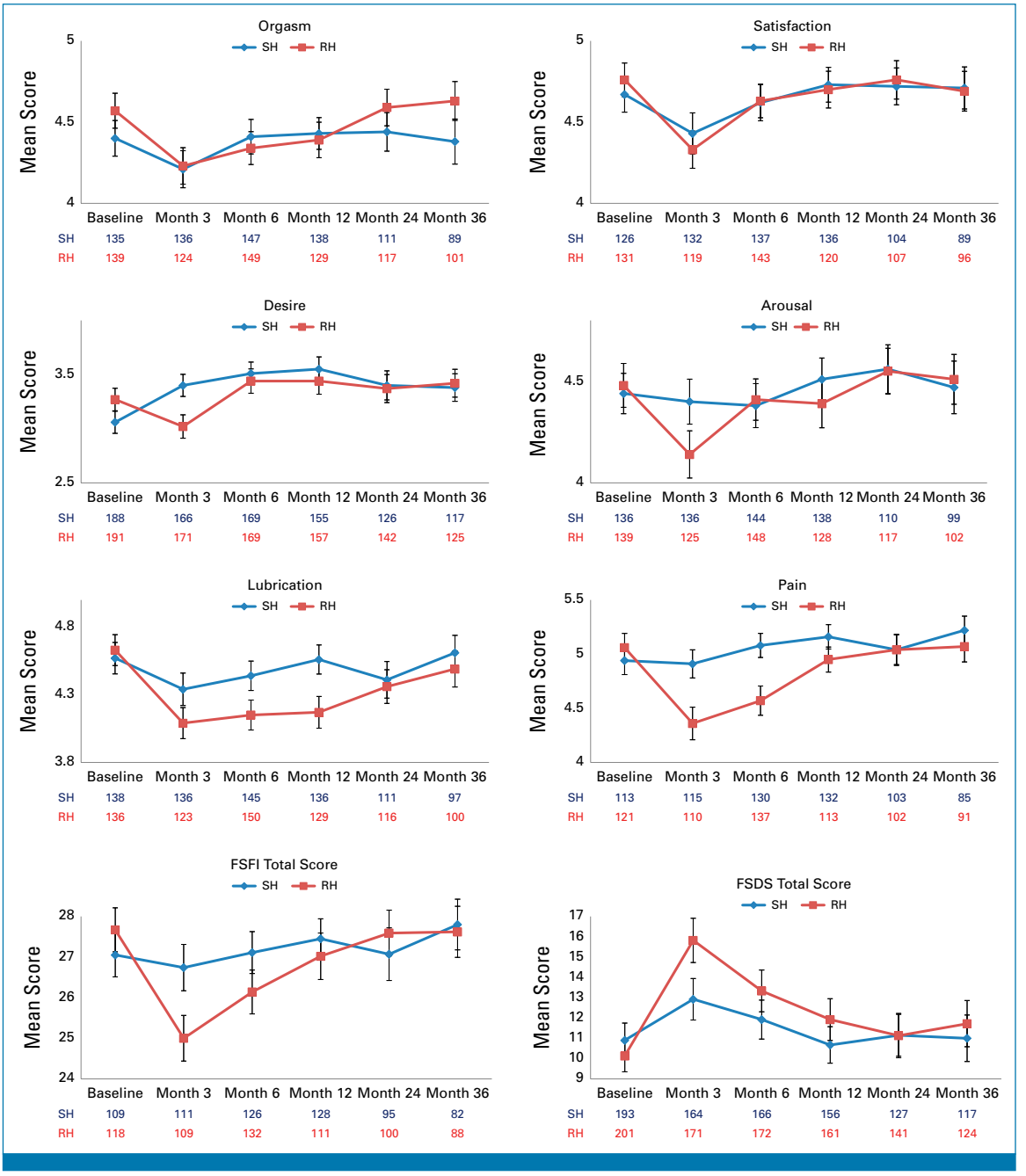

FIG 2. Sexual health outcomes between SH and RH. FSFI subscales and total FSFI and Female Sexual Distress Scale-Revised. FSFI, Female Sexual Functioning Index; RH, radical hysterectomy; SH, simple hysterectomy.

worse in the radical hysterectomy group at all time points up to 24 months (moderate effect size). Sexual worry was higher in the radical hysterectomy group ($P < .0001$) at 3 months only and improved in both groups over time. Sexual activity was higher with simple compared with radical hysterectomy at months 3, 6, 12, and 36 (all small effect sizes), and sexual enjoyment was similarly higher in the simple hysterectomy group at 3 months. Finally, there were more body image symptoms in the radical hysterectomy group at 3 ($P = .001$), 24 ($P = .002$), and 36 months ($P = .011$; all small effect sizes).

