A 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 (GCIG) Trial led by the NCIC CTG

NCIC CTG Protocol Number: CX.5

SURGERY / PATHOLOGY MANUAL

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PREAMBLE

The CX.5/SHAPE study is a multi-centre, international, prospective, randomized phase III trial of radical hysterectomy and pelvic node dissection versus simple hysterectomy and pelvic node dissection in subjects with previously untreated, low-risk cervical cancer.

The main objective is to evaluate whether treatment with simple hysterectomy and pelvic node dissection is non-inferior to treatment with radical hysterectomy and pelvic node dissection in terms of pelvic relapse-free survival.

This study will recruit subjects with previously untreated, histologically confirmed, low-risk, early-stage, invasive, cervical cancer and subjects will be deemed eligible following a clinical examination of the cervix AND local pathology review of the loop electrosurgical excision procedure (LEEP), cone or biopsy specimen.

The CX.5/SHAPE study is unique in that it is asking an important surgical question that has the potential to change practice worldwide. It is imperative that we produce and collect high quality, meaningful data. As a result, the trial committee, composed of experts in the field, has created this manual to serve as the surgery/pathology quality assurance protocol for the CX.5 trial.

In addition to identifying a competent, experienced, gynecologic oncologist who will perform the protocol-assigned surgery as outlined in this manual, each participating centre/group will identify one gynecologic pathologist (called the local reference pathologist or LRP) who will be responsible for reviewing all specimens relating to the trial.

The first part of this manual contains detailed instructions regarding the **SURGERY** that comprises "protocol treatment" for the purposes of this trial. This includes the hysterectomy procedure (radical and simple), the sentinel node mapping technique and the pelvic lymph node dissections. This section will also describe the specific surgical quality assurance measures that have been built-in to the protocol.

The second part of this manual contains detailed **PATHOLOGY** instructions for the LRP in terms of how they are expected to review the pre-randomization and post-surgery specimens. In addition, instructions related to the processing of the samples are provided.

The third part of this manual describes the **CHECKLISTS** which were written to help facilitate the review by the LRP and data entry by the clinical research associates. These checklists are essentially summaries of the pathology-specific sections of the case report forms for this trial and may be given to the LRP to aid in their review of the trial specimens. These checklists are meant as "stand-alone" supporting documentation and are <u>not</u> case report forms and are <u>not</u> to be submitted to NCIC CTG.

PART ONE: SURGICAL PROCEDURES

Section 1.1 - HYSTERECTOMY

Extrafascial Hysterectomy (Simple hysterectomy) with upper vaginectomy:

This procedure may be performed abdominally, laparoscopically, robotically or vaginally. Extrafascial hysterectomy involves removal of the uterus with cervix without adjacent parametria. The uterine arteries are transected medial to the ureters at the level of the isthmus and the uterosacral ligaments are transected at the level of the cervix. A maximum of 0.5cm of upper vagina is removed *en bloc* with the specimen.

Type 2 radical hysterectomy (modified radical hysterectomy):

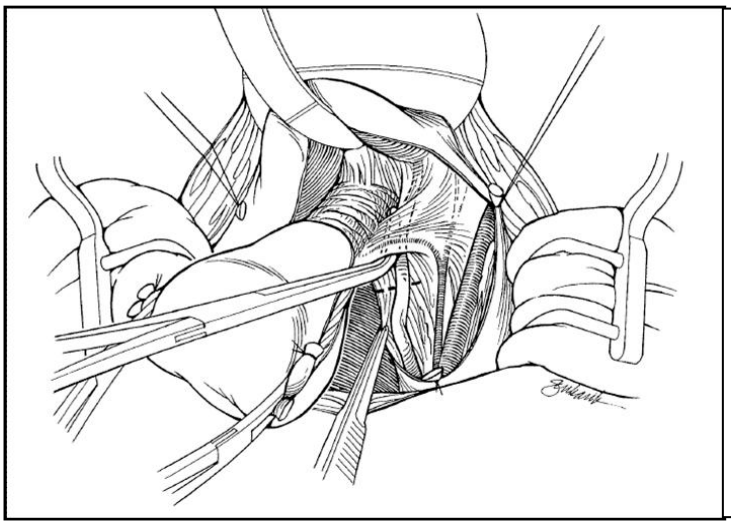
This procedure may be performed abdominally, laparoscopically, robotically or vaginally. The uterus, cervix, medial 1/3 of parametria, 2 cm of the uterosacral ligaments and upper 1-2 cm of the vagina is removed *en bloc*. The uterine artery is ligated laterally to the ureters and the ureters are unroofed to the ureterovesical junction.

