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A RANDOMIZED 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 (GCIG) Trial led by the NCIC CTG

GCIG Trial Designation: The SHAPE Trial
NCIC CTG Protocol Number: CX.5

Chair: Dre Marie Plante

Cervix Cancer Education Symposium, January 2017, Mexico

- **Standard treatment for stage IA2-IB1**
  - Radical hysterectomy
  - Pelvic lymph node dissection
- **To rule out**
  - Parametrial spread
  - Lymph node metastasis

- **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%**

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

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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

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

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

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Gynecologic Oncology 132 (2014) 624–627

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Non-radical surgery for small early-stage cervical cancer. Is it time?

Geneviève Bouchard-Fortier, Clare J. Reade, Allan Covens *

Division of Gynecologic Oncology, Odette Cancer Centre, University of Toronto, Toronto, Canada

Gynecologic Oncology 132 (2014) 254–259

Contents lists available at ScienceDirect

Gynecologic Oncology

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

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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[b] Department of Gynecologic Oncology, Instituto de Cancerología Las Américas, Medellín, Colombia
[c] Department of Gynecology, Hospital Quiron, Murcia, Spain

- **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**

- **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**

Trial schema

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Low-risk cervical cancer as defined by:

- Stage IA2-IB1 squamous cell, adenocarcinoma/adenosquamous carcinoma
- < 2cm, at least 3mm of intact cervical stroma and < 50% stromal invasion
- Grade 1-3

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)

- **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

- **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**

- **Stratification by**
  - **Centers (performing SLN mapping vs not)**
  - **Stage (IA2 vs IB1)**
  - **Histology (squamous vs adenoca)**
  - **Grade (1-2 vs 3)**

Note: LVSI will not be included as a stratification factor but will be evaluated separately in the final data analysis

- **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

- **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

- QoL questionnaires are optional BUT we STRONGLY encourage your patients to participate and fill them up as QoL is an important part of the study
- Not mandatory to avoid accrual issues

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

- **Interim analysis**
  - **Once at least 50% of required number of pelvic relapse is reached (n=49)**
- **Trial closure**
  - **If pelvic relapse free survival (PRFS) in experimental arm is significantly lower**

- **Adjuvant Therapy**
  - **As per local center policy**
    - **If intermediate or high risk features on final pathology**
    - **RT +/- CT**
  - **Most patients will not require adjuvant Tx**

