Gynecologic Cancer InterGroup
Cervix Cancer Research Network

The SHAPE Trial

Comparing radical hysterectomy and pelvic node dissection against simple hysterectomy and pelvic node dissection in patients with low risk cervical cancer

Chair: Marie Plante
Laval University, Quebec City

A CCTG Clinical Trials Group proposal for the Gynecological Cancer Inter Group (GCIG)

CCRN Educational Symposium, Johannesburg January 2019

SHAPE

- **Morbidity of the rad hyst comes from**
  - **Parametrectomy**
    - **Damage to autonomic nerve fibers a/w bladder, bowel and sexual dysfunction**
    - **Late urological/rectal dysfunctions: 20-30%**

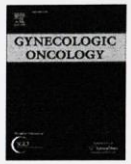
SHAPE

- **Question is:**
  - **Does the probability of parametrial spread in low-risk early-stage cervical cancer justify the morbidity of the radical hysterectomy ?**

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

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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

Retrospective studies **N=1117** **< 1%**

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

Gynecologic Oncology 132 (2014) 254–259

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Review

Management of low-risk early-stage cervical cancer: Should conization, simple trachelectomy, or simple hysterectomy replace radical surgery as the new standard of care?☆

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SHAPE

- Concept of the trial
  - To demonstrate that simple hyst and nodes **is not inferior** to radical hyst and nodes in terms of pelvic relapse rate and is associated with **better quality of life/sexual health**

Trial Schema

Low-risk cervical cancer as defined by:

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

RANDOMIZE

↗ ARM 1 (Control) Radical Hysterectomy*

↘ Arm 2 (Experimental) Simple Hysterectomy*

→→Pelvic relapse

* 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.

Planned sample size: 700 (non-inferiority at 0.05 level with 80% power)

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Definition

- « Low-risk » early-stage cervical cancer
  - IA2
  - IB1 < 2 cm
  - Limited stromal invasion
    - < 10mm SI on LEEP/cone
    - < 50% SI on pelvic MRI
    - At least 3mm of intact stroma on MRI

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Inclusion criteria

- Histologically confirmed invasive cx cancer
  - Cone, LEEP or cervical biopsy
- Squamous, adenoca or adenosquamous
- Stage IA2-IB1< 2 cm
  - < 50% stromal invasion (MRI)
  - < 10mm depth of invasion on LEEP/cone
  - at least 3mm of intact cervical stroma (pelvic MRI)
- Grade 1, 2, 3
- Lymph vascular space invasion (LVSI) allowed
- Pelvic MRI (optional for IA2) and CXR

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Exclusion criteria

- High risk histology
  - clear cell, small cell
- Stage IA1
- Evidence of lymph node metastasis or extrauterine disease **(pelvic MRI)**
- Neoadjuvant chemotherapy
- Pregnancy
- Desire to preserve fertility

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- **Primary trial objective:**
  - **To show that simple hysterectomy in low risk cervix cancer patients is safe and is associated with less morbidity than radical surgery**
  - **To show that overall survival will not be significantly different between rad hyst and simple hyst**

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Primary endpoint

- Pelvic relapse-free survival (PRFS)

Secondary endpoints

- Treatment-related toxicity
- Extrapelvic relapse-free survival
- Overall survival
- Rate of sentinel node detection
- Rate of parametrial, margins, and pelvic node involvement
- Patient Reported Outcome (PRO)
  - Quality of life (including measures of sexual health)
  - Cost effectiveness and cost utility

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- QoL and Sexual Health Questionnaires
  - Female Sexual Function Index (19 items)
  - Female Sexual Distress Scale (12 items)
  - EORTC QLQ-CX24 (24 items)
- Health Related Economic Evaluations
  - NCIC CTG economic-related case report forms
  - EQ-5D
- Frequency
  - At randomization (pre-surgery)
  - At 3, 6, 12, 24 and 36 months post surgery

