

# Gynecologic Cancer InterGroup Cervix Cancer Research Network



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, February 2018, Bucarest

- **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** ?



Contents lists available at ScienceDirect

**Gynecologic Oncology**

journal homepage: [www.elsevier.com/locate/ygyno](http://www.elsevier.com/locate/ygyno)

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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: lymphovascular space involvement  
\*\*DOI: depth of invasion

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

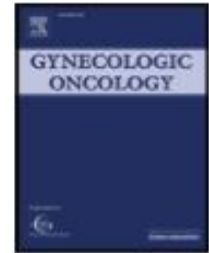
**Schmeler K et al. Gynecol Oncol 120:321, 2011**  
**Cervix Cancer Education Symposium**



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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?** ☆

Pedro T. Ramirez <sup>a,\*</sup>, Rene Pareja <sup>b</sup>, Gabriel J. Rendón <sup>b</sup>, Carlos Millan <sup>c</sup>,  
Michael Frumovitz <sup>a</sup>, Kathleen M. Schmeler <sup>a</sup>

<sup>a</sup> Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

<sup>b</sup> Department of Gynecologic Oncology, Instituto de Cancerología Las Américas, Medellín, Colombia

<sup>c</sup> Department of Gynecology, Hospital Quiron, Murcia, Spain

- **Problem:**
  - Conclusion based on **retrospective** data
- **Developed SHAPE**
  - Large **prospective** randomized international trial

- **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**



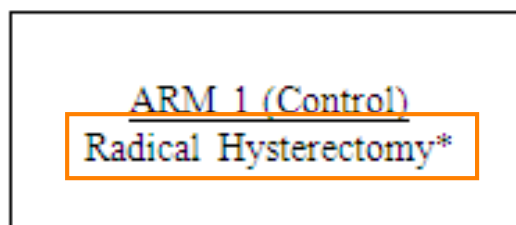
# Trial schema

Low-risk cervical cancer as defined by:

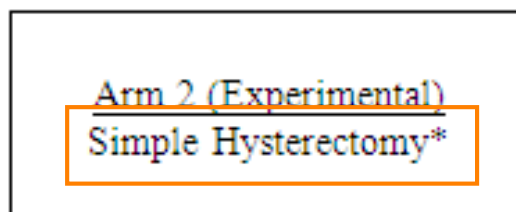
- Stage IA2-IB1 squamous cell, adenocarcinoma/adenosquamous carcinoma
- < 2cm, at least 3mm of intact cervical stroma and < 50% stromal invasion
- Grade 1-3

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→→ 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