QOL and Menopausal Symptoms

There were no differences in baseline measures on the EORTC QLQ-C30 between arms, and both groups scored very high on five functional subscales at all time points (Appendix Table A2; Table 4). One exception was the emotional subscale, which had relatively lower scores at baseline (indicating lower emotional health at presurgery) but improved over time in both groups. The only functional domain that saw a significant group difference was the physical subscale, where those in the simple hysterectomy group had significantly

TABLE 3. Patient-Reported Quality-of-Life Outcomes as Measured by the EORTC QLQ-CX24

	Simple Hysterectomy		Radical Hysterectomy			
Quality-of-Life Outcome	No.	Mean (SD)	No.	Mean (SD)	*P*	Cohen *d*
Symptom experience						
Month 3	195	11.4 (10.5)	207	14.34 (11.81)	.004	0.26
Month 6	194	10.91 (10.43)	203	12.84 (10.77)	.052	
Month 12	195	0.07 (10.2)	195	10.74 (10.14)	.012	0.16
Month 24	168	8.81 (10.4)	177	11.03 (10.49)	.031	0.21
Month 36	149	8.92 (9.79)	161	10.48 (11.02)	.393	
Body image						
Month 3	193	19.75 (23.99)	206	26.56 (26.60)	.001	0.27
Month 6	191	21.55 (27.29)	202	22.66 (26.53)	.305	
Month 12	194	15.98 (21.79)	193	20.26 (26.52)	.184	
Month 24	167	12.18 (18.94)	178	19.35 (24.03)	.002	0.33
Month 36	148	13.81 (20.68)	160	19.65 (25.94)	.011	0.25
Sexual-vaginal functioning						
Month 3	123	14.81 (18.33)	125	26.47 (24.78)	<.0001	0.53
Month 6	143	14.26 (19.39)	147	24.21 (24.60)	<.0001	0.45
Month 12	155	12.87 (18.05)	134	19.82 (20.46)	.002	0.36
Month 24	124	11.96 (18.60)	123	17.57 (21.98)	.022	0.28
Month 36	107	13.71 (19.57)	104	15.87 (20.00)	.103	
Lymphedema						
Month 3	195	8.72 (22.15)	206	8.58 (22.50)	.259	
Month 6	194	13.57 (27.02)	202	15.51 (30.13)	.468	
Month 12	195	14.02 (28.67)	195	14.87 (27.31)	.612	
Month 24	168	11.71 (26.34)	178	14.98 (26.52)	.203	
Month 36	149	10.96 (23.07)	161	12.22 (25.74)	.103	
Peripheral neuropathy						
Month 3	195	14.19 (25.29)	207	14.33 (25.09)	.666	
Month 6	193	15.37 (27.00)	203	13.30 (24.67)	.275	
Month 12	194	13.74 (23.87)	193	17.10 (27.45)	.280	
Month 24	168	13.10 (22.79)	177	14.50 (23.77)	.628	
Month 36	149	11.19 (21.09)	160	12.92 (22.74)	.928	
Menopausal symptoms						
Month 3	194	24.57 (33.73)	207	30.27 (35.62)	.070	
Month 6	194	23.88 (32.32)	203	29.39 (33.10)	.019	0.17
Month 12	194	25.77 (33.25)	195	26.32 (30.68)	.394	
Month 24	168	25.20 (31.49)	177	24.48 (31.23)	.854	
Month 36	149	20.81 (29.63)	161	22.57 (29.72)	.478	
Sexual worry						
Month 3	186	38.35 (34.98)	201	50.4 (35.29)	<.0001	0.34
Month 6	184	28.44 (31.66)	199	31.32 (35.08)	.285	
Month 12	188	19.50 (28.18)	189	25.93 (32.50)	.097	
Month 24	162	16.26 (26.33)	167	17.56 (31.01)	.727	
Month 36	143	15.15 (25.86)	150	19.56 (29.71)	.364	
Sexual activity						
Month 3	189	32.45 (29.66)	204	27.45 (27.45)	.037	0.17
Month 6	183	38.80 (29.35)	198	34.68 (29.25)	.015	0.14
Month 12	188	40.43 (29.80)	192	34.55 (31.52)	.007	0.19
Month 24	164	37.80 (30.79)	172	34.30 (30.04)	.059	
Month 36	143	37.80 (30.79)	157	30.15 (30.14)	.024	0.24

(continued on following page)

TABLE 3. Patient-Reported Quality-of-Life Outcomes as Measured by the EORTC QLQ-CX24 (continued)

	Simple Hysterectomy		Radical Hysterectomy			
Quality-of-Life Outcome	No.	Mean (SD)	No.	Mean (SD)	*P*	Cohen *d*
Sexual enjoyment						
Month 3	123	64.23 (32.55)	125	54.67 (32.35)	.028	0.29
Month 6	141	62.88 (32.14)	147	56.24 (30.92)	.125	
Month 12	154	63.42 (33.17)	132	62.63 (31.38)	.705	
Month 24	124	63.52 (32.02)	121	59.50 (33.94)	.885	
Month 36	106	63.21 (31.18)	104	57.69 (33.25)	.520	

Abbreviations: EORTC QLQ-CX24, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire cervical cancer-specific module; SD, standard deviation.

better physical function scores at 36 months ($P = .042$; small effect size, Cohen $d = 0.13$). Symptom scales also did not differ between the groups at baseline, and a few subscales differed at certain time points, all favoring simple hysterectomy (Appendix Table A2; Table 4). Specifically, radical hysterectomy had more pain at 3 months ($P = .022$; Cohen $d = 0.14$), and simple hysterectomy had better global health status at 36 months ($P = .025$; moderate effect size, Cohen $d = 0.31$). Global health status was high (>73) at all time points and surpassed baseline levels at 6 months in both groups.

