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A Phase III Randomized Study of Pretherapeutic Paraaortic Lymphadenectomy in Women with Locally Advanced Cervical Cancer Dispositioned to Definitive Chemoradiotherapy

1.0 OBJECTIVES

1.1 Primary Objective

1.1.1 To determine if patients with locally advanced cervical cancer have longer overall survivals with pretherapeutic paraaortic surgical staging followed by tailored chemoradiation when compared to patients who undergo standard radiologic staging followed by whole pelvic chemoradiation therapy.

1.2 Secondary Objectives

1.2.1 To determine if patients with locally advanced cervical cancer have longer disease-free survival with pretherapeutic paraaortic surgical staging when compared to radiologic staging.

1.2.2 To determine short- and long-term morbidity of pretherapeutic surgical staging in patients with locally advanced cervical cancer

1.2.3 To determine sensitivity of pretreatment staging radiologic examinations in detecting metastatic disease.

1.2.4 To determine site of paraaortic metastatic disease along aorta as related to the inferior mesenteric artery (i.e. above or below) in patients with locally advanced cervical cancer

1.2.5 To evaluate surgical complication rates of the laparoscopic extraperitoneal paraaortic lymphadenectomy in a large cohort of patients.

2.0 BACKGROUND

According to the International Federation of Gynecology and Obstetrics (FIGO), cancer of the uterine cervix remains a clinically staged disease. Although tumor stage can only be assigned using clinical examination, cystoscopy, proctoscopy, chest X-ray, and intravenous pyleogram, many gynecologic oncologists use more advanced technology for more thorough assessment and treatment planning.

It is not uncommon for patients to undergo computed tomography (CT) scan, magnetic resonance imaging (MRI), and/or positron emission tomography (PET) in the work-up of their disease. Clinicians may glean important information from these tests. First, the presence of positive paraaortic lymph nodes remains the most important prognostic factor for survival in patients with cervical cancer [1,2]. In addition, presence or absence of metastatic disease to the lymph nodes guides treatment planning. This includes the choice of primary surgery or radiotherapy as well as definition of the radiation fields used.

Unfortunately, none of the imaging modalities currently available has proven to be very sensitive in detecting metastatic paraaortic lymph nodes in patients with locally advanced cervical cancer (stages IB2-IVA). CT scan provides a sensitivity of only 67% [4]. While MRI may be beneficial at detecting parametrial, bladder, or rectal invasion from the primary lesions, it is poor at detecting lymph node metastasis. In a meta analysis of MRI and lymph node metastasis, Scheidler et al. [5] reported an overall sensitivity of MRI in detecting lymph node metastasis of 38%. Other authors have found a sensitivity of 0% for the MRI detection of positive paraaortic lymph nodes when compared to the surgical gold standard [6].

Currently, FDG-PET scanning is being utilized in attempts to better detect paraaortic lymph node spread. When combining four prospective studies that compared FDG-PET to gold standard surgical staging, Havrilesky et al. [7] found an overall sensitivity of 84% (95% CI 68-94%). Although this modality is an improvement over CT scan, it remains that 16% (and as high as 32%) of patients will be classified as node negative when in reality they have metastatic disease to their para-lymph nodes. The implications of undertreating these patients are disastrous, especially when one considers that the survival for patients with histologically positive paraaortic lymph nodes is as high as 50% if these metastases are detected and extended field radiation therpay is given [3,8].

The concept of surgical staging for patients with locally advanced cervical cancer has evolved over the last three decades. Surgical staging as a method of assessing lymph node status in patients with locally advanced cervical cancer may lead to a change in the radiation treatment plan in as many as 43% of patients [3]. Initially, patients were staged with traditional laparotomy and a transperitoneal approach. However, this led to a high complication rate from radiation effects on small bowel adhered to dissected areas in the pelvis. The description of the open extraperitoneal approach by Berman et al. [9] led to a sharp decrease in small bowel complications from radiation therapy [10]. Advances in endoscopic equipment and techniques have allowed for even less invasive approaches to lymph node dissection with laparoscopy either transperitoneally [6,11] or extraperitoenally [12-14]. Neither of these approaches appears to increase postoperative radiotherapy complications when surgeries are limited to lymph node dissection only. These procedures do not significantly delay definitive therapy as patients typically go on to receive their radiotherapy 7-10 days following laparoscopic staging.

