2023 ASCO ANNUAL MEETING

GCIG GYNECOLOGIC CANCER INTERGROUP

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer

A Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group

CCTG CX.5 - SHAPE

NCT01658930

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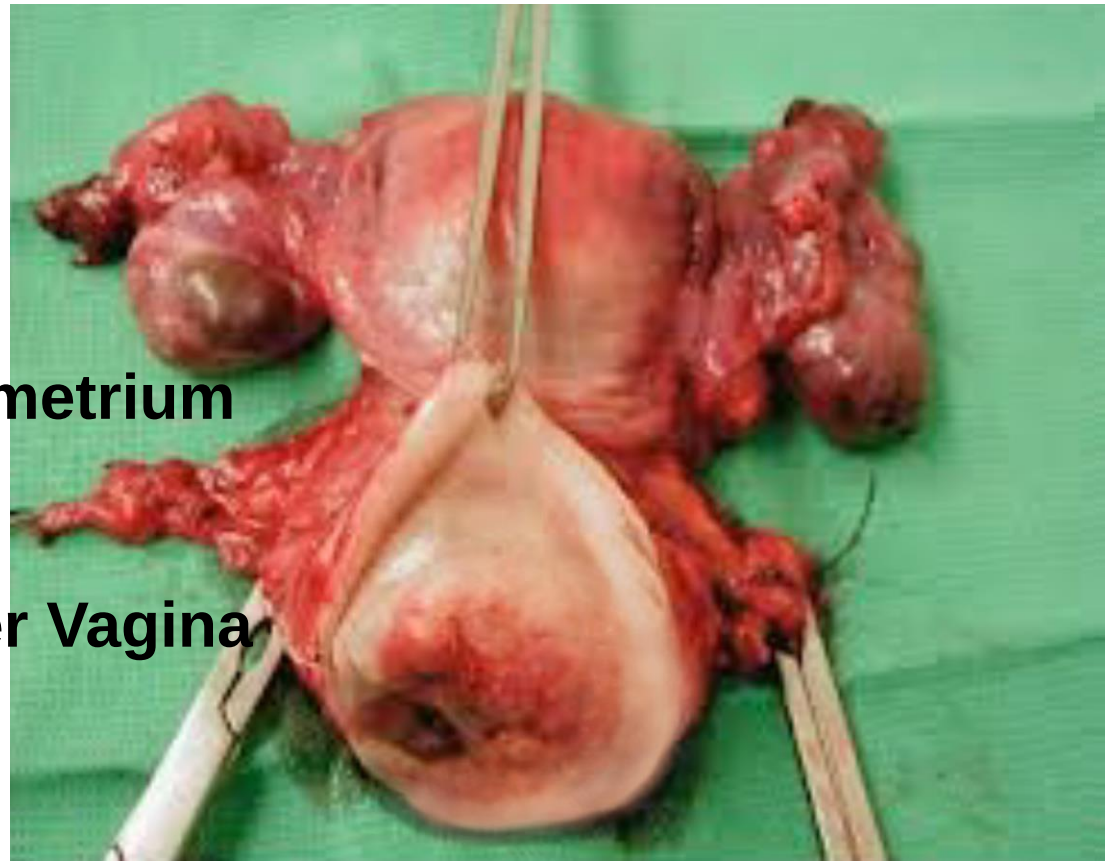
On behalf of the SHAPE investigators