The EORTC QLQ-CX24 has one multi-item (symptom experience) and three single items (lymphedema, peripheral neuropathy, and vasomotor symptoms) that measure cervical cancer-specific concerns involving QOL that are not specifically related to sexual health. There were no baseline differences on any of these subscales between the two groups and a low symptom burden overall (Appendix Table A2). Radical hysterectomy had worse symptom experience than simple hysterectomy at all time points to 24 months (small effect size, Cohen $d = 0.16$ to 0.26), and the return to baseline levels of symptoms occurred at 6 months for the simple hysterectomy group and at 24 months for the radical hysterectomy group (Table 3). On single-item symptom measures, there were no group differences in lymphedema and peripheral neuropathy, and symptoms in both groups improved over time (Table 3). Menopausal symptoms (vasomotor) were worse in the radical compared with the simple hysterectomy group at 6 months ($P = .019$, small effect size; Table 3).

DISCUSSION

There are growing efforts to decrease morbidity in the surgical management of cancer while ensuring adequate oncologic outcomes. Here, we report the first surgical trial assessing sexual health a priori as an important clinical outcome and demonstrate significant sexual morbidity in patients undergoing radical hysterectomy for low-risk, early-stage cervical cancer. Using validated patient-reported outcome measures, we found that patients undergoing simple hysterectomy experienced less sexual dysfunction and distress as compared with radical hysterectomy. Although there was no impact on orgasm or sexual satisfaction between surgical groups, there were short-term adverse effects on arousal and desire for patients undergoing radical hysterectomy. The most striking impact of radical surgery in this patient sample was the adverse effect on sexual vaginal functioning with a clinically meaningful difference (>10 for the QLQ-CX24).[22] Although these between-group differences decreased over time, they persisted for 2 years. Moreover, neither surgical group returned to their baseline sexual vaginal functioning. There was consistency between sexual health measures when assessing vaginal health with worse vaginal pain and lubrication for up to 1 year when measured using the FSFI, thereby increasing the validity of these results. These changes resulted in more sexual worry, decreased sexual enjoyment, and less sexual activity (up to 3 years) in those treated with radical hysterectomy. In light of the noninferiority of simple compared with radical hysterectomy for oncologic outcomes, these results have become increasingly relevant when discussing surgical treatment in a young patient population who have a very small chance of recurrence and a high overall survival rate.[9]

There are limited data assessing the impact of radical surgery alone on the sexual health of cervical cancer survivors. A prospective longitudinal study assessing sexual health in women with cervical cancer treated with radical hysterectomy alone compared with an age-matched nonsurgical control group up to 2 years after surgery[8] found transient short-term adverse effects of radical hysterectomy. These included increased dyspareunia, difficulty obtaining orgasm, dissatisfaction with sex life, vaginal size being bothersome during intercourse, and not being able to complete intercourse which returned to baseline by 3-6 months after surgery. However, the lack of a surgical comparison arm makes it difficult to know whether these changes were related to the emotional impact of cancer diagnosis, the trauma of any type of surgery, or the radicality of surgery itself. They reported persistent adverse effects on vaginal functioning with decreased vaginal lubrication that lasted for 2 years, which is in alignment with our findings. Because