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Surgical aspects

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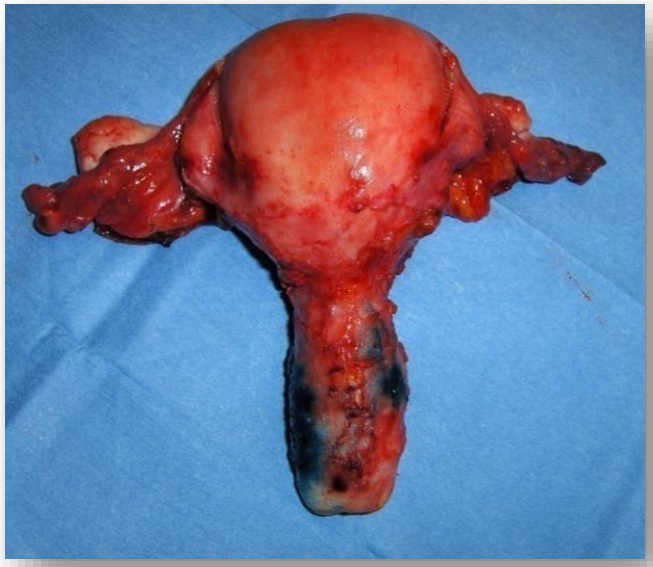
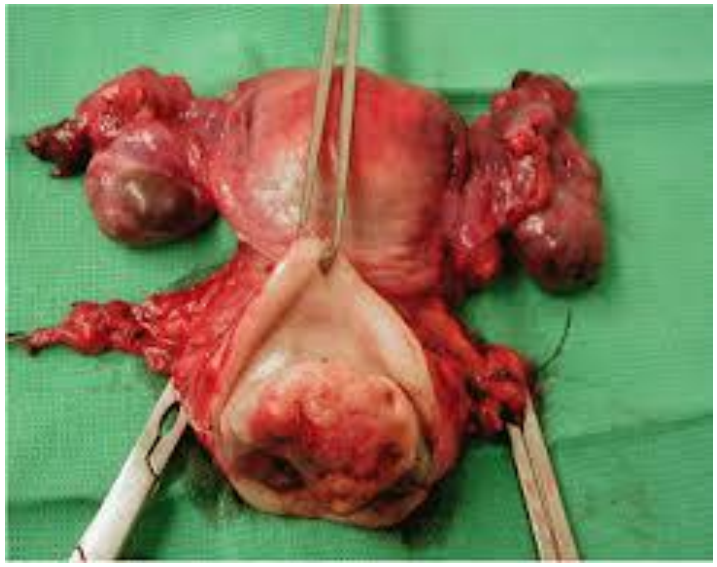
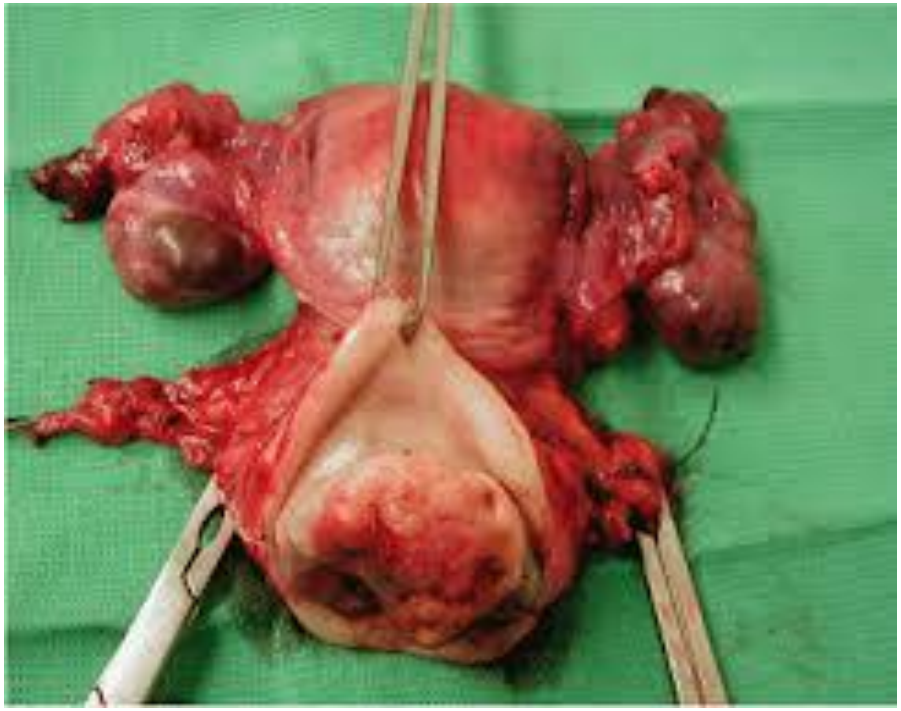
- **Simple Hysterectomy**
  - **The uterus with cervix but without adjacent parametria and a maximum of 0.5 cm of vaginal cuff**



- **Radical Hysterectomy (Type II)**
  - **The uterus, cervix, medial 1/3 of parametria, 2 cm of the uterosacral ligaments and upper 2 cm of the vagina are to be removed *en bloc***



- **Surgical approach**
  - **Abdominally**
  - **Laparoscopically**
  - **Robotically**
  - **Vaginally**



Provide un-pinned picture of the hysterectomy specimen

- **Lymphadenectomy**
  - **Pelvic (mandatory)**
  - **Para-aortic (as required)**
- **Frozen Section**
  - **NOT ALLOWED unless LN clinically suspicious**