## 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

- **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**



# **Surgical aspects**

- **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**

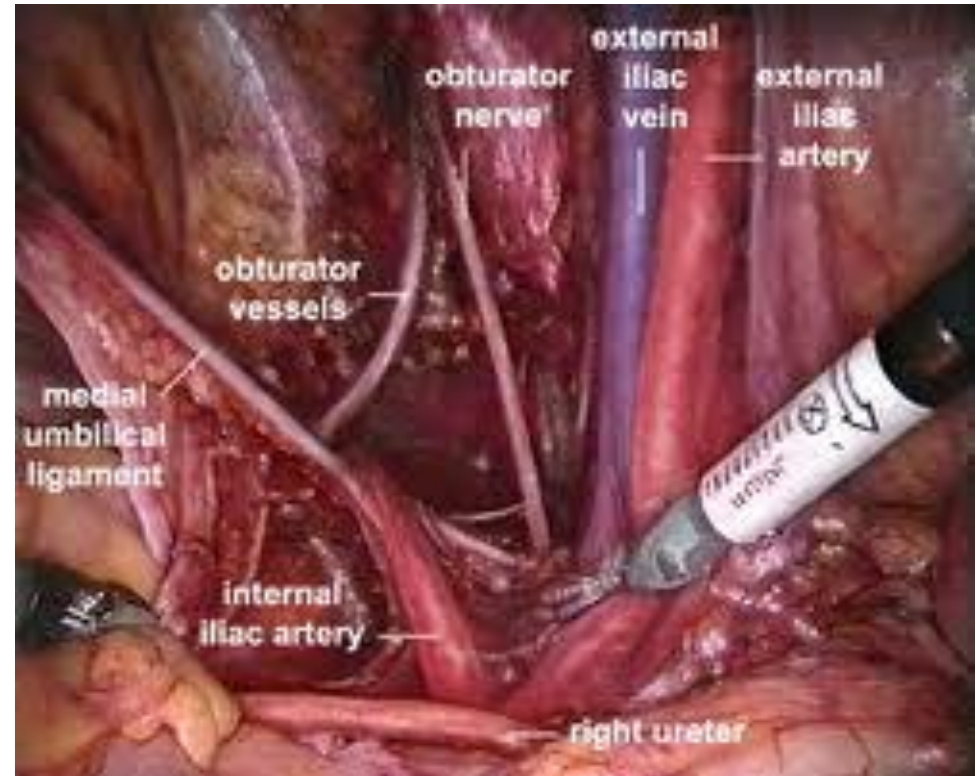
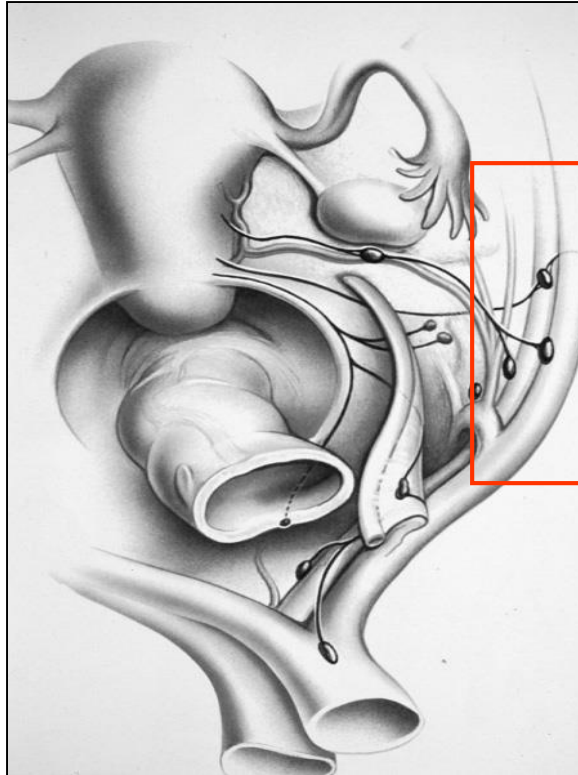