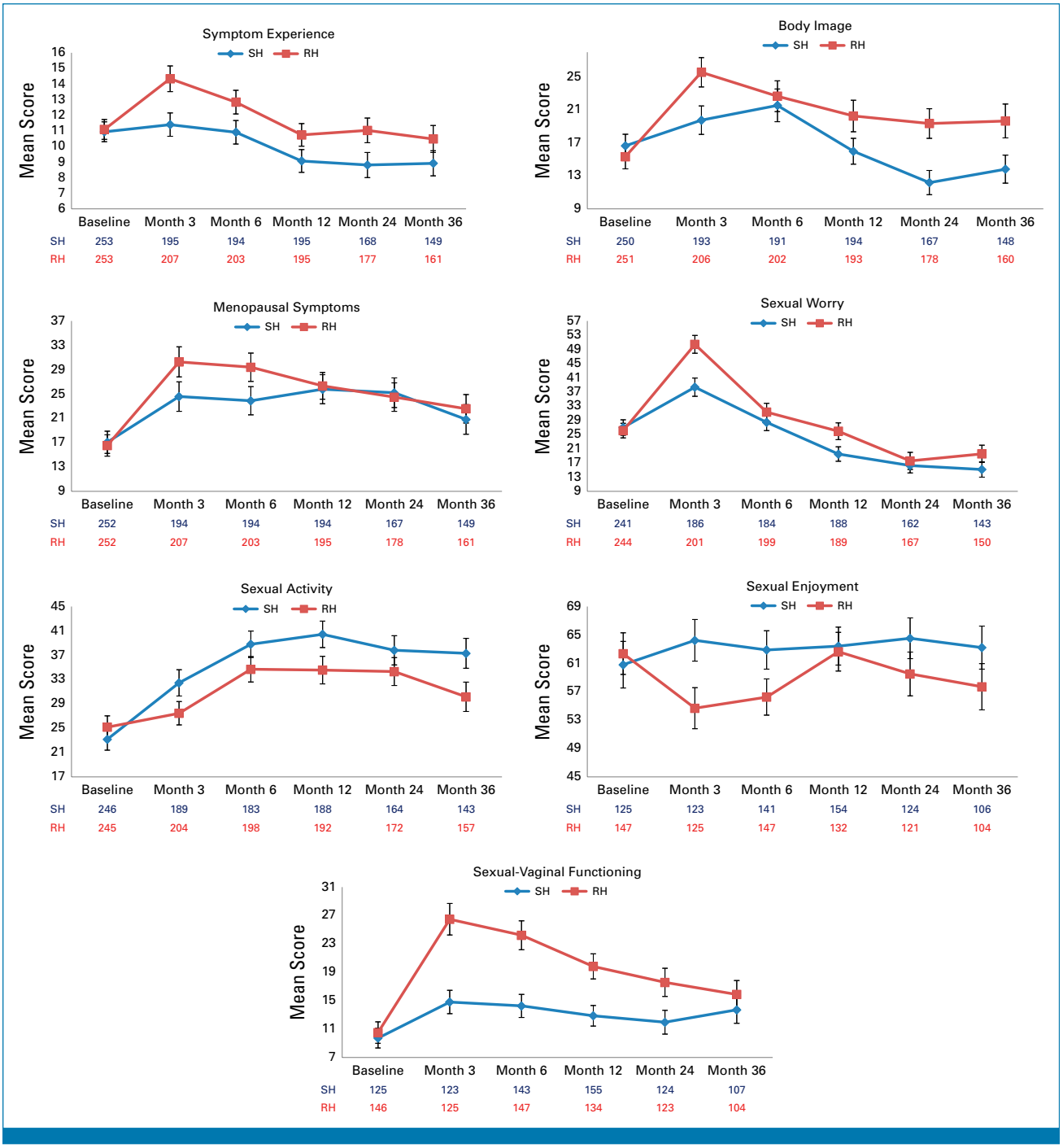

FIG 3. Sexual health and menopausal outcomes between SH and RH as measured by the EORTC QLQ-CX24. EORTC QLQ-CX24, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire cervical cancer-specific module; RH, radical hysterectomy; SH, simple hysterectomy.

of the randomized design of SHAPE with an appropriate surgical control arm, we can conclude that the observed adverse effects of radical hysterectomy on sexual health are due to the radicality of the procedure. The cause of sexual vaginal dysfunction is likely due to the anatomic shortening of the vagina by removal of the vaginal cuff and disruption of the pelvic autonomic nerves with removal of the parametrium and utero-sacral ligaments.[23-25] The proposed neurogenic cause of pelvic dysfunction, both sexual and bladder, has been supported by the identification of an increased number of autonomic nerves and ganglia in the uterosacral ligament and parametrium of radical compared with simple hysterectomy specimens at the level they are transected.[23] There has been growing interest in nerve-sparing radical hysterectomy to mitigate the bladder and sexual morbidity associated with radical

TABLE 4. Summary of Patient-Reported Quality of Life as Measured by the EORTC QLQ-C30