Pelvic lymphadenectomy:

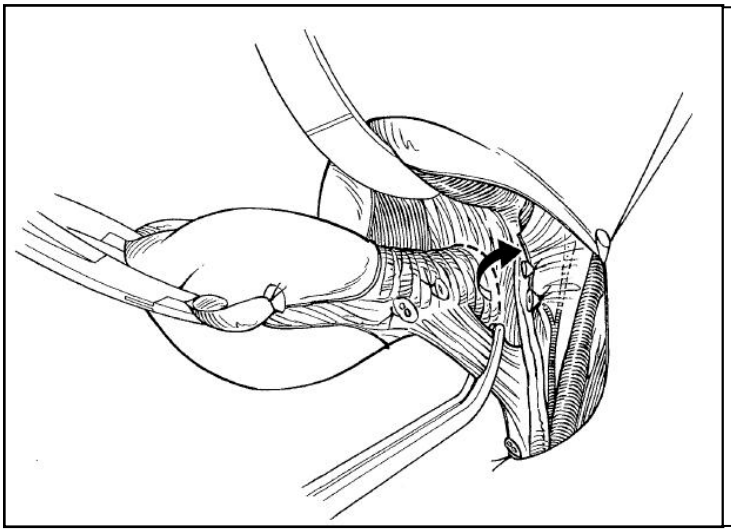
This procedure can be performed by open or laparoscopic technique. Bilateral skeletonization with removal of all lymph node tissue from lower half of common iliac vessels, external iliac vessels, internal iliac vessels and the obturator fossa. The anatomic boundaries include the lower half of the common iliac artery proximally, the deep circumflex iliac vein distally, the mid portion of the psoas muscle laterally, to the ureters medially and above the obturator nerve in the obturator fossa inferiorly.

Para-aortic lymphadenectomy:

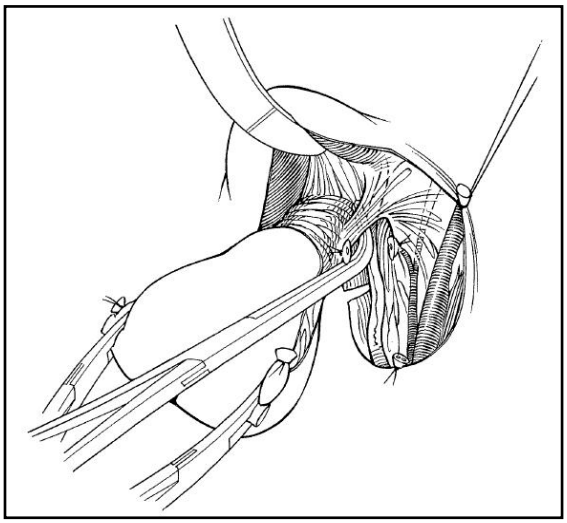
If indicated (positive pelvic nodes, or suspicious para-aortic nodes, as per protocol), this procedure can be performed by an open or laparoscopic technique. The right sided para-aortic lymphadenectomy will involve removal of all lymph node tissue superior and lateral to the inferior vena cava below the level of the inferior mesenteric artery proximally and to the upper half of the common iliac artery distally. The left sided para-aortic lymphadenectomy will involve removal of all lymph node tissue between the aorta and left ureters from the level of the inferior mesenteric artery proximally to the upper half the left common iliac artery.



Modified radical hysterectomy. The pelvic wall retroperitoneal space and the superficial parts of the pararectal and paravesical spaces are dissected to expose the ureter, uterine vessels and the superior portion of the cardinal ligament. After developing the bladder flab and bladder pillars, the ureter is traced down to the tunnel and the ureter plied from the periotoneum (broken line) to expose the tunnel. Then the tunnel is enlarged with a clamp and the uterine vessels ligated and divided directly over the ureter.