Provide **un-pinned** picture of  
the hysterectomy specimen

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



# Gynecologic Cancer InterGroup Cervix Cancer Research Network



- **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**



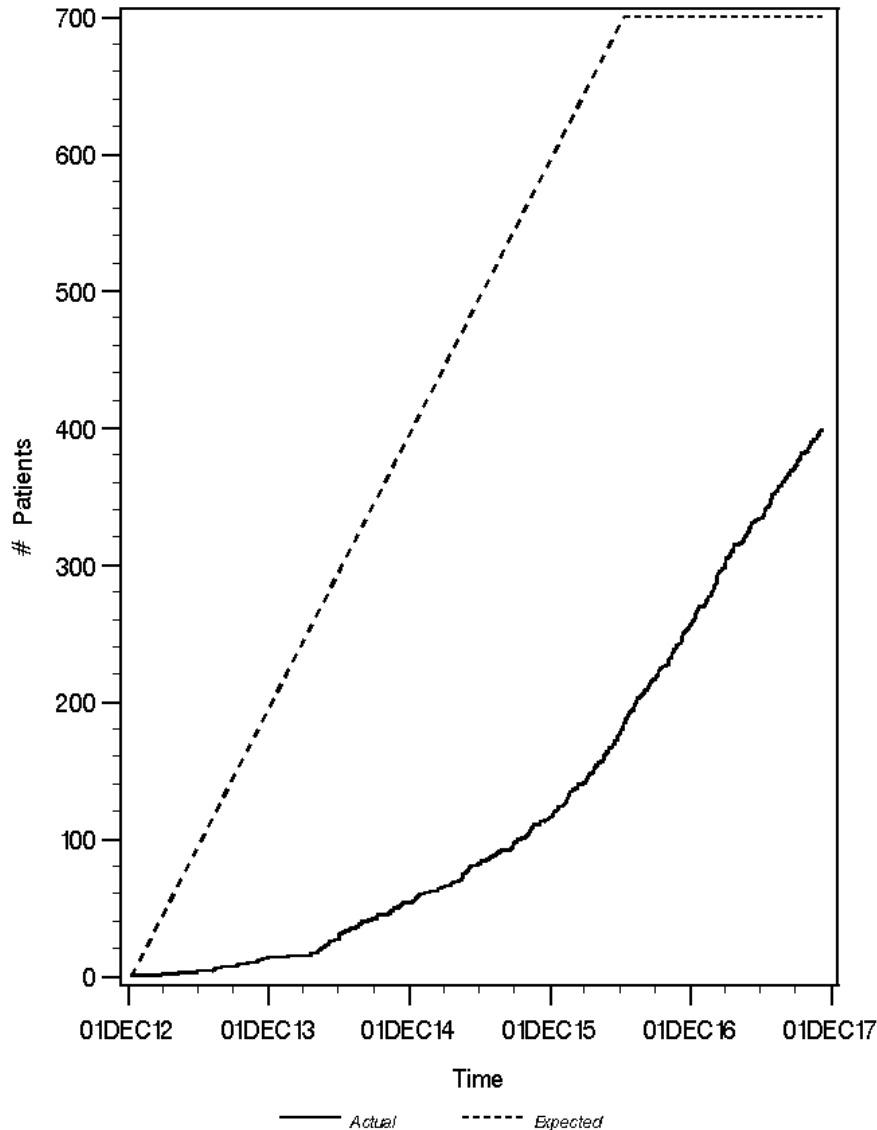
# Results

# Current Status

Country	# Sites Activated
Canada	15
France	33
United Kingdom	23
Belgium	8
The Netherlands	7
Austria	7
South Korea	3
Ireland	1
China	1
Russia	1
Germany	1
<b>Total</b>	<b>100</b>

Country	# Patients Accrued
Canada	141
France	80
United Kingdom	59
The Netherlands	63
Belgium	29
Austria	21
Ireland	10
South Korea	11
China	2
Russia	2
Germany	3
<b>Total</b>	<b>421</b>

# Current Status



- We have reached **60%** of total accrual
- A single study centre in Norway will be activated in January 2018.
- We hope to be able to activate two CCRN sites in Brazil in Q1 of 2018.
- It is our current estimation that accrual will continue until **Q4 2019.**

# Patient Characteristics

	Radical Hyst (N=187)	Simple Hyst (N=193)	Total (N=380)
Age (median)	43	42	43
Intended SLN mapping			
yes	68 (36%)	69 (36%)	137 (36%)
no	119 (64%)	124 (64%)	243 (64%)
FIGO Stage			
IA2	16 (9%)	18 (9%)	34 (9%)
IB1 (low risk)	171 (91%)	175 (91%)	346 (91%)
Histology			
Squamous	115 (61%)	120 (62%)	235 (62%)
Adenocarcinoma	72 (39%)	73 (38%)	145 (38%)