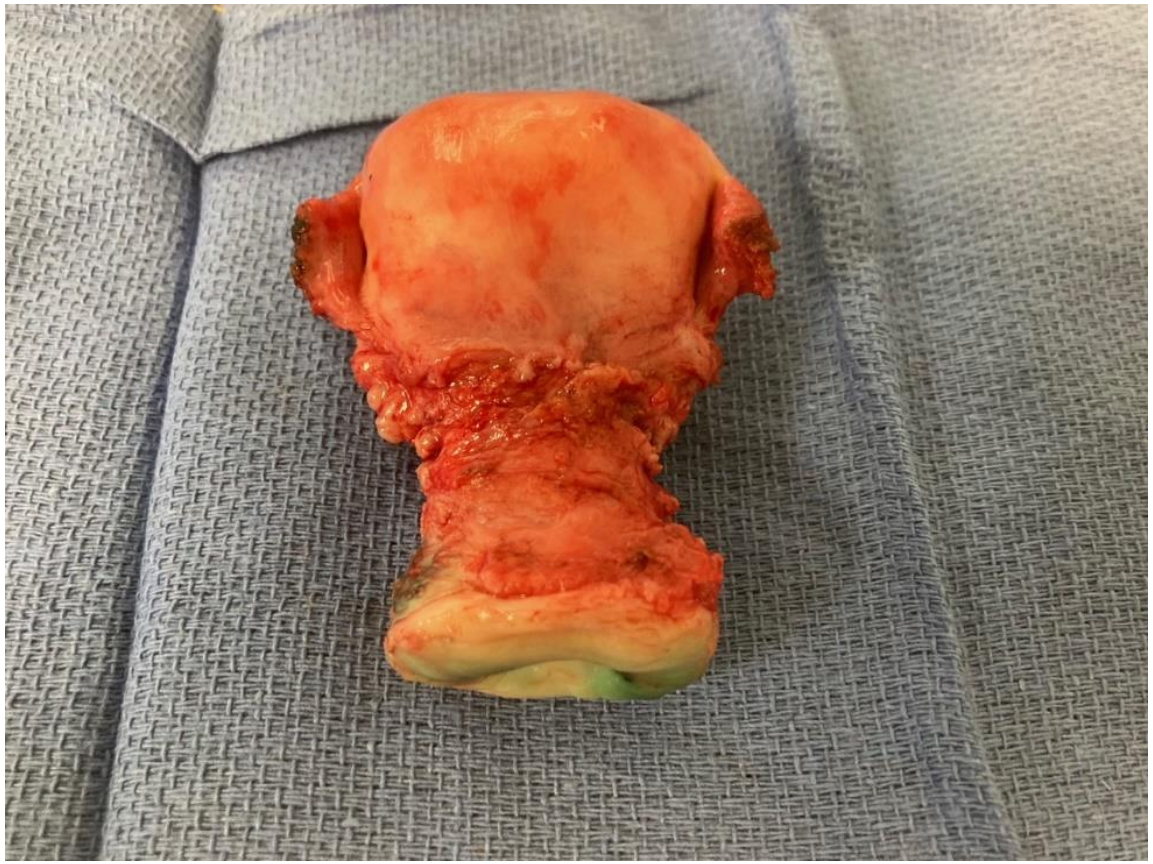
SHAPE – Background and Rationale

- Cancer of the cervix is the second leading cause of cancer death in women worldwide
- As a result of effective screening in developed countries, the overall incidence of cervical cancer has decreased over the past 20 years, with a **higher proportion** of women presenting at a **younger age** and with **low-risk, early-stage disease**
- Although radical surgery is highly effective for the treatment of low-risk disease, women are at risk of suffering **"survivorship" issues** related to long-term **surgical side effects** including compromised bladder, bowel and sexual function

Types of Hysterectomy



Radical Hysterectomy



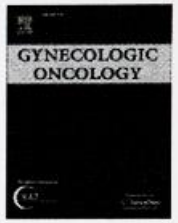
Simple Hysterectomy

Less radical surgery

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



Review

Conservative management of early stage cervical cancer: Is there a role for less radical surgery?

Kathleen M. Schmeler *, Michael Frumovitz, Pedro T. Ramirez

Department of Gynecologic Oncology, The University of Texas M.D. Anderson Cancer Center, 1155 Herman Pressler Drive, Houston, TX 77030, USA

Author	Year	Low-risk criteria	N	Parametrial involvement in low-risk group (%)
Kinney [13]	1995	Squamous histology only, tumor <2 cm, no LVSI*	83	0.0%
Covens [14]	2002	All histologies, tumor <2 cm, DOI** <10 mm, negative pelvic lymph nodes	536	0.6%
Stegeman [15]	2007	Squamous, adenocarcinoma, adenosquamous or clear cell histology, tumor <2 cm, DOI** <10 mm, no LVSI*, negative pelvic lymph nodes	103	0.0%
Wright [16]	2008	All histologies, tumor <2 cm, no LVSI*, negative pelvic lymph nodes	270	0.4%
Frumovitz [19]	2009	Squamous, adenocarcinoma or adenosquamous histology, tumor <2 cm, no LVSI*	125	0.0%

*LVSI: lymphvascular space involvement
**DOI: depth of invasion

All retrospective data

N=1117 < 1%

Schmeler K et al. Gynecol Oncol 120:321, 2011

Less radical surgery

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Review

Conservative management of early stage cervical cancer: Is there a role for less radical surgery?

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suggesting that less radical surgery
may be a safe option
associated with decreased morbidity
surgical de-escalation

Author	ametrial involvement ow-risk group (%)
Kinney [13]	%
Covens [14]	%
Stegeman [15]	%
Wright [16]	%
Frumovitz [19]	%

*LVSI: lymphvascular space involvement
**DOI: depth of invasion

All retrospective data

N=1117 **< 1%**

Schmeler K et al. Gynecol Oncol 120:321, 2011

Hypothesis of the SHAPE trial (2012)

Less radical surgery – **simple hysterectomy** – will be associated with **similar efficacy** and **less surgical morbidity** compared to radical hysterectomy in patients with **low-risk disease**

Trial Schema

Low-risk cervical cancer as defined by:

- Squamous cell, adenocarcinoma, adenosquamous carcinoma
- Stage IA2 and IB1
- < 10 mm stromal invasion on LEEP/cone
- < 50% stromal invasion on MRI
- Max dimension of ≤ 20 mm
- Grade 1-3 or not assessable

Stratification:

1. **Cooperative Group**
2. **Sentinel node mapping** (Yes vs No)
3. **Stage** (IA2 vs IB1)
4. **Histological type** (Squamous vs adenocarcinoma/adenosquamous)
5. **Grade** (1-2 vs 3 vs not assessable)

RANDOMIZE 1:1

Arm 1 (Control)
Radical Hysterectomy*

Arm 2 (Experimental)
Simple Hysterectomy*

Pelvic recurrence rate at 3 years

*Regardless of treatment assignment, surgery will include **pelvic lymph node dissection** with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