We recently presented the results of a phase II study of pretherapeutic extraperitoneal paraaortic lymphadenectomy. This study, performed at MD Anderson Cancer Center (MD Anderson), enrolled 65 women with locally advanced cervical cancer. All patients had stage IB2-IVA cervical cancer and underwent PET/CT scan followed by surgical staging via removal of the paraaortic nodes utilizing the laparoscopic extraperitoneal approach. This technique was safe and feasible and did not delay initiation of definitive chemoradiation therapy (median enrollment to treatment time: 10 days). This is not longer than what we would expect for typical time it would take for a patient with newly diagnosed cervical cancer to undergo radiation simulation and treatment planning. Importantly, in women with PET scans showing radiologically positive pelvic nodal metastasis and negative paraaortic metastasis, 22% were found to have pathologically positive metastases after surgical removal. Had treatment planning been based

solely on best available imaging (PET scan), a significant number of women would have received pelvic radiation only and been completely undertreated.

In addition to the prognostic and therapy-directing factors obtained from lymph node dissection, recent data points to a therapeutic benefit of pre-radiotherapy lymph node dissection. Marnitz et al. [11] reported their experience with laparoscopic transperitoneal surgical staging in 84 patients with clinically advanced cervical cancer. They found that patients with microscopically-positive paraaortic lymph nodes that were resected laparoscopically had the same survival as those patients with pathologically negative lymph nodes on surgical staging. LeBlanc et al. [13] also have published their data surgical staging via a laparoscopic extraperitoneal approach in 156 patients with locally advanced cervical cancer. They too found that patients with microscopically-positive and resected paraaortic lymph nodes who then received tailored extended field radiotherapy had the same survival as patients with negative lymph nodes who received pelvic irradiation.

A recent review of three phase III chemoradiation studies by the Gynecologic Oncology Group also showed a survival advantage for women who underwent surgical staging when compared to those who were treated on radiologic findings alone [15]. On multivariate analysis, the relative risk of death for women staged radiologically was 1.46 when compared to women who had surgical staging (p=0.43) For women with stage III/IV disease, surgical staging had an even bigger impact with surgically staged women having a 4 year overall survival of 54.3% compared to 40% for those who did not have surgical staging (RR 1.60, p=0.038). Whether the survival benefit of surgical staging women with locally advanced cervical cancer is a result of tumor debulking, tailored radiotherapy, or a combination of the two is unknown. Regardless, these important findings should be explored prospectively.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

- 3.1.1 Women with clinical stage IB2-IVA cervical squamous cell carcinoma, adenosquamous, or adenocarcinoma
- 3.1.2 Women with FDG-PET positive or indeterminate pelvic lymph nodes or indeterminate low common iliac nodes (See addendum) and negative paraaortic nodes
- 3.1.3 Women with planned treatment of primary definitive chemoradiation therapy
- 3.1.4 4) An approved Informed consent and authorization permitting release of personal health information must be signed by the patient or guardian.