**Required adjuvant therapy: 35 (9.2%)**  
 (Rad Hyst = 17; Simple Hyst = 18)

**SHAPE !!**

**PRACTICE CHANGING TRIAL**

**LEVEL I EVIDENCE**



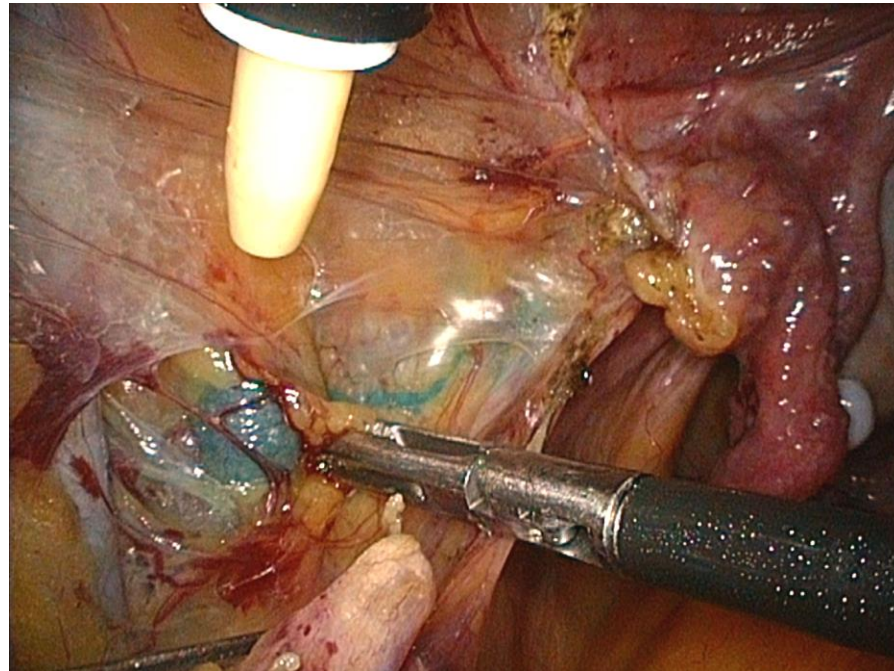




# **Credentialing**

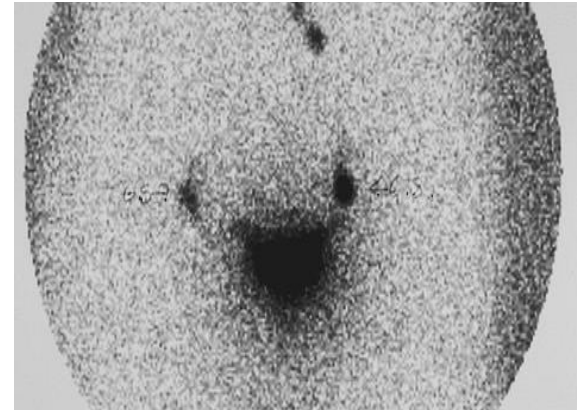
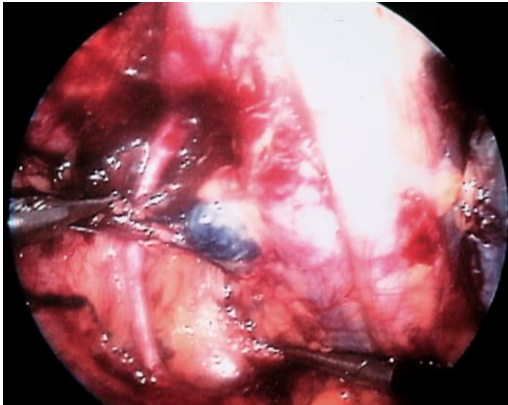
- **Sentinel Lymph Node Mapping**
  - Each participating cooperative group will need to **credential their centers** for their sentinel node mapping procedures.
  - The protocol will provide the recommended process, but it is up to each group to perform the credentialing prior to activating a center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

# Gynecologic Cancer InterGroup Cervix Cancer Research Network



**Cervix Cancer Education Symposium**

**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.

# Trial schema

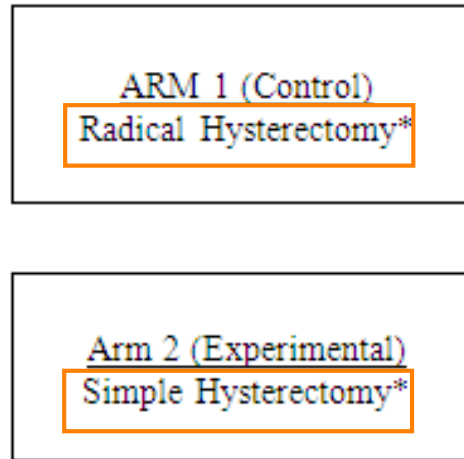
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→ → Pelvic relapse

\* 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)

20 weeks

4 weeks

Follow-up

Diagnostic Procedure

- ✓ MRI
- ✓ Chest Xray
- ✓ PRO
- ✓ Hx/PE
- ✓ Review pathology
- ✓ RANDOMIZATION

Surgery

Adjuvant chemoradiation (if necessary)