CX.5 Endpoints

Primary Endpoints

- **Pelvic recurrence rate at 3 years (PRR3)**

Secondary Endpoints

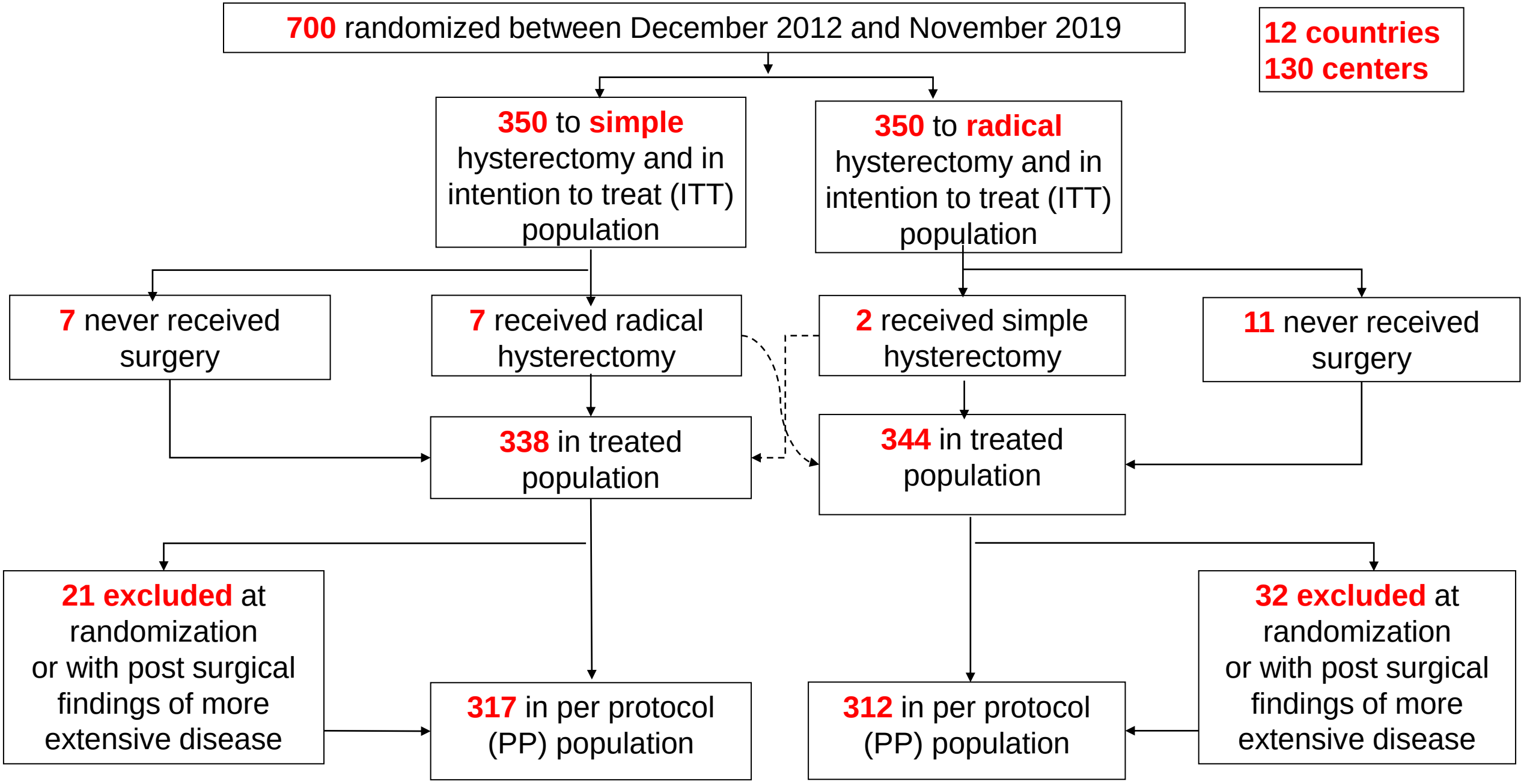
- Pelvic relapse free survival (PRFS)
- Extra pelvic relapse free survival (EPRFS)
- Relapse free survival (RFS)
- Overall Survival (OS)
- Rates of sentinel node detection, parametrial involvement, involved surgical margins, positive pelvic nodes
- Patient reported outcomes

CX.5 Statistical Considerations

- **Non-inferiority (NI) Phase 3 design**
  - **Intention to Treat (ITT) analysis** as **primary analysis**
  - **Per-protocol (PP) analysis**, as **secondary analysis**
- Primary endpoint in original design
  - **Pelvic relapse free survival (PRFS**)
  - 49 pelvic relapses required for final analysis
- Primary endpoint **changed** to:
  - **Pelvic recurrence rate at 3 years (PRR3)** due to very low event rate
  - Amendment approved by CCTG Data and Safety Monitoring Committee (DSMC), June 2022

CX.5 Statistical Considerations

- PRR3 was estimated using **Kaplan-Meier** method
- NI of SH to RH is claimed when the upper 1-sided 95% confidence limit for the difference in PRR3 for SH to RH is lower than or equal to **4%**
- With **700** patients randomized and followed for a **minimum of 3 years**, the study has **85% power** to claim NI of SH to RH when PRR3 in both arms are assumed to be same



Key Baseline Patient Characteristics

Characteristics	Simple Hysterectomy N=350 (%)	Radical Hysterectomy N=350 (%)	Total N=700
Age (years): Median (range)	42 (26-77)	45 (24-80)	44 (24-80)
• ≤ 50 years old (%)	271 (77.4)	246 (70.3)	517 (73.9)
ECOG status: 0	336 (96)	335 (95.7)	671 (95.9)
BMI: median (range)	25 (16.4-53.3)	24.8 (16.1-52)	24.8 (16.1-57.6)
Diagnostic Procedure			
• LEEP / Cone	254 (72.6)	226 (64.6)	480 (68.6)
• Cervical Biopsy	52 (14.9)	77 (22)	129 (18.4)
• Both	40 (11.4)	41 (11.7)	81 (11.6)
• Missing	4 (1.1)	6 (1.7)	10 (1.4)