Modified radical hysterectomy. After unroofing the ureter, it is rolled laterally but not dissected from its bed. If necessary, the rectovaginal space is developed for a short distance, depending on the depth of the pouch of Douglas and the amount of vagina that is going to be removed. Then a clamp is placed across the uterosacral ligament and medial cardinal ligament together. One or more bites may need to be taken to divide the cardinal ligament and the posterior leaf of the vesicouterine ligament to the level at which the vagina will be transected.



Modified radical hysterectomy. Sometimes a second bite is necessary to free the ureter from the proximal portion of the bladder pillar, as shown in this illustration.

Section 1.2 - SENTINEL NODE TECHNIQUE

Injection of Technetium 99 (Tc99)

Prior to surgery, 0.5-1.0 ml of radiolabeled Tc99 microsulfur colloid is injected intradermally in the 4 quadrants of the cervix (total of 2.0 mL) or at 3 and 9 o'clock only.

Sulfur colloid is injected with a 25 gauge spinal needle, 3.5 inches long

The half-life of the radionuclide is about 6 hours. Injection is ideally performed 1-6 hours prior to surgery or the day prior to surgery if the injection is done late in the day and the surgery performed early the next day

Other radionuclides can be substituted if the Tc99 microsulfur colloid is not available

Preoperative Lymphoscintigraphy

A lymphoscintigram is performed 20-30 minutes after the injection.

Injection of Blue Dye

At the time of surgery, after induction of general anesthesia, 0.5-1.0 ml of dye is injected intradermally in the 4 quadrants of the cervix (total of 2.0 – 4.0mL) or at 3 and 9 o'clock only.

Dye is injected with a long 25 gauge spinal needle, 3.5 inches long.

An examination under anesthesia is performed after the injection. The cervix can be gently massaged.

Methylene blue, Patent blue, or Isosulfan blue can be used.

Intraoperative SN Identification with Laparoscopic/Hand Held Gamma Counter and Blue Dye

Following the injection of blue dye, the subject is prepped and draped.

The laparoscopy or laparotomy procedure is started.

Blue channels should be seen in the parametrium, exiting laterally at the level of the isthmus alongside the uterine vessels, and followed until a blue node is identified.

A laparoscopic or hand held gamma counter is covered with a sterile sleeve and is used to assist in the localization of the SN. Probe counts for the SN should be at least 2 times higher than background counts and is reported as counts per second (CPS).

Following removal, the SN is moved off the surgical field away from the background counts, and the gamma counter is used to confirm that the SN removed is "hot." Extracorporeal counts should be concordant with the counts obtained *in vivo*.

The surgical site is then re-examined with the gamma counter to see if there are any remaining "hot" nodes.

The half-life of the radionuclide is much longer than the blue dye; therefore the radiotracer is much more likely to be transported to second echelon lymph nodes than blue dye is. For this reason there may be more "hot" nodes than blue nodes.

The primary echelon SN is the one with the highest radioactive count. Secondary echelon SN can also be removed and labeled separately.

The "hottest" node should be submitted as the SN.

A complete bilateral pelvic lymph node dissection is then performed.

In up to 10-15% of cases, the SN may be located in unusual sites such as low para-aortic chain or presacral area. These sites should be carefully evaluated with the probe, particularly if no pelvic uptake is identified.

At least one SN should be identified on the right and on the left side (basin).

Labeling the Specimens

If a lymph node is blue but not "hot" it should be labeled "blue sentinel node."

If a lymph node is "hot" but not blue it should be labeled "hot sentinel node."

If a lymph node is BOTH blue and "hot" label as "blue/hot sentinel node."

Localization of the SN

Localization of the SN should be carefully recorded

- Bifurcation: medial aspect of the external iliac artery and vein near the bifurcation
- Obturator: under the external iliac vein and above the obturator nerve
- External iliac: between external iliac artery and psoas muscle
- Presacral: at the level of the sacral promontory
- Internal iliac (hypogastric): medial to the common iliac and lateral to the ureter
- Common iliac: lateral aspect of the common iliac artery

Section 1.3 - DRUG INFORMATION – LYMPHAZURIN AND METHYLENE BLUE

Isosulfan Blue (Lymphazurin)

Formulation: Sterile aqueous solution in 5 ml vials.

Preparation: None.