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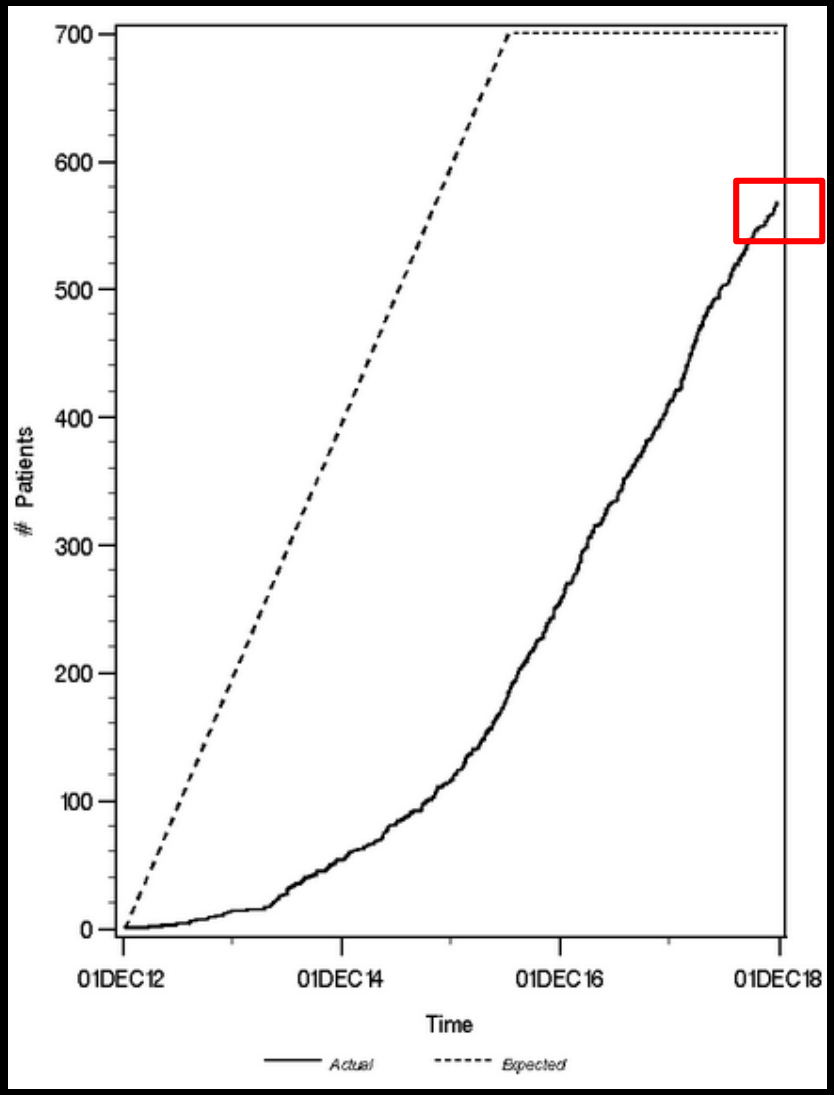
- **Trial Design**
  - **1:1 multicenter prospective randomized trial**
  - **Non-inferiority trial design at 0.05 level with 80% power**
  - **Sample size : 700 patients**