Key Baseline Patient Characteristics

Characteristics	Simple Hysterectomy N=350 (%)	Radical Hysterectomy N=350 (%)	Total N=700
FIGO Stage:			
• IA2	30 (8.6)	28 (8.0)	58 (8.3)
• IB1	320 (91.4)	322 (92.0)	642 (91.7)
Histology			
• Squamous	218 (62.3)	214 (61.1)	432 (61.7)
• Adenocarcinoma	114 (32.6)	131(37.4)	245 (35.0)
• Adenosquamous	18 (5.1)	5 (1.4)	23 (3.3)
Grade:			
• 1 or 2	205 (58.6)	210 (60.0)	415 (58.2)
• 3	49 (14)	49 (14)	98 (14)
• Not assessed	96 (27.4)	91 (26)	187 (26.7)

All Treated Patients Post Surgery

Characteristics	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P-value
Type of Surgical Approach *			
• Abdominal	57 (16.9)	99 (28.8)	**0.0003**
• Laparoscopic	188 (55.6)	152 (44.2)	**0.0036**
• Robotic	82 (24.3)	87 (25.3)	0.79
• Vaginal	11 (3.3)	4 (1.2)	0.07
Sentinel Node Mapping			
• Planned	126 (37.3)	131 (38.2)	0.87
• Successful	78/126 (61.9)	83/131 (63.4)	0.90

* Surgical approach: at the discretion of the surgeon; not a randomization factor

All Treated Patients Post Surgery

Key post surgical findings on final pathology	Simple hysterectomy N=338 (%)	Radical hysterectomy N=344 (%)	P-value
• Residual cervical cancer detected	154 (45.6)	163 (47.4)	0.65
• Lymphovascular space invasion (LVSI)	45 (13.3)	45 (13.1)	1.00
• Positive nodes (from sentinel or non sentinel nodes)	11 (3.3)	15 (4.4)	0.55
• Positive vaginal margins	7 (2.1)	10 (2.9)	0.62
• Positive parametrium	0	6 (1.7)	0.03
• Lesions > 2cm	15 (4.4)	14 (4.1)	0.85

All Treated Patients Post Surgery

Adjuvant Treatment	Simple hysterectomy N=338 (%)	Radical hysterectomy N=344 (%)	P-value
• **Adjuvant Post Operative Treatment**	31 (9.2)	29 (8.4)	0.79
• Chemotherapy only	1	0	
• Radiation therapy only	15	11	
• Chemoradiation	15	18	