Storage: Room temperature, avoid excess heat.

Adverse Effects:

- All adverse effects are allergic in nature and occur in < 1% of subjects.
- These include localized swelling and pruritus of the hands, feet, abdomen and neck.
- Severe reactions including edema of the face and glottis, respiratory distress and shock have been occasionally reported with other similar compounds.
- In rare instances, isosulfan blue can cause a transient drop in oxygen saturation as measured by pulse oximetry.
- Isosulfan blue will turn the urine blue-green for up to 24 hours following injection.

Contraindications: Known hypersensitivity to phenylethane compounds.

Methylene Blue

Formulation: Sterile solution of 1% methylene blue in water for injection in 1 ml and 10 ml vials.

Preparation: None.

Storage: Room Temperature (15-25 ^{o}C).

Dose: Up to 4 ml subcutaneous. Not for IV use for this protocol.

Metabolism: Methylene blue is reduced in tissues to leucomethylene blue.

Adverse Effects:

- Subcutaneous necrosis has been reported at injection sites. In this study the injection site is resected with the primary tumour. This complication has not been described in lymphatic mapping studies.
- Allergic reactions such as rash, hives, or hypersensitivity reactions have been described. They appear to occur in approximately 1% of subjects.

Contraindications: No contraindications for subcutaneous use other than a history of allergic reaction to this compound.

Drug-lab interactions: Pulse Oximetry: inaccurate and artificially low.

Section 1.4 - SURGICAL QUALITY ASSURANCE

1.4.1 HYSTERECTOMY QUALITY ASSURANCE

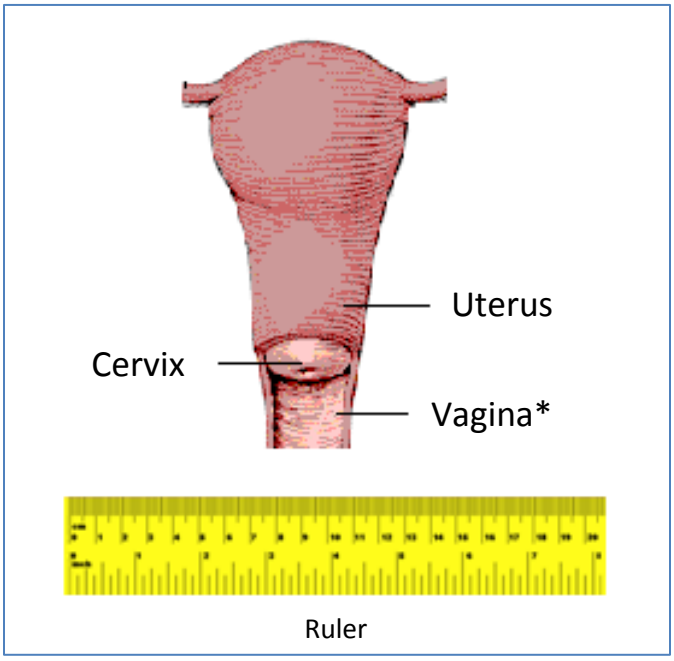
The hysterectomy quality assurance exercise described below must be performed for each hysterectomy that is done on the CX.5 protocol. This is regardless of whether a radical or simple hysterectomy was performed and regardless of whether the subject received their protocol-assigned surgery.

Prior to fixing the excised hysterectomy specimen, it should be placed "unpinned" on a flat surface with a ruler underneath, as shown below. The parametrium (if present) should be "laid out" but remain "upstretched". A de- identified, digital photograph of the specimen must be taken and will be submitted as part of the supporting documentation required for the case report form titled "Surgery Report". The photograph should be saved as a ".jpeg" file and the file should be named as follows: NCIC CTG Subject ID _ Subject initials _ HysterectomyImage _ date of surgery. For example: CAXX0001_AAA_HysterectomyImage_2012JUN01.jpeg.

In addition, the de-identified operative report must be scanned and saved as a ".pdf" file. This file should be named as follows: NCIC CTG Subject ID_Subject Initials_Operative Report_Date of surgery. For example: CAXX0001_AAA_OperativeReport_2012JUN01.pdf

The photograph and operative report, will be "uploaded" electronically to the EDC system (see Section 1.3.3). The CX.5 Study Chair/designate will access the EDC system to review the images and operative report as part of the surgical quality assurance process.