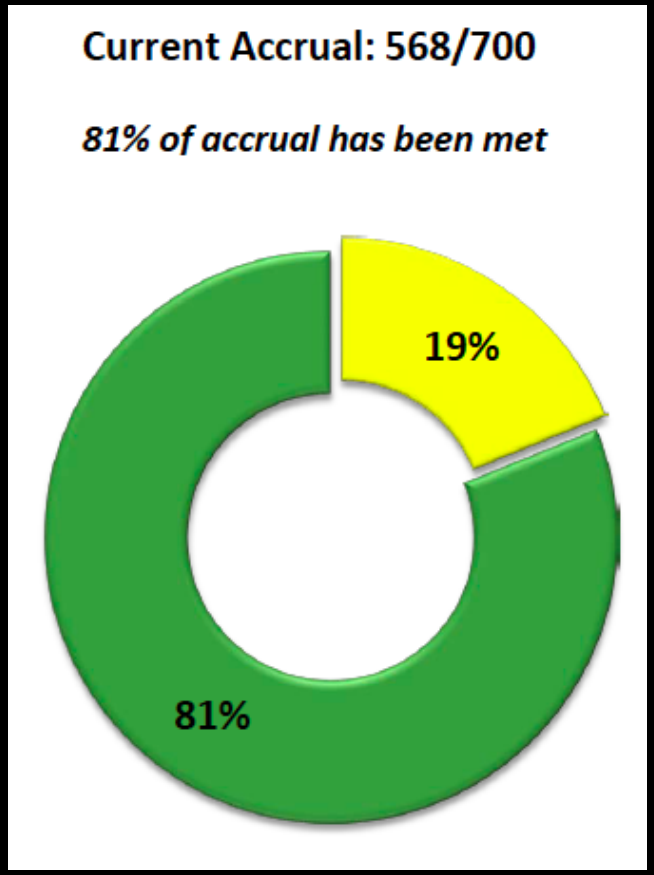
Results

Current Status (end of november 2018)



- We have reached **81%** of total accrual **(568/700)**
- We are still exploring the potential participation of two CCRN sites in Brazil in 2019.
- It is our current estimation that accrual will continue until Q4 2019.