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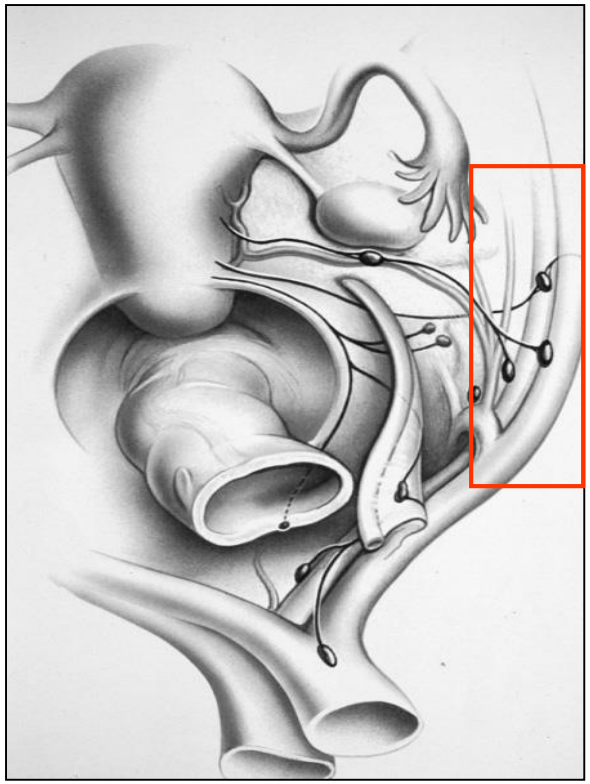

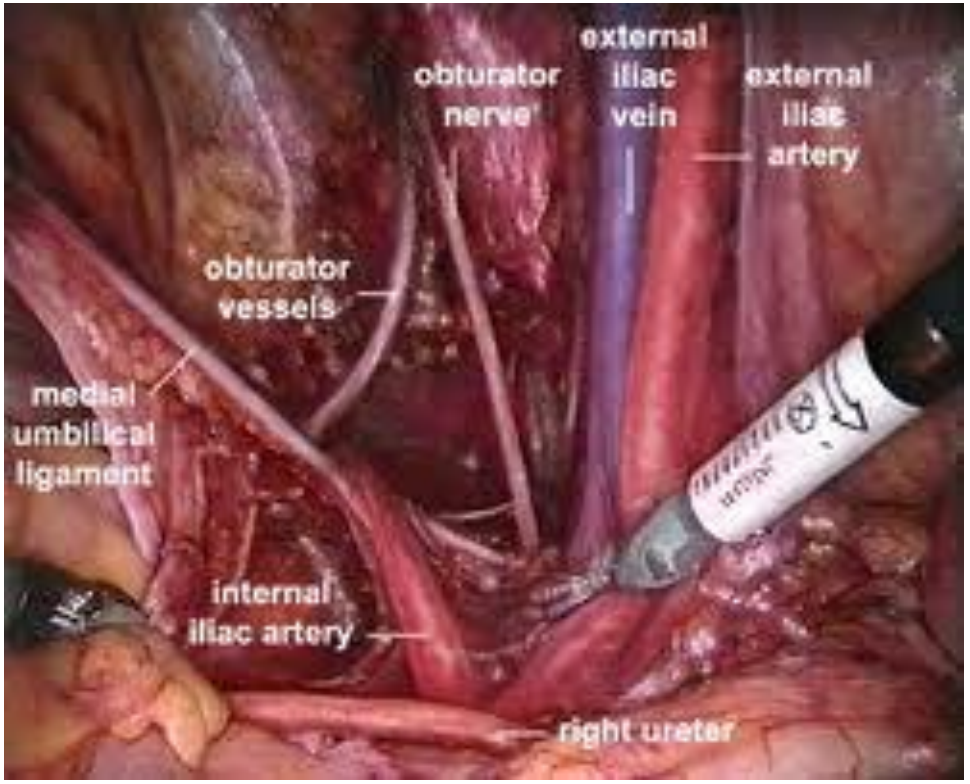

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- **Sentinel Lymph Node Mapping**
  - **Based upon previous credentialing**
  - **Blue dye and Tc-99**
  - **Lymphoscintigram (LSG) preferred but optional**
  - **Frozen Section of SLN NOT ALLOWED**