	Simple Hysterectomy		Radical Hysterectomy			
Quality-of-Life Outcome	No.	Mean (SD)	No.	Mean (SD)	*P*	Cohen *d*
Physical						
Month 3	193	89.33 (13.93)	209	87.40 (16.12)	.34	
Month 6	193	90.75 (13.11)	204	90.21 (14.67)	.74	
Month 12	194	93.29 (11.70)	195	90.89 (14.68)	.37	
Month 24	167	94.44 (10.80)	178	92.28 (14.57)	.66	
Month 36	147	93.59 (15.25)	161	91.64 (15.83)	.04	0.13
Emotional						
Month 3	193	74.47 (23.69)	208	74.69 (23.08)	1.00	
Month 6	191	76.13 (24.75)	203	76.63 (21.46)	.94	
Month 12	196	80.16 (21.01)	195	77.99 (23.85)	.43	
Month 24	165	80.10 (22.87)	178	77.15 (21.77)	.42	
Month 36	147	81.63 (20.89)	162	77.37 (22.59)	.19	
Role						
Month 3	191	79.84 (27.62)	206	80.66 (26.49)	.37	
Month 6	192	85.16 (24.26)	204	84.64 (23.12)	.36	
Month 12	193	91.02 (18.16)	193	87.74 (23.49)	.34	
Month 24	166	91.67 (16.28)	177	89.45 (21.66)	.52	
Month 36	147	90.70 (19.42)	160	88.96 (21.47)	.46	
Cognitive						
Month 3	193	84.37 (22.15)	208	84.46 (20.30)	.95	
Month 6	192	84.90 (21.92)	203	87.19 (19.63)	.20	
Month 12	196	88.01 (19.08)	195	86.07 (20.68)	.32	
Month 24	165	85.45 (20.84)	178	88.95 (17.44)	.21	
Month 36	144	86.92 (20.78)	158	87.03 (19.79)	.52	
Social						
Month 3	194	80.50 (25.26)	208	82.29 (24.08)	.88	
Month 6	190	87.46 (21.19)	203	86.86 (20.58)	.29	
Month 12	193	89.72 (20.33)	196	87.16 (23.71)	.17	
Month 24	166	93.27 (15.99)	178	90.82 (20.28)	.80	
Month 36	148	92.68 (17.95)	162	89.30 (23.62)	.28	
Fatigue						
Month 3	192	30.67 (25.41)	209	30.65 (24.62)	.73	
Month 6	193	27.35 (24.84)	203	25.40 (22.32)	.65	
Month 12	197	22.11 (21.50)	194	24.34 (24.62)	.29	
Month 24	167	20.83 (22.13)	178	23.94 (23.78)	.20	
Month 36	148	20.38 (21.42)	160	23.16 (24.21)	.43	
Nausea and vomiting						
Month 3	192	4.95 (13.10)	209	4.94 (12.53)	.60	
Month 6	193	4.84 (12.01)	203	4.60 (14.00)	.38	
Month 12	196	3.66 (9.06)	193	3.71 (11.63)	.34	
Month 24	167	3.19 (8.17)	179	4.38 (11.49)	.69	
Month 36	148	4.39 (10.89)	160	4.90 (11.15)	.81	
Pain						
Month 3	193	19.17 (22.84)	208	22.52 (23.78)	.02	0.14
Month 6	191	19.90 (23.57)	201	20.81 (23.62)	.18	
Month 12	196	14.46 (20.62)	194	16.75 (22.67)	.12	
Month 24	164	12.70 (18.72)	178	14.98 (22.06)	.39	
Month 36	146	13.24 (18.66)	159	17.30 (24.37)	.22	

(continued on following page)

TABLE 4. Summary of Patient-Reported Quality of Life as Measured by the EORTC QLQ-C30 (continued)

	Simple Hysterectomy		Radical Hysterectomy			
Quality-of-Life Outcome	No.	Mean (SD)	No.	Mean (SD)	*P*	Cohen *d*
Dyspnea						
Month 3	193	12.95 (22.55)	208	13.94 (23.24)	.58	
Month 6	192	12.85 (20.39)	204	13.24 (20.24)	.76	
Month 12	194	9.97 (18.38)	193	10.88 (19.01)	.70	
Month 24	167	6.99 (14.09)	177	11.49 (21.61)	.32	
Month 36	147	10.43 (17.36)	161	10.97 (19.64)	.58	
Sleep						
Month 3	192	30.21 (29.77)	209	34.93 (32.81)	.20	
Month 6	193	28.50 (32.27)	203	31.03 (31.90)	.54	
Month 12	197	24.37 (28.25)	194	27.49 (27.36)	.20	
Month 24	167	23.95 (30.15)	179	28.86 (30.88)	.29	
Month 36	147	25.17 (28.02)	160	30.42 (31.59)	.06	
Appetite loss						
Month 3	192	11.28 (21.97)	209	8.29 (21.06)	.04	0.14
Month 6	193	9.67 (20.94)	202	7.92 (20.03)	.24	
Month 12	196	6.63 (16.75)	194	5.67 (14.67)	.48	
Month 24	166	7.23 (18.38)	179	6.15 (15.59)	.62	
Month 36	148	6.76 (16.48)	160	7.92 (19.24)	.81	
Constipation						
Month 3	194	14.09 (24.39)	207	19.00 (27.94)	.16	
Month 6	193	10.54 (20.65)	203	16.91 (27.43)	.11	
Month 12	194	11.34 (21.93)	195	14.87 (23.47)	.15	
Month 24	167	13.77 (23.21)	180	14.81 (24.21)	.73	
Month 36	147	12.24 (23.11)	161	14.49 (20.68)	.32	
Diarrhea						
Month 3	194	10.65 (24.25)	207	8.53 (21.47)	.71	
Month 6	193	8.29 (19.25)	204	7.19 (17.59)	.86	
Month 12	196	8.50 (17.42)	195	7.01 (17.65)	.32	
Month 24	166	8.23 (18.51)	180	6.30 (17.19)	.12	
Month 36	147	6.35 (15.77)	161	9.32 (20.82)	.31	
Financial difficulties						
Month 3	194	13.40 (25.24)	208	18.11 (28.90)	.06	
Month 6	190	11.40 (22.84)	203	11.82 (24.43)	.46	
Month 12	195	9.74 (22.24)	195	9.74 (23.49)	.55	
Month 24	166	6.22 (17.06)	176	7.95 (22.25)	.93	
Month 36	146	5.02 (16.30)	162	9.05 (24.37)	.06	
Global health status						
Month 3	192	73.48 (21.10)	209	72.45 (19.72)	.34	
Month 6	190	75.09 (20.41)	202	75.54 (17.46)	.36	
Month 12	194	77.02 (21.20)	194	77.10 (21.28)	.91	
Month 24	166	78.82 (18.86)	179	76.35 (18.47)	.17	
Month 36	147	80.73 (15.72)	161	75.26 (19.73)	.03	0.31