Example of "unpinned" simple hysterectomy specimen photograph
(Parametria which would be present in the radical hysterectomy specimen)



**Note: the anterior vaginal wall is to be rolled upwards in order to uncover the cervix so one can see the length of vagina removed.*

1.4.2 SENTINEL LYMPH NODE QUALITY ASSURANCE

It is understood that subjects will undergo surgery performed by a trained gynecologic oncologist. Prior to local activation, the site must declare:

1. Whether or not they will be employing sentinel node mapping for some or all of their CX.5 subjects (to be determined prior to randomization).
2. Whether each gynecologic oncology surgeon listed on the Participants List has treated at least 10 cervical and/or endometrial cancer subjects using the SN mapping technique per the standards outlined in the protocol and this manual.

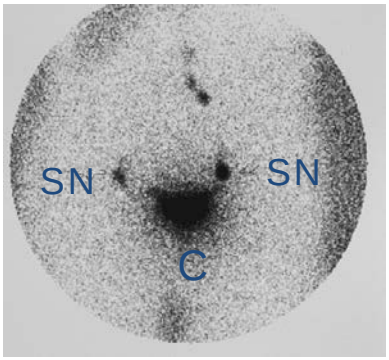
This attestation is included in the Study Acknowledgement & Disclosure Page found at the front of the protocol.

Following the surgery, the first 5 cases for each qualified surgeon performing SN mapping as part of the CX.5 trial must undergo quality assurance. This involves the centre submitting de-identified files that contain the lymphoscintigram and photographs of the detection of blue sentinel nodes bilaterally; see below for examples.

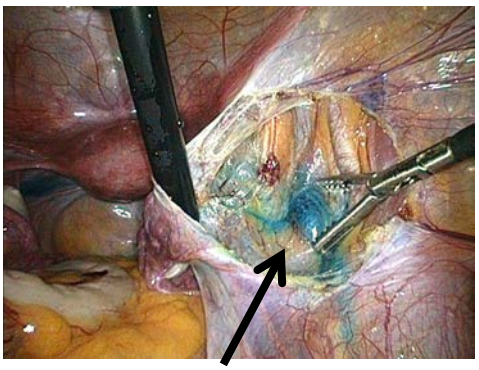
The lymphoscintigram file should be named as follows: NCIC CTG Subject ID_Subject Initials_Lymphoscintigram_Date of surgery.
For example: CAXX0001_AAA_Lymphoscintogram_2012JUN01.

The photographs should be saved as "jpeg" files and the files should be named as follows: NCIC CTG Subject ID _ Subject initials _ SentinelNodeImage(1,2,3 etc) _ date of surgery.
For example: CAXX0001_AAA_SentinelNodeImage1_2012JUN01.jpeg,
then CAXX0001_AAA_SentinelNodeImage2_2012JUN01, etc.

The lymphoscintigram and photographs will be "uploaded" electronically to the EDC system (see Section 1.3.3). The CX.5 Study Chair/designate will access the EDC system to review the images and operative report as part of the surgical quality assurance process.



SN = sentinel node
C = cervix



External Iliac Node

1.4.3 PROCESS FOR "UPLOADING" QA IMAGES AND DOCUMENTATION TO EDC

1. From the patient-specific menu in EDC, click on "CX.5 Surgery Quality Assurance – Hysterectomy and Sentinel Node Upload Tool". This can be found in the "Reports" section.
2. Click on the  icon to upload the required documents (*Note*: *The uploaded files must not contain patient identifiers and must be named according to the instructions in sections 1.3.1 and 1.3.2)*
    a. Hysterectomy Operative Report and Hysterectomy Image **required for all patients.**
    b. Sentinel Node Image and Lymphoscintigram Image **required for each surgeon's first 5 patients who undergo Sentinel Node Mapping.**
3. Click on the  icon to review the upload or to make changes.
4. Click on the patient ID (on the left side) to see a summary of all of the items that have been uploaded for a given patient.

PART TWO: SPECIMEN PROCESSING & MACROSCOPY

Section 2.1 - LEEP/CONE/BIOPSY

An optimal specimen is not fragmented, received unfixed and oriented by surgeon, preferably with a stitch at 12 o'clock (this is not mandatory). This is seen more often with a cone specimen but not usually with a LEEP specimen.