- **ICG NOT ALLOWED**

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Credentialing

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- **Sentinel Lymph Node Mapping**
  - **Each participating cooperative group will need to credential their centers for their sentinel node mapping procedures.**
  - **The protocol will provide the recommended process, but it is up to each group to perform the credentialing prior to activating a center and allowing randomizations.**
  - **Provide pictures of the blue SLN and LSG for the first 5 cases**

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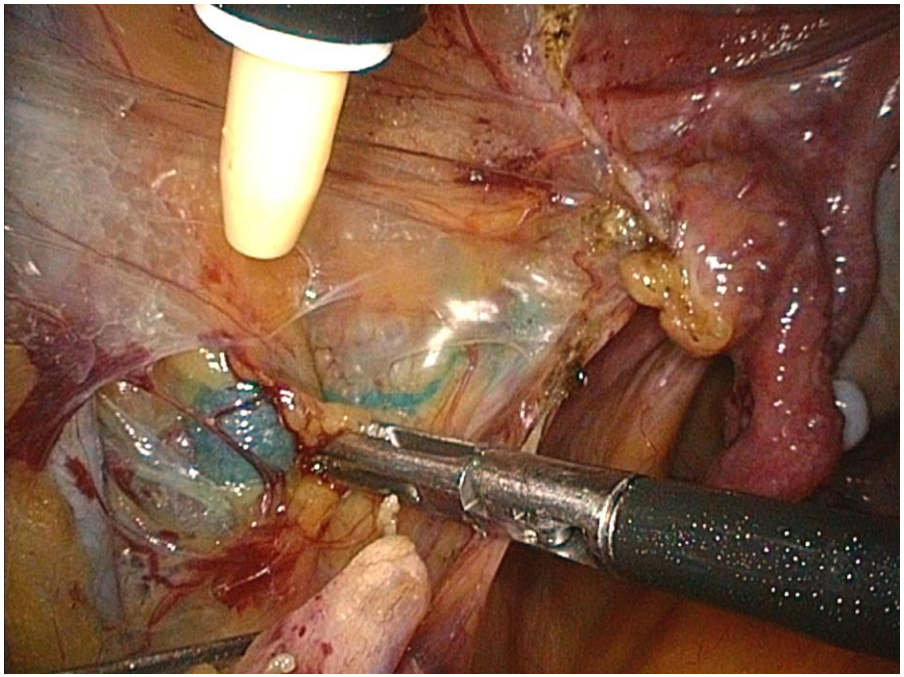

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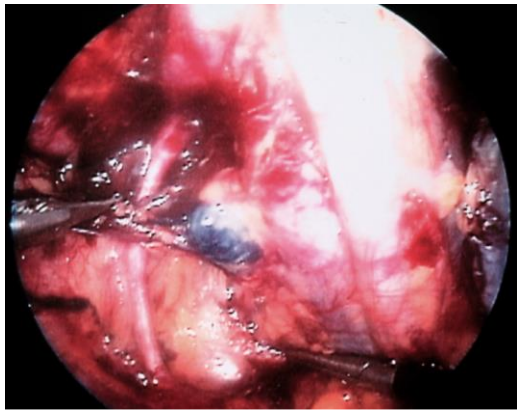
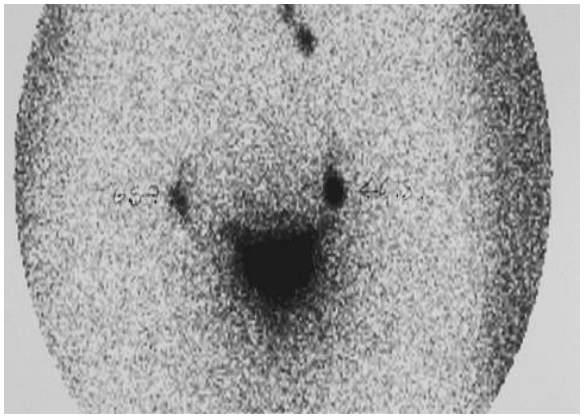
Provide pictures of the blue nodes on each side and lymphoscintigram