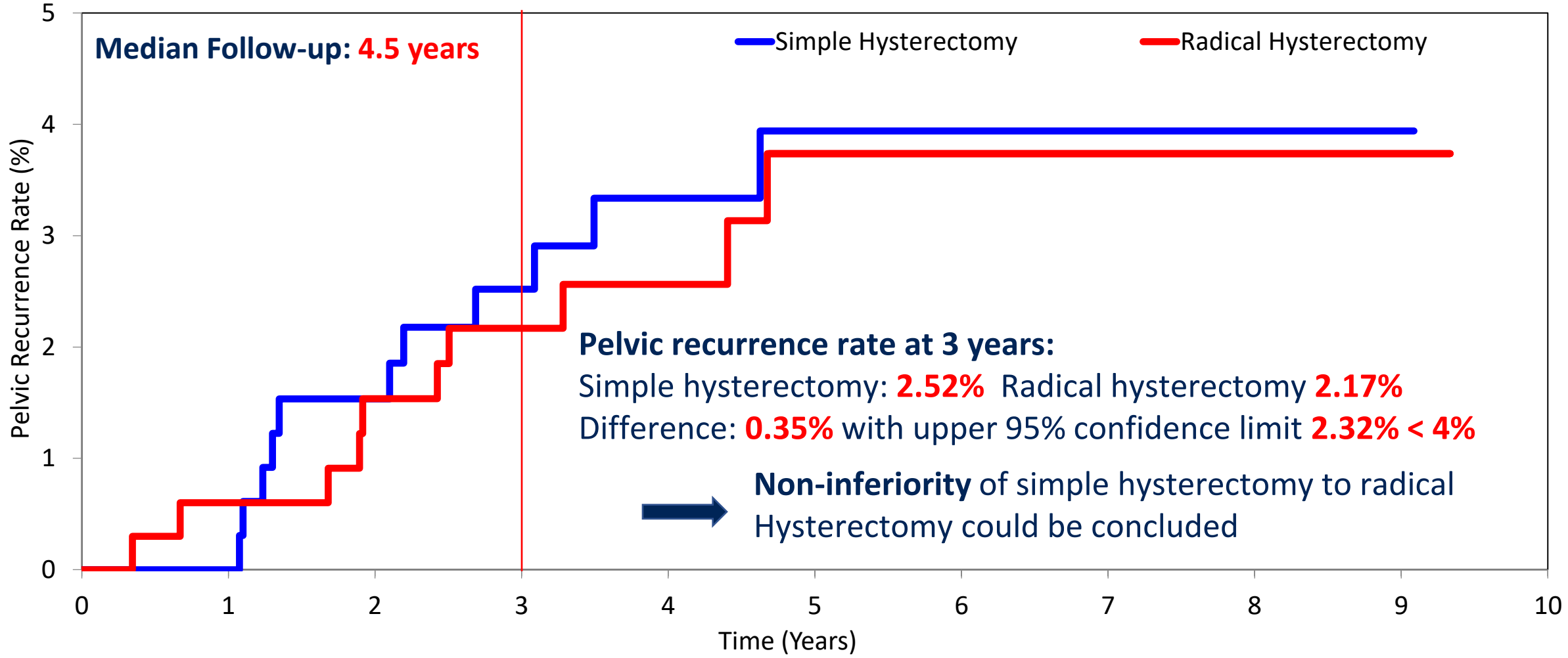
Recurrences

Events	Simple Hysterectomy N=350 (%)	Radical Hysterectomy N=350 (%)	Total N=700 (%)
Pelvic recurrences	11 (3.1)	10 (2.9)	21 (3.0)
• Vaginal Vault	9 (0.4)	8 (2.3)	17 (2.4)
• Parametrium	1 (0.3)	0	1 (0.1)
• Pelvic Lymph Nodes	0	0	0
• Other	1 (0.3)	2 (0.6)	3 (0.4)
Extra Pelvic recurrences	7 (2.0)	2 (0.6)	9 (1.3)
• Abdomen	2 (0.6)	0	2 (0.3)
• Para-aortic lymph nodes	2 (0.6)	2 (0.6)	4 (0.6)
• Supraclavicular L N	1 (0.3)	0	1 (0.1)
• Other	2 (0.6)	0	2 (0.3)
Pelvic and extra pelvic recurrences	3 (0.9)	2 (0.6)	5 (0.7)
Extra pelvic only recurrences	4 (1.1)	0	4 (0.6)
Pelvic or extra pelvic recurrences	15 (4.3)	10 (2.9)	25 (3.6)

Deaths

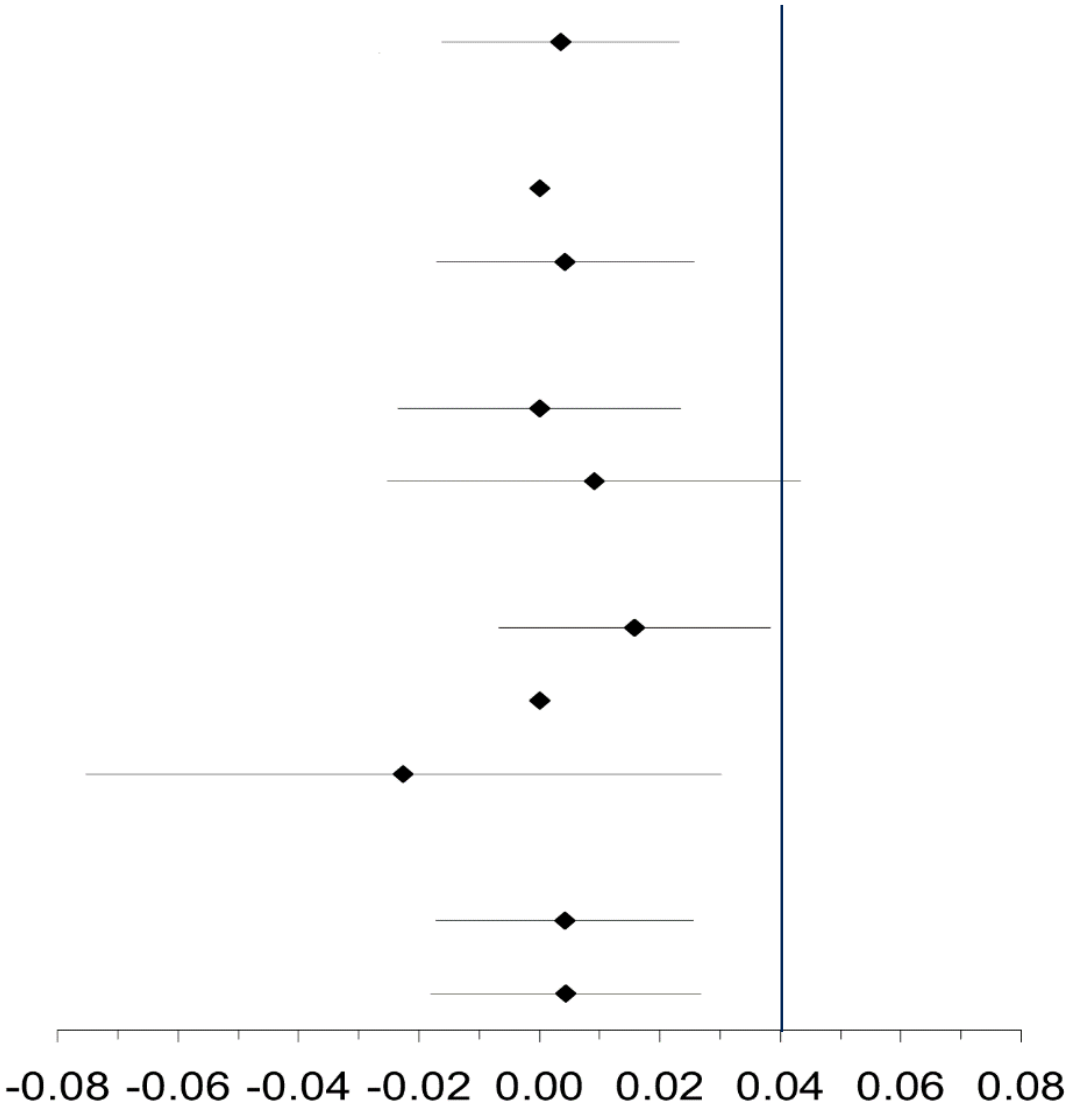
Events	Simple Hysterectomy N=350 (%)	Radical Hysterectomy N=350 (%)	Total N=700 (%)
Deaths	7 (2.0)	7 (2.0)	14 (2.0)
• Cervical Cancer	4 (1.1)	1 (0.3)	5 (0.7)
• Other primary malignancy	1 (0.3)	3 (0.9)	4 (0.6)
• Other medical condition	2 (0.6)	3 (0.9)	5 (0.7)