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; SD, standard deviation.

hysterectomy.[24,25] Currently, there is little evidence on the oncologic safety and improved bladder and sexual function for nerve-sparing radical hysterectomy.[26] Further research is warranted to determine whether nerve-sparing radical hysterectomy is a reasonable surgical option for patients with larger cervical cancers (>2 cm) that still require radical hysterectomy and its impact on sexual health and QOL.

The primary results of the SHAPE trial reported similar pelvic recurrence rates after simple and radical hysterectomy at 3 years, combined with worse short- and long-term sexual and bladder function for patients undergoing radical hysterectomy. These results support de-escalation of surgical treatment of low-risk early-stage cervical cancer. The knowledge of the significant adverse sexual health outcomes with radical surgery has implications for patients with higher-risk early-stage (stage IB2 and IB3) disease who still require radical hysterectomy. Preoperative counseling and informed decision making are necessary to ensure all surgical morbidity, including sexual health, is discussed with reassurance that sexual health will improve over time. There is an opportunity to intervene early to address these sexual health symptoms and potentially shorten the duration. A systematic review and meta-analysis reported improvement of sexual function with pelvic floor physiotherapy after gynecologic cancer treatment, including patients with cervical cancer treated with surgery alone.[27] Other interventions to address sexual health may include estrogen replacement therapy, both local and systemic, vaginal moisturizers and lubricant, and psychosexual counseling.[28,29]

This study has many strengths because of the study design and resulted in both surgical groups being well balanced for known factors that may affect sexual health, such as pelvic radiation, oophorectomy, and surgical approach. In addition, we had a large participation and retention rate in the sexual health and QOL assessments. One potential limitation is that information on the rate of treatment-induced menopausal status and hormone replacement therapy, including systemic and local estrogen, was not collected. However, oophorectomy is not a routine part of cervical cancer surgery and in patients younger than 50 years ovarian conservation would be recommended. In addition, the standard of care is to give estrogen replacement therapy for the minority of patients who have treatment-induced menopause to prevent adverse effects of premature menopause.[30] Therefore, it is unlikely that the sexual morbidity observed in the radical hysterectomy group was related to estrogen deprivation and is supported by the lack of vasomotor symptom burden in this study.

In conclusion, the sexual health and QOL outcomes of the SHAPE trial showed that simple hysterectomy was associated with significantly improved short- and long-term sexual health compared with radical hysterectomy. The combination of noninferiority of simple hysterectomy for oncologic outcomes, as well as improved urologic and sexual health outcomes, supports simple hysterectomy as the new standard of care for women with low-risk early-stage cervical cancer.[9]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Sexual Health and Quality of Life in Patients With Low-Risk Early-Stage Cervical Cancer: Results From GCIG/CCTG CX.5/SHAPE Trial Comparing Simple Versus Radical Hysterectomy

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APPENDIX

TABLE A1. Clinical and Demographic Characteristics of Patients Who Completed At Least One QOL Questionnaire at Any Time Point