- **MRI Capabilities**
  - **IB1 patients must undergo a pelvic MRI to confirm minimum of 3mm of intact cervical stroma and less than 50% stromal invasion.**
  - **IA2 patients: MRI optional**
  - **Each cooperative group must credential their sites prior to activation to ensure that the necessary MRI procedures are in place to confirm eligibility (gadolinium)**

- **Pathology**

  - Each center/cooperative group will need to designate a "Reference Pathologist" who will have to attest to the patient's eligibility as well as to confirm the validity of the surgical intervention

  - This will be done via a checklist that is completed by the reference pathologist for the diagnostic procedure and the surgery

  - A photograph of the "unpinned" hysterectomy specimen will be sent to NCIC CTG for review

- Most common problem
- Accurate assessment
  - Depth of stromal invasion
  - Lesion size
  - Diagnostic LEEP/cone in multiple pieces
  - Difficulty assessing margins
  - More than one excision procedure
  - Residual disease on MRI post LEEP/Cone

- **Quality assurance / control**
  - OR dictation
  - Pathology report
  - Picture of the hysterectomy specimen
  - Picture of the LSG
  - Picture of the SLN

- **In the event of cancer recurrence**
  - Pathology and MRI will be centrally reviewed

- **Funding**

  - **All participating cooperative groups will be required to secure their own funding for running this trial.**

  - **CCTG will act as the "lead group" but will not be able to provide funding to other groups for trial conduct.**

  - **Note: there is no specimen banking component of this trial and most data is captured electronically.**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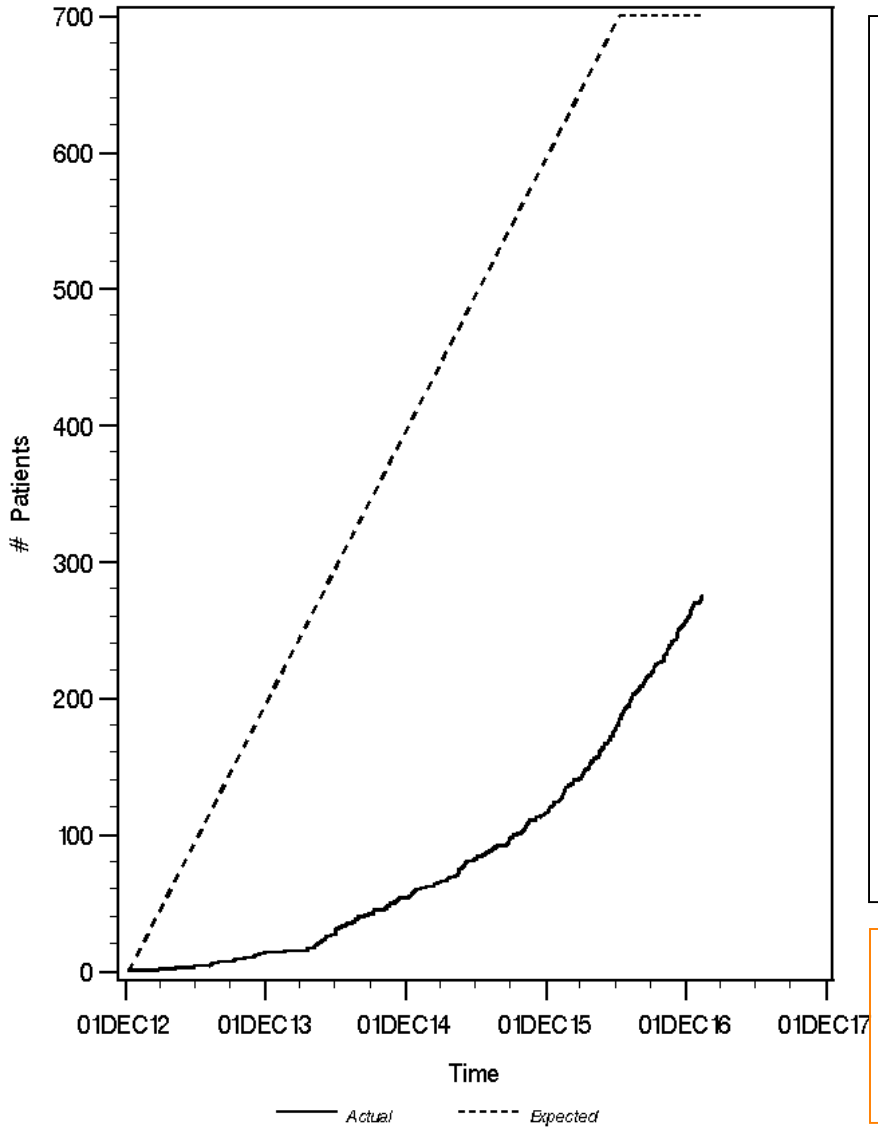
Results