- Measure specimen and any obvious lesion [specimen dimensions include length of ectocervix surface i.e. diameter (or circumference if specimen opened), length of endocervical canal (cranio-caudal distance) and thickness (deep stromal measurement i.e. maximum perpendicular distance between stromal resection edge and surface epithelium); tumour dimensions x3].
- Ink Margins (after drying and before opening specimen):
  - Not required for LEEP specimen since thermal artifact is present at the resection margins
  - Required for cone biopsy (preferably one colour for endocervical margin and another colour on peripheral and deep margins)
- Open along the cervical canal at suture mark (usually 12 o'clock position) or at any site if specimen is not oriented
- Pin the opened specimen on corkboard with the mucosa facing up
- Fix in 10% buffered formalin for at least 3 hours
- Radial sectioning of the entire specimen at 1 to 3 mm interval from center is the preferred method. Another option is to cut in parallel slices at 1 to 3 mm interval from one side to the other (i.e. left to right or vice versa).
- For optimal evaluation, each section is placed in separate cassettes and numbered consecutively from 1 to 12 o'clock (or randomly if no orientation).

Proceed with routine processing with serial sectioning at 4 micron and staining with H&E.

Section 2.2 - HYSTERECTOMY SPECIMEN PROCESSING

- Orient the specimen.
- Ink all resection margins, including bilateral parametrium, anterior and posterior soft tissue.
- Open uterus on one lateral aspect.
- Examine cervix. If gross lesion, specify tumour site, dimension (3 dimensions) and evaluate extension to lower uterine segment, parametrium, anterior and posterior soft tissue.
- Parametrium (PM):
  - measurements i.e. longest dimension in cm
  - identify palpable lymph nodes and document if gross evidence of tumour
  - entire parametrium should be submitted
  - parametrium length is to be measured in an unstretched specimen

If no tumour grossly, separate PM from specimen leaving a 1 to 2 mm rim of PM attached to cervix. Serially sectioned PM at 3-4 mm thick sections and submit entirely for routine histological examination.

If tumour present grossly, removed surgical margins and submit for histological examination. Submit full thickness section of tumour in contiguity with the PM . Submit entire remaining PM tissue cut at 3-4 mm for routine histological examination

- Note: If lymph node present, submit in separate cassettes

- Amputate cervix from the corpus, pin on corkboard and fix in 10% buffered formalin. When fixed, process similarly to cone biopsy i.e. serially blocked; 3-4 mm sections along the long axis of cervical canal in clockwise fashion including the maximum amount of endocervix that fits in the cassette. Each section should be full thickness to include exocervix and endocervix segments, squamocolumnar junction and corresponding part of vaginal cuff and outer adventitia and/or rim of PM. [Sections need to demonstrate both maximum length of invasive tumour and relationship of tumour to resection margins]. If the wall is too thick or tumour too large for one cassette, divide the section in two. The rest of the cervix is cut longitudinally through the endocervix and region of internal os and lower uterine segment including full thickness of cervix, endometrium and surrounding soft tissue.
- Another option is to section the rest of the cervix transversally from the internal os caudally to a level of approximately 1 cm from ectocervix if no gross tumour; in this instance, the inferior part of the cervix and vaginal cuff are then sectioned radially.
- Process all sections for routine histological examination and H&E staining.
- Vaginal Cuff: Measure distance from exocervix to line of resection. As indicated above, if possible, should be included with sections of cervix. If not, section circumferential or perpendicular to the line of resection and submit entirely.
- Uterine body and adnexa are processed routinely.

Section 2.3 - SENTINEL LYMPH NODE PROCESSING

Gross examination:

- Trim perinodal fat
- Indicate size and number of nodes
- Each lymph node should be serially sectioned perpendicular to its long axis at 2-3 mm intervals. The node should be cut from the hilum to periphery whenever possible. If node is too small then submit uncut.
- Fix tissue in 10% buffered formalin and submit for permanent section and ultrastaging protocol

Ultrastaging protocol (3 levels each with 1 H&E and 2 unstained)

- 3 consecutive sections (5 micron thick), each obtained at 3 levels (40 to 80 micron intervals)
- The first section of each level is stained with H&E.
- The second and third sections from each level are to be stained with keratin cocktail (ex.AE1/AE3) to confirm the negative histology if H&E stained levels are negative for metastasis or show atypical cells.