No. of Patients	Simple Hysterectomy (n = 326)	Radical Hysterectomy (n = 337)	Total (N = 663)
Race, No. (%)			
White	250 (76.7)	252 (74.8)	502 (75.7)
Asian	14 (4.3)	19 (5.6)	33 (5.0)
Black or African American	4 (1.2)	4 (1.2)	8 (1.2)
American Indian or Alaska Native	1 (0.3)	1 (0.3)	2 (0.3)
Not reported (or refused)	45 (13.8)	48 (14.2)	93 (14.0)
Unknown	12 (3.7)	13 (3.9)	25 (3.8)
Age, years[a]			
Median (range)	42 (26-74)	45 (24-77)	44 (24-77)
≤50, No. (%)	256 (78.5)	235 (69.7)	491 (74.1)
>50, No. (%)	70 (21.5)	102 (30.3)	172 (25.9)
ECOG performance status, No. (%)			
0	312 (95.7)	323 (95.8)	635 (95.8)
1	14 (4.3)	12 (3.6)	26 (3.9)
3	0	1 (0.3)	1 (0.2)
Missing	0	1 (0.3)	1 (0.2)
BMI			
Median (range)	24.8 (16.4-53.3)	25.0 (16.1-57.6)	24.8 (16.1-57.6)
Histological type,[a] No. (%)			
Squamous	195 (59.8)	204 (60.5)	399 (60.2)
Adeno	113 (34.7)	128 (38.0)	241 (36.3)
Adenosquamous	18 (5.5)	5 (1.5)	23 (3.5)
FIGO stage, No. (%)			
IA2	29 (8.9)	25 (7.4)	54 (8.1)
IB1	297 (91.1)	312 (92.6)	609 (91.9)
Histologic grade, No. (%)			
1	72 (22.1)	86 (25.5)	158 (23.8)
2	116 (35.6)	120 (35.6)	236 (35.6)
3	45 (13.8)	46 (13.6)	91 (13.7)
Not assessable	93 (28.5)	85 (25.2)	178 (26.8)
Diagnostic procedure,[a] No. (%)			
LEEP/cone ± cervical biopsy	277 (85.0)	261 (77.4)	538 (81.1)
Cervical biopsy only	47 (14.4)	70 (20.8)	117 (17.6)
Missing	2 (0.6)	6 (1.8)	8 (1.2)
Unilateral/bilateral oophorectomy,[a] No. (%)			
Yes	125 (38.4)	156 (46.3)	281 (42.3)
No	196 (60.1)	172 (51.0)	368 (55.5)
Missing	5 (1.5)	9 (2.7)	14 (2.1)
Surgical approach,[a] No. (%)			
Minimally invasive (laparoscopic/ robotic/vaginal)	271 (83.1)	239 (70.9)	510 (76.9)
Open (abdominal)	55 (16.0)	96 (28.5)	151 (22.8)
Missing	0	2 (0.6)	2 (0.3)

(continued on following page)

TABLE A1. Clinical and Demographic Characteristics of Patients Who Completed At Least One QOL Questionnaire at Any Time Point (continued)

No. of Patients	Simple Hysterectomy (n = 326)	Radical Hysterectomy (n = 337)	Total (N = 663)
Adjuvant radiotherapy, No. (%)			
Yes	30 (9.2)	28 (8.3)	58 (8.8)
No	296 (90.8)	309 (91.7)	605 (91.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC CX24, European Organization for Research and Treatment of Cancer cervical cancer-specific module; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FIGO, International Federation of Gynecology and Obstetrics; LEEP, loop electrosurgical excision procedure; QOL, quality of life.
[a]$P < .05$ for the comparison between two treatment groups.

TABLE A2. Summary of Baseline Patient-Reported Scale Scores

	Simple Hysterectomy		Radical Hysterectomy		
PRO Domain/Subscale/Item	No.	Mean (SD)	No.	Mean (SD)	*P*[a]
EORTC QLQ-C30					
Physical	252	94.7 (10.3)	253	93.3 (13.4)	.41
Emotional	253	68.8 (23.0)	251	67.2 (24.6)	.59
Role	250	90.7 (18.7)	252	91.7 (18.1)	.39
Cognitive	252	86.6 (20.2)	252	86.0 (19.1)	.44
Social	253	85.3 (22.5)	252	88.0 (20.3)	.18
Fatigue	253	24.5 (21.6)	253	24.1 (21.8)	.85
Nausea and vomiting	253	5.1 (13.7)	253	4.4 (10.5)	.91
Pain	252	15.1 (21.9)	253	13.8 (21.9)	.44
Dyspnea	253	8.0 (17.1)	253	9.9 (18.2)	.20
Sleep	252	29.9 (27.7)	252	32.0 (31.5)	.72
Appetite loss	253	10.7 (21.7)	253	11.9 (22.8)	.46
Constipation	252	7.0 (17.6)	254	8.7 (17.6)	.14
Diarrhea	251	7.7 (18.0)	254	7.4 (16.5)	.99
Financial difficulties	249	11.0 (22.7)	251	11.0 (22.3)	.94
Global health status	251	75.3 (19.5)	254	75.4 (19.2)	.97
EORTC QLQ-CX24					
Symptom experience	253	10.9 (10.1)	253	11.1 (10.1)	.80
Body image	250	15.6 (22.3)	251	15.3 (23.3)	.73
Sexual-vaginal functioning	125	9.7 (15.6)	146	10.5 (18.2)	.75
Lymphedema	253	4.0 (14.3)	252	5.7 (15.7)	.09
Peripheral neuropathy	253	7.8 (19.4)	251	8.9 (18.3)	.20
Menopausal symptoms	252	17.1 (29.1)	252	16.5 (27.7)	.96
Sexual worry	241	27.0 (33.7)	244	26.1 (32.3)	.96
Sexual activity	246	76.8 (27.9)	245	74.8 (29.1)	.47
Sexual enjoyment	125	39.2 (36.7)	147	37.6 (35.6)	.77
FSFI					
Desire	188	3.1 (1.4)	191	3.3 (1.4)	.15
Arousal	136	4.4 (1.2)	139	4.5 (1.3)	.51
Lubrication	138	4.6 (1.4)	136	4.6 (1.3)	.76
Orgasm	135	4.4 (1.3)	139	4.6 (1.3)	.23
Satisfaction	126	4.7 (1.2)	131	4.8 (1.2)	.55
Pain	113	4.9 (1.4)	121	5.1 (1.4)	.18
FSFI total score	109	27.1 (5.6)	118	27.6 (5.9)	.34
FSDS-R					
FSDS total score	193	10.9 (11.7)	201	10.1 (11.0)	.53