Current Status

Country	# Sites Activated
Canada	16
France	33
South Korea	1
The Netherlands	7
Belgium	10
Austria	7
Ireland	1
United Kingdom	20
China	1
Russia	1
Total	**97**

Country	# Patients Accrued
Canada	115
France	43
South Korea	8
The Netherlands	36
Belgium	20
Austria	12
Ireland	10
United Kingdom	29
China	2
Russia	0
Total	**275 (40%)**

Accrual Graph



CX5 Accrual by Month as of 2017-JAN-16

Year	Month	Randomizations
2017	JAN	5
2016	DEC	14
2016	NOV	13
2016	OCT	16
2016	SEP	10
2016	AUG	11
2016	JUL	13
2016	JUN	16
2016	MAY	13
2016	APR	10
2016	MAR	13

Average accrual over the past 12 months = 13 patients / month

Patient's Characteristics

	Radical Hyst N=120	Simple Hyst N=124	Total N=244
Age (median)	42	43	43
Intended SLN mapping			
yes	47 (39%)	45 (36%)	92 (38%)
no	73 (61%)	79 (64%)	152 (62%)
FIGO Stage			
IA2	11 (9%)	10 (8%)	21 (9%)
IB1	109 (91%)	114 (92%)	223 (91%)
Histology			
Squamous	74 (62%)	75 (60%)	149 (61%)
Adenocarcinoma	46 (38%)	49 (40%)	95 (39%)

Patients who received adjuvant treatment

	Radical Hyst N=120	Simple Hyst N=124	Total N=244
Adjuvant Treatment	12 (10%)	10 (8.1%)	22 (9.0%)

Reason for Adjuvant Therapy	Radical Hyst N=120	Simple Hyst N=124	Total N=244
Non-SLN mets	2 (1.7%)	1 (0.8%)	3 (1.2%)
SLN mets	4 (3.3%)	1 (0.8%)	5 (2.0%)
Extrauterine disease	5 (4.2%)	3 (2.4%)	8 (3.3%)
Both non-SLN mets and extrauterine disease	1 (0.8%)	1 (0.8%)	2 (0.8%)
Both SLN mets and extrauterine disease	4 (3.3%)	0 (0.0%)	4 (1.6%)
Deep stromal invasion	1 (0.8%)	2 (1.6%)	3 (1.2%)
Positive margins	2 (1.7%)	2 (1.6%)	4 (1.6%)
Lymphatic invasion	3 (2.5%)	2 (1.6%)	5 (2.0%)
Both deep stromal invasion and lymphatic invasion	0 (0.0%)	2 (1.6%)	2 (0.8%)

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We welcome your participation to SHAPE !!

PRACTICE CHANGING TRIAL

LEVEL I EVIDENCE

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- **Surgico-pathology manual is posted on the NCIC website**
  - Developed to help your pathologist know the data we wish to capture
- **Checklist for pathologists**
  - LEEP/cone and Hyst
- **Case Report Form (CRF)**
  - LEEP/cone and Hyst