  In order to save time, another option would be to do "reflex" keratin stain on one of the 2 consecutive slides obtained from the first level.

** Fibroadipose tissue accompanying SLN entirely submitted for routine processing and H&E staining (optional)

** Number of SLN, size of metastasis (<0.2mm=ITC's; 0.2 to 2mm; > 2mm) and presence or absence of extracapsular invasion should be indicated on the pathology checklist.

Section 2.4 - NON SENTINEL LYMPH NODES PROCESSING

- Fix in 10% buffered formalin
- Each node serially sectioned perpendicular to their long axis at 3 mm intervals and entirely submitted for permanent section (If LN < 4mm, leave uncut)
- One 5 micron thick H&E obtain from each block
- All palpable lymph nodes to be submitted
- Residual fat (possible non-palpable LN) submitted entirely (optional; to the discretion of the pathologist at different institution)
- Pathology Form/Report should include: number of lymph nodes, number of metastases and size of largest metastasis (<0.2mm; 0.2-2mm; >2mm), Extracapsular invasion (Yes/No)
- Separately identified lymph nodes within fibroadipose tissue should be counted and fragments thought to represent trim fragments should not be counted.

Section 2.5 - DEFINITIONS: LVSI, TUMOUR DIMENSION, HISTOLOGY AND GRADE

Lympho-Vascular Space Invasion

Defined as unequivocal presence of viable malignant cells in endothelial lined spaces. To be determine on H&E histology (i.e. no immunohistochemistry)

- best evaluated at the periphery of the tumour where tissue retraction artifacts are less frequent.
- presence of endothelial cells lining may not be conspicuous.
- in LEEP specimen attention to displaced neoplastic epithelium into vascular space during injection of anesthetic.

Tumour Dimensions

Accurate measurements of depth of invasion and lateral extent are best made with an ocular micrometer.

- Depth of invasion (DI) is measured from the epithelial-stromal junction at the site of origin to the deepest point of invasion.
- If the carcinoma originates from the surface epithelium, the measurement is from the basement membrane of the surface epithelium overlying the invasive focus.
- When invasive carcinoma arises from endocervical gland, the depth of invasion is measured from the basement membrane of the gland to the point of maximal invasion.

- If the invasive carcinoma is not in continuity with the surface or the gland from which it originated and the site of origin is not clear, the DI should be measured vertically from the basement membrane of the surface epithelium to the point of deepest invasion (in this setting, the DI is equivalent to the thickness of the tumour).
- For adenocarcinoma, in most cases, the depth is measured from the surface rather than the point of origin, which is hard to establish in some cases. Thus tumour thickness rather than "DI" is measured. The depth of invasion is measured from the basal lamina of the overlying surface squamous epithelium if it is present. Otherwise, the measurement is from the surface to the deepest point of invasion.

Horizontal length is the greatest distance between the lateral edge of the invasive carcinoma and the other edge. Although FIGO includes horizontal extent in staging, it does not delineate how to measure it. In unifocal cancer, the maximum horizontal dimension is usually straightforward and is measured in the section in which the width is the greatest. In the event that this measurement is <7mm but the tumour is present in 3 or more consecutive blocks, the lateral extent should be done by calculating the number of blocks involved considering that each block measures 2-3 mm in thickness. If the tumor is present on 3 or more sequential slices, then the lateral extension is probably in the range of 6-9 mm, since each slice usually measures 2-3 mm deep. These subjects would be included as IB1.

In the cases of multifocal carcinomas (i.e. foci of cancer are present on one slide and are separated by normal tissue and/or foci of cancer are separated by section(s) without invasive carcinoma present) it is unclear how the horizontal extent should be measured. An attempt to provide horizontal extent is only needed in cases in which the tumor depth is 5 mm or less. In these cases, one should refer to the article by Reich O & Pickel H: Multifocal stromal invasion in microinvasive squamous cell carcinoma of the cervix: how to measure and stage. Int J Gynecol Pathol 21:416-417, 2002.