Pelvic Recurrence Rate (ITT)



Simple	350	328	311	273	204	133	61	31	14	4	0
Radical	350	329	315	286	208	132	66	31	16	2	0

Subgroup	Difference in PRR3 and 90% CI	PRR3 (%) on SH	PRR3 (%) on RH	Difference (%) (90% CI)
Overall (ITT)		2.52	2.17	0.35 (-1.62, 2.32)
Stage				
IA2		0.00	0.00	0.00 (0.00, 0.00)
IB1		2.76	2.33	0.43 (-1.71, 2.57)
Histology				
Squamous		2.05	2.05	0.00 (-1.71, 2.57)
Adenocarcinoma /adenosquamous		3.26	2.35	0.91 (-2.52, 4.34)
Tumor grade				
1-2		2.63	1.05	1.58 (-0.68, 3.84)
3		0.00	0.00	0.00 (0.00, 0.00)
Not assessable		3.53	5.79	-2.26 (-7.54, 3.02)
Per-protocol patients				
Pre-defined		2.76	2.34	0.42 (-1.72, 2.56)
+Excluding eligibility not met after surgery		2.89	2.45	0.44 (-1.80, 2.68)



Secondary Efficacy Endpoints (ITT)

Endpoints	Simple Hysterectomy N=350	Radical Hysterectomy N=350		
	3 year outcomes		Hazard Ratio (90% confidence interval)	P-value
Pelvic Recurrence Free Survival	97.5%	97.8%	1.12 (0.54-2.32)	0.79
Extra-Pelvic Recurrence Free Survival	98.1%	99.7%	3.82 (0.79-18.4)	0.10
Relapse Free Survival	96.3%	97.8%	1.54 (0.69-3.45)	0.30
Overall Survival	99.1%	99.4%	1.09 (0.38-3.14)	0.87

All Treated Patients Post Surgery

Intraoperative complications	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P-value
Intraoperative Injury	24 (7.1)	22 (6.4)	0.77
• Bladder	3	9	0.14
• Ureter	3	5	0.73
• Nerve	5	2	0.28
• Bowel	2	2	1.00
• Vein	4	1	0.21
• Other	7	3	0.22

Surgery-Related Adverse Events (All Grades with incidence ≥ 5% in one of the Arms)

Adverse Event	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P value	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P value
	Within 4 weeks of surgery (acute)			After 4 weeks of surgery (late)		
Any adverse event	144 (42.6)	174 (50.6)	**0.04**	181 (53.6)	208 (60.5)	**0.08**
• Abdominal pain	33 (9.8)	42 (12.2)	0.33	36 (10.7)	47 (13.7)	0.24
• Constipation	16 (4.7)	22 (6.4)	0.40	13 (3.8)	19 (5.5)	0.37
• Fatigue	19 (5.6)	23 (6.7)	0.63	19 (5.6)	28 (8.1)	0.23
• Paresthesia	14 (4.1)	22 (6.4)	0.23	17 (5.0)	22 (6.4)	0.51
• Peripheral sensory neuropathy	- (-)	- (-)	- (-)	21 (6.2)	13 (3.8)	0.16
• Urinary incontinence	8 (2.4)	19 (5.5)	**0.048**	16 (4.7)	38 (11.0)	**0.003**
• Urinary retention	2 (0.6)	38 (11.0)	**<0.0001**	2 (0.6)	34 (9.9)	**<0.0001**
• Dyspareunia	- (-)	- (-)	- (-)	21 (6.2)	19 (5.5)	0.75
• Pelvic pain	19 (5.6)	9 (2.6)	0.054	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

Patient Reported Outcomes (PRO)

- Quality of Life and Sexual Health were assessed using validated questionnaires at different time points
  - EORTC QLQ-C30
  - EORTC QLQ-CX24
  - Female Sexual Function Index (FSFI)
  - Female Sexual Distress Scale (FSDS-R)
  - Before randomization (baseline) and at 3, 6, 12, 24, and 36 months after surgery
    - Compliance (completion) rate **at baseline**
      - 73% for EORTC QOL assessments
      - 86% for sexual health assessments
    - Compliance (completion) rate **after baseline**
      - 56% to 69% for EORTC QOL assessments
      - 63% to 79% for sexual health assessments

Quality of Life and Sexual Health

Significant differences were seen between the 2 groups over time and **all were in favor of the simple hysterectomy group**