Accrual

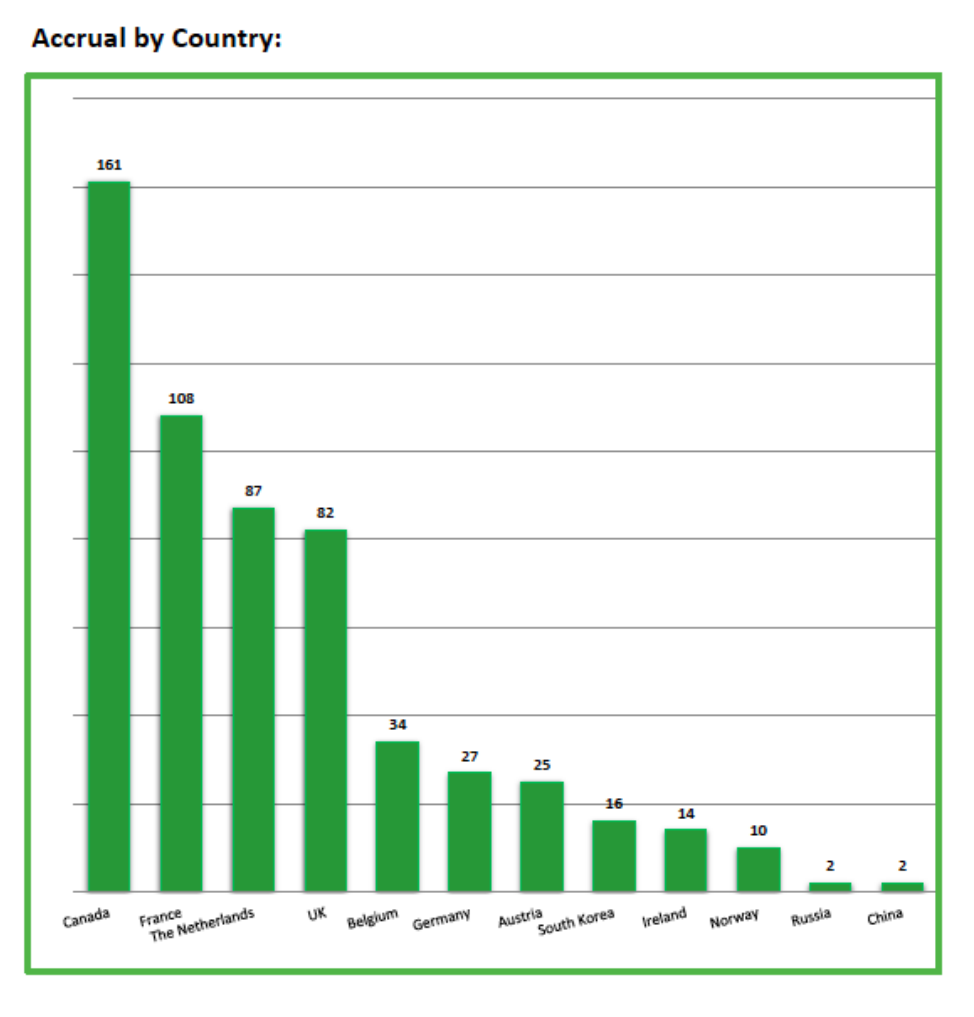


Current Status

Country	# Sites Activated
Canada	20
France	33
The Netherlands	7
UK	27
Belgium	10
Austria	7
Germany	21
Ireland	1
South Korea	3
Norway	1
Russia	1
China	1
Total	132

Country	# Patients Accrued
Canada	161
France	108
The Netherlands	87
UK	82
Belgium	34
Germany	27
Austria	25
South Korea	16
Ireland	14
Norway	10
Russia	2
China	2
Total	568 (81%)

Accrual by country



Patient Characteristics

	Radical Hyst (N=255)	Simple Hyst (N=257)	Total (N=512)
Age (median)	44	42	43
Intended SLN mapping			
yes	88 (35%)	86 (33%)	174 (34%)
no	167 (65%)	171 (67%)	338 (66%)
FIGO Stage			
IA2	21 (8%)	23 (9%)	44 (9%)
IB1 (low risk)	234 (92%)	234 (91%)	468 (91%)
Histology			
Squamous	151 (59%)	160 (62%)	311 (61%)
Adenocarcinoma	104 (41%)	97 (38%)	201 (39%)

Required adjuvant therapy: 51 (10.0%)
(Rad Hyst = 25; Simple Hyst = 26)
Total # of deaths reported to date: 5 (1%)
Total # of pelvic recurrences to date: 3 (0.6%)

Patients who received Adjuvant Treatment

	Radical Hyst N=255	Simple Hyst N=257	Total N=512
Adjuvant Treatment	**25 (9.8%)**	**26 (10.1%)**	**51 (10.0%)**

Reason for Adjuvant Therapy	Radical Hyst N=25	Simple Hyst N=26	Total N=51
Lesion is > 2cm	6 (24.0%)	5 (19.2%)	11 (21.6%)
Positive margins	4 (16.0%)	4 (15.4%)	8 (15.7%)
Sentinel lymph node metastasis	2 (8.0%)	2 (7.7%)	4 (7.8%)
Sentinel lymph node metastasis by IHC only	0	0	0
Non-sentinel lymph node metastasis	1 (4.0%)	5 (19.2%)	6 (11.8%)
Extrauterine/Parametrial spread	1 (4.0%)	0	1 (2.0%)
Extra pelvic spread	0	0	0
LVSI	6 (24.0%)	6 (23.0%)	12 (23..5%)
Other	3 (12.0%)	3 (11.5%)	6 (11.7%)
Unknown	2 (8.0%)	1 (3.8%)	3 (5.9%)

Event Rate and Time-Driven Analysis

- It was projected that approximately **25 events** would been seen by the time accrual was complete.
- The current event rate seems much **lower than expected**; this is being closely monitored
- The trial committee may consider amending the protocol to a **"time-driven" analysis** based on a landmark time point if it requires very long time to observe the required number of events for final analysis
  - The final analysis would be performed after all patients are followed for at least 3 years or when the required number of events observed, whichever is the earliest
- A revised statistical analysis plan will be presented to DSMC if/when a decision has been made. Assuming current accrual rates continue, this **"time-driven"** analysis could take place in **2022.**

SHAPE

- Will provide level 3 evidence
- Will likely be a “practice-changing” trial