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-CX24, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire cervical cancer-specific module; FSDS-R, Female Sexual Distress Scale-Revised; FSFI, Female Sexual Functioning Index; PRO, patient reported outcome; SD, standard deviation.

[a]From Wilcoxon test for the difference between two treatment groups.

TABLE A3. Summary of Patient Reported Sexual Functioning as Measured by FSFI Subscales and Total Score and Sexual Distress as Measured by FSDS-R

	Simple Hysterectomy		Radical Hysterectomy			
Sexual Health PROs With Subscales	No.	Mean (SD)	No.	Mean (SD)	*P*	Cohen *d*
FSFI-desire						
Month 3	166	3.40 (1.31)	171	3.02 (1.41)	.001	0.28
Month 6	169	3.51 (1.37)	169	3.44 (1.46)	.23	
Month 12	155	3.55 (1.40)	157	3.44 (1.53)	.10	
Month 24	126	3.40 (1.51)	142	3.37 (1.54)	.20	
Month 36	117	3.38 (1.38)	125	3.42 (1.44)	.76	
FSFI-arousal						
Month 3	136	4.40 (1.29)	125	4.14 (1.30)	<.0001	0.20
Month 6	144	4.38 (1.30)	148	4.41 (1.24)	.35	
Month 12	138	4.51 (1.23)	128	4.39 (1.34)	.03	0.09
Month 24	110	4.56 (1.26)	117	4.55 (1.22)	.13	
Month 36	99	4.47 (1.29)	102	4.51 (1.24)	.58	
FSFI-lubrication						
Month 3	136	4.34 (1.40)	123	4.09 (1.27)	.02	0.19
Month 6	145	4.44 (1.31)	150	4.15 (1.35)	.02	0.22
Month 12	136	4.56 (1.26)	129	4.17 (1.33)	.003	0.30
Month 24	111	4.41 (1.42)	116	4.36 (1.34)	.21	
Month 36	97	4.61 (1.27)	100	4.49 (1.33)	.24	
FSFI-orgasm						
Month 3	136	4.21 (1.33)	124	4.23 (1.25)	.80	
Month 6	147	4.41 (1.29)	149	4.34 (1.23)	.49	
Month 12	138	4.43 (1.15)	129	4.39 (1.24)	.23	
Month 24	111	4.44 (1.25)	117	4.59 (1.22)	.93	
Month 36	98	4.38 (1.31)	101	4.68 (1.20)	.13	
FSFI- satisfaction						
Month 3	132	4.43 (1.46)	119	4.33 (1.31)	.050	0.07
Month 6	137	4.62 (1.31)	143	4.63 (1.32)	.27	
Month 12	136	4.73 (1.25)	120	4.70 (1.30)	.67	
Month 24	104	4.72 (1.16)	107	4.76 (1.22)	.55	
Month 36	89	4.71 (1.22)	96	4.69 (1.26)	.97	
FSFI-pain						
Month 3	115	4.91 (1.39)	110	4.36 (1.58)	<.0001	0.37
Month 6	130	5.08 (1.27)	137	4.57 (1.58)	.01	0.36
Month 12	132	5.16 (1.29)	113	4.95 (1.23)	.001	0.17
Month 24	103	5.04 (1.46)	102	5.04 (1.38)	.48	
Month 36	85	5.22 (1.21)	91	5.07 (1.36)	.08	
FSFI total score						
Month 3	111	26.74 (6.00)	109	25.00 (5.88)	<.0001	0.29
Month 6	126	27.11 (5.80)	132	26.14 (6.19)	.02	0.16
Month 12	128	27.45 (5.56)	111	27.02 (6.03)	.07	
Month 24	95	27.07 (6.31)	100	27.59 (5.64)	.80	
Month 36	82	27.80 (5.66)	88	27.62 (5.89)	.90	
FSDS total score						
Month 3	164	12.92 (13.09)	171	15.82 (14.29)	.02	0.21
Month 6	166	11.92 (12.38)	172	13.33 (13.48)	.17	
Month 12	156	10.67 (11.23)	161	11.92 (13.03)	.60	
Month 24	127	11.15 (11.63)	141	11.13 (12.95)	.97	
Month 36	117	11.00 (12.41)	124	11.72 (12.69)	.74	

Abbreviations: FSDS-R, Female Sexual Distress Scale-Revised; FSFI, Female Sexual Functioning Index; PROs, patient reported outcomes; SD, standard deviation.