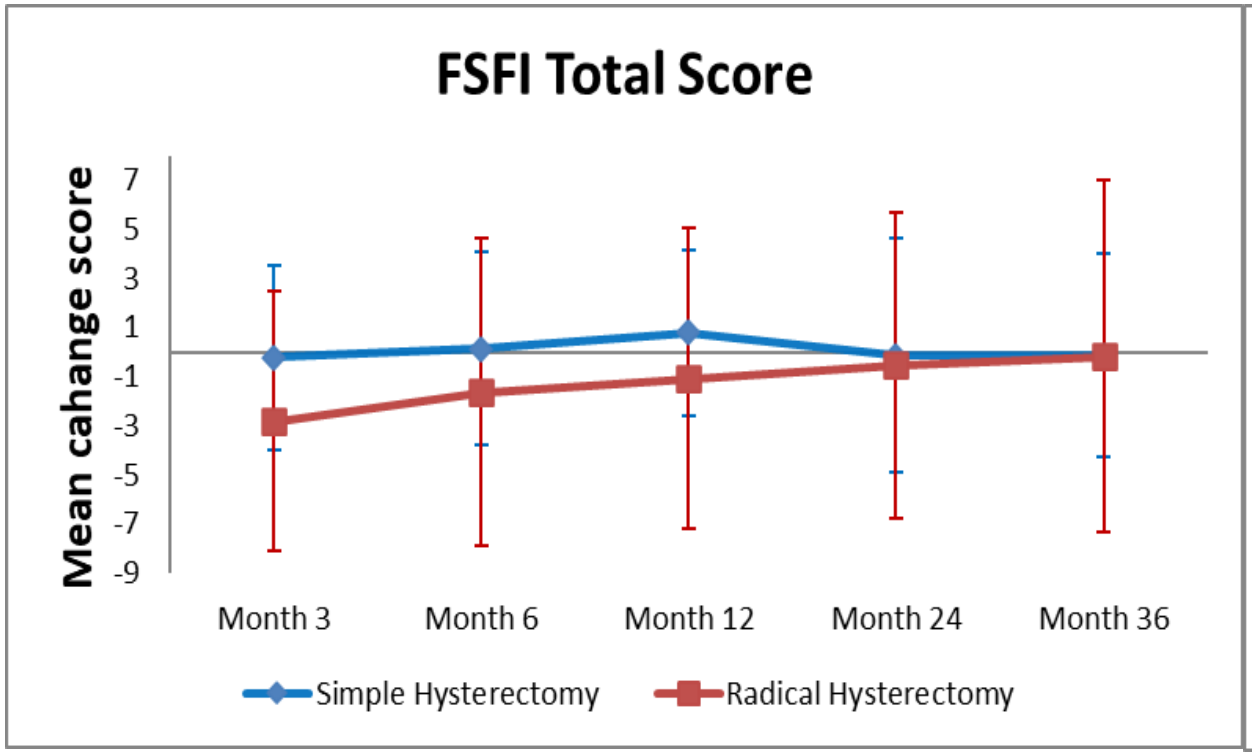
*From linear mixed models for change scores from baseline over time

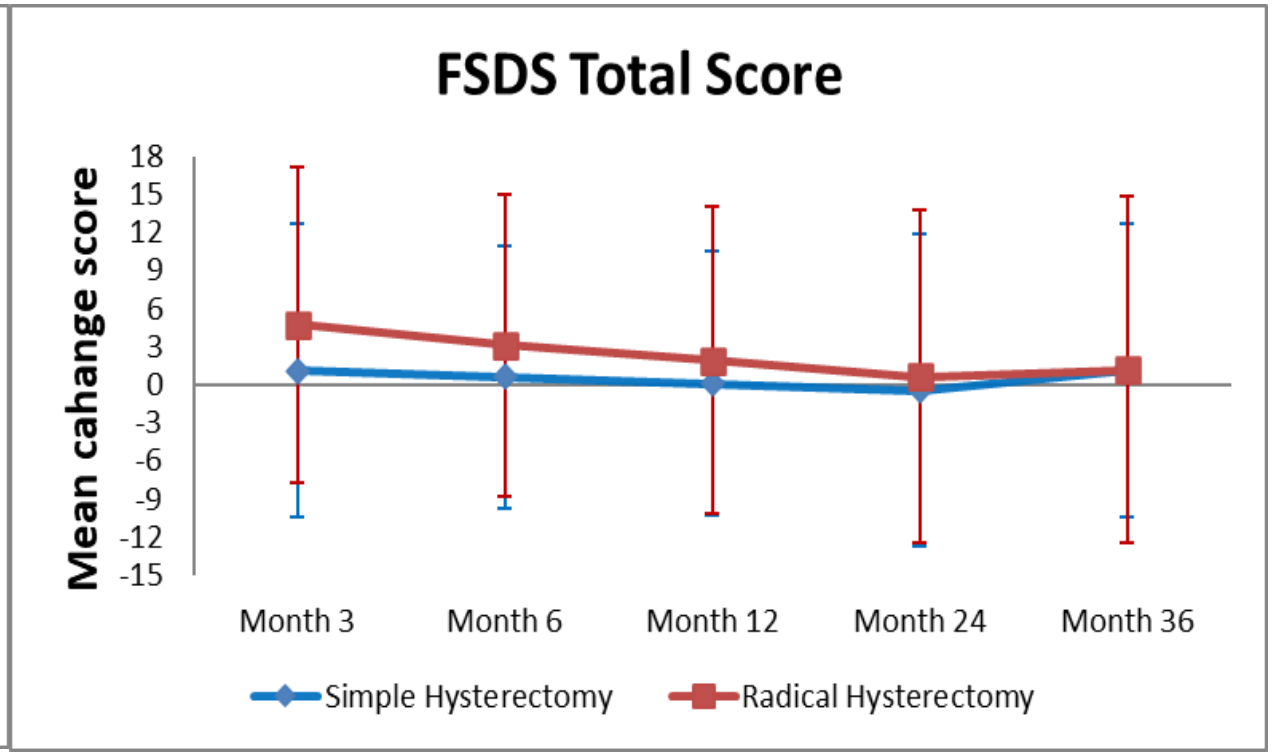
Scale	Effect Estimate*	P-value
EORTC QLQ-C30 pain scale	-4.53	p=0.02
EORTC QLQ-CX24 • **Symptom experiences**	-2.12	p=0.02
• **Body Image**	-5.22	p=0.02
• **Sexual Worry**	-6.67	p=0.04
• **Sexual Activities**	-7.59	p=0.003
• **Sexual Enjoyment**	-7.67	p=0.049
FSFI Desire	0.37	p=0.002
FSFI Arousal	0.38	p=0.003
FSFI Lubrication	0.36	p=0.008
FSFI Total Score	1.82	p=0.006
FSDS Total Score	-2.47	p=0.02