Histological Type and Grade

Squamous cell carcinoma:

There is no widely accepted grading system; therefore, grade can be declared "not assessable" or reported according to any of the classification systems listed below.

Modified Broders classification system:

Grade 1: Well-differentiated (*mature squamous cells with abundant keratin, pearl formation, and sometimes intercellular bridges*).
Grade 2: Moderately differentiated (*less abundant cytoplasm, cell borders less distinct, nuclei with greater pleopmorphism and high mitotic activity*).
Grade 3: Poorly differentiated (*masses and nests of oval cells with scant cytoplasm and hyperchromatic and spindle-shaped nuclei with high mitotic activity*).

Reagan classification

- Large cell keratinizing (*large cells with abundant eosinophilic cytoplasm and many show individual keratinization; keratin pearls are present*).
- Large cell non keratinizing (*keratin pearls are absent; uniform cells with indistinct cells borders, round to oval nuclei with coarse chromatin and numerous mitotic figures; individual cell keratinization often present*).
- Small cell nonkeratinizing (*small basaloid cells, hyperchromatic nuclei with abundant mitosis; **Not to be confused with small cell carcinoma*).

Adenocarcinoma:

Grading should be done either by nuclear or architectural grade.

Architectural grade (based on the degree of gland formation):

Grade 1: well-differentiated *(10% or less of solid growth)*
Grade 2: moderately differentiated *(10 to 50% of solid growth)*
Grade 3: poorly differentiated *(>50% of solid tumour nests)*

Nuclear G***rade:***

Grade 1: cells with oval nuclei and evenly dispersed chromatin
Grade 2: features between grades 1 & 3
Grade 3: cells with markedly enlarged nuclei, irregular coarse chromatin and prominent nucleoli

Section 2.6 - REFERENCES:

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Section 2.7 - 2009 FIGO NOMENCLATURE

Table 1: Carcinoma of the cervix uteri: FIGO nomenclature (2009)

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≤ 7 mm.
IA_1	Measured stromal invasion of ≤ 3.0 mm in depth and horizontal extension of ≤ 7.0 mm.
IA_2	Measured stromal invasion of > 3.0 mm and not > 5.0 mm with a lateral extension of not > 7.0 mm.
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA. *
IB_1	Clinically visible lesion ≤ 4.0 cm in greatest dimension.
IB_2	Clinically visible lesion > 4.0 cm in greatest dimension.
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.
IIA	Without parametrial invasion but extension to the upper two thirds of the vagina.
IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension.
IIA2	Clinically visible lesion > 4.0 cm in greatest dimension.
IIB	With obvious palpable parametrial invasion.
Stage III	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney.**
IIIA	Tumour involves lower third of the vagina, with no extension to the pelvic wall.
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV.
IVA	Spread of the growth to adjacent organs.
IVB	Spread to distant organs.

* *All macroscopically visible lesions – even with superficial invasion – are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not > 7.00 mm. Depth of invasion should not be > 5.00 mm taken from the base of the epithelium of the original tissue – superficial or glandular. The depth of invasion should be always reported in mm, even in those cases with "early (minimal) stromal invasion" (~ 1mm). The involvement of vascular / lymphatic spaces should not change the stage allotment.*

** *On rectal examination, there is no cancer-free space between the tumour and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to other causes.*

PART THREE: DATA COLLECTION AND MANAGEMENT TOOLS

The CX.5 trial asks an important surgical question, and as a result some of the most critical study data will be collected on the "Baseline Report" and the "Surgery Form".

To aid data managers and clinical research associates in the collection of these important data, two checklists have been created: the LEEP/Cone/Biopsy Checklist and the Hysterectomy Checklist. These checklists can be downloaded from the CX.5 trial website.

These checklists are tools to be used if desired. They are meant as "stand-alone" supporting documentation and to aid in completion of the electronic case report forms "Baseline Report" and "Surgery Form".

The checklists are designed to be completed by the CX.5 Local Reference Pathologist at the time that the initial diagnostic and the hysterectomy specimens are reviewed.

The checklists are considered source documents / tools and are NOT CASE REPORT FORMS.

If completed, these checklists should remain on site in the subject chart and SHOULD **NOT** be mailed to NCIC CTG.