Quality of Life and Sexual Health

Sexual-Vaginal Functioning (EORTC QLQ-CX24): Lower Score is Better			
	SH (Mean change score)	**RH (Mean change score)**	**P-value**
Month 3	4.41	16.03	p<0.0001
Month 6	0.93	11.85	p<0.0001
Month 12	0.94	9.16	p<0.0001
Sexual Pain (FSFI Pain Scale): Higher Score is Better			
	SH (Mean change score)	**RH (Mean change score)**	**P-value**
Month 3	0.03	-0.78	p=0.003
Month 6	0.10	-0.56	p=0.02
Month 12	0.35	-0.22	p=0.002

Quality of Life and Sexual Health





Higher score indicating a **better level of sexual function**

Higher score indicating a **greater level of sexual-related distress**

Conclusion

- In early-stage low-risk cervical cancer, pelvic recurrence rate at three years with **simple hysterectomy** was **not inferior** to radical hysterectomy
- Fewer urological surgical complications following **simple hysterectomy**
- Better quality of life and sexual health measures were seen following **simple hysterectomy**
- Following adequate / rigorous preoperative assessment, **simple hysterectomy** can now be considered the **new standard of care** for patients with low-risk early-stage cervical cancer, supporting the concept of **surgical de-escalation** in those patients
  - Stage IA2-IB1 ≤ 2cm
  - < 10 mm depth of stromal invasion (LEEP/cone) or
  - < 50% depth of stromal invasion (preop MRI)

Acknowledgements

With thanks to the **700 hundred women** who agreed to participate in this study and **all the investigators** and **clinical trial support staff** who ensured the success of the trial !

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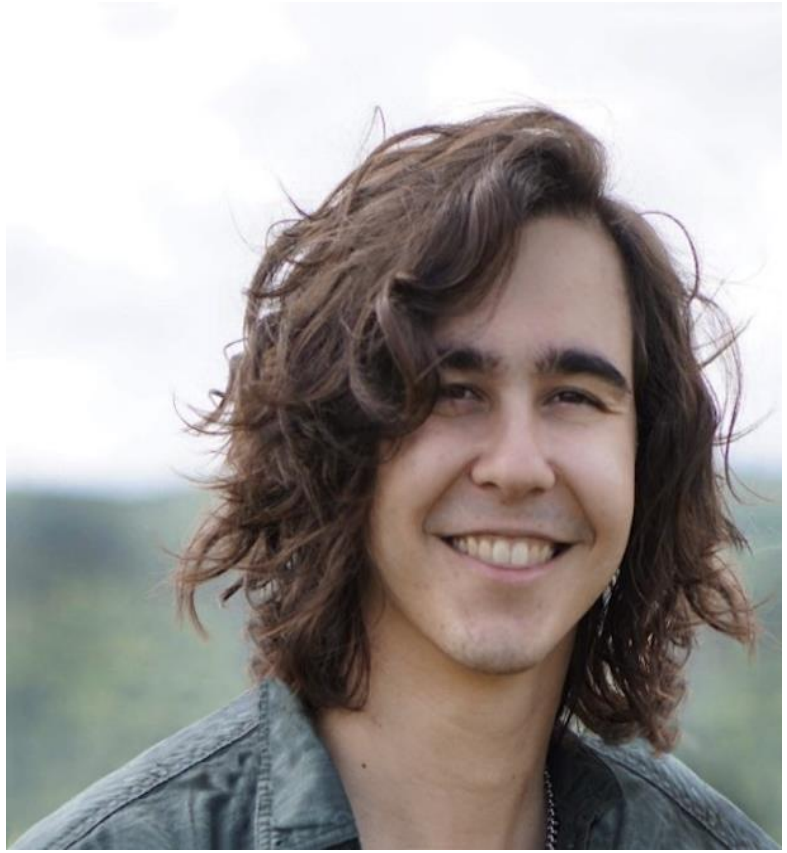
- **Canadian Cancer Society (grant #707213)**
- **Canadian Institutes of Health Research (grant #119446)**

To CCTG

Lois Shepherd, MD, CCTG Senior Staff

Donsheng Tu, PhD, CCTG Statistician

To My Family



Patient Lay Summary

Available on cancer.net

An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection (RH) vs simple hysterectomy and pelvic node dissection (SH) in patients with low-risk early-stage cervical cancer (LRESCC). A Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group (CCTG CX.5-SHAPE).

Visit the webpage

https://www.cancer.net/CX5-SHAPE

Scan QR code