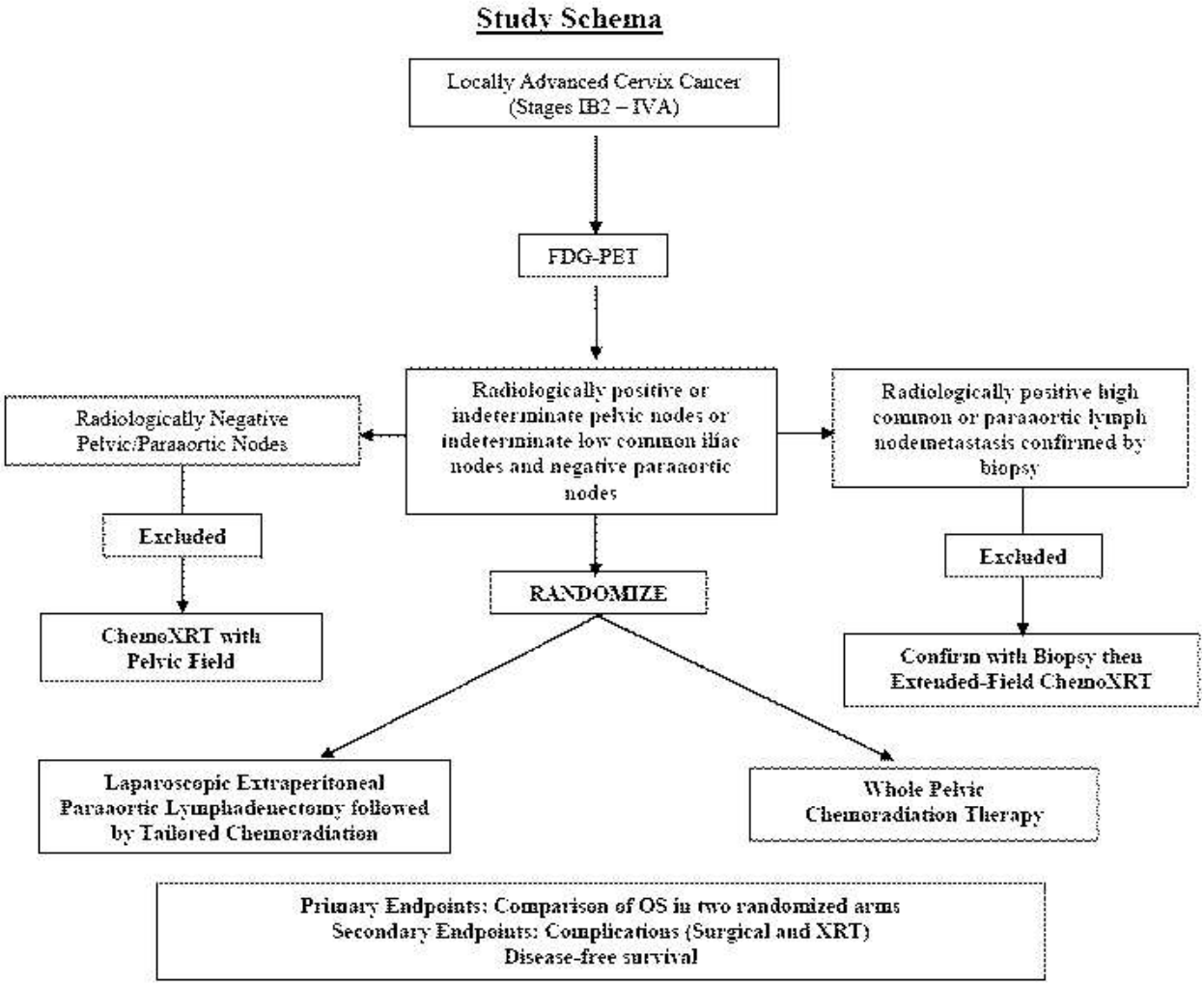
3.2 Exclusion Criteria

- 3.2.1 Women with stage IA or IB1 cancer
- 3.2.2 Women with prior radiotherapy to the pelvis or retroperitoneal surgery
- 3.2.3 Women with neuroendocrine histologies, or histologies other than squamous, adenosquamous or adenocarcinoma

3.2.4 Women with FDG PET positive high common or paraaortic lymph node metastasis confirmed by biopsy (please see addendum).
3.2.5 Women who have undergone simple or radical hysterectomy prior to radiotherapy
3.2.6 Women with planned treatment of radiotherapy only (without chemotherapy)
3.2.7 Women with planned treatment of palliative radiotherapy
3.2.8 Women with metastatic disease outside of pelvis.
3.2.9 Women who have completed treatment for other malignancies (except non-melanomatous skin cancer) < 5 years from their new diagnosis of cervical cancer
3.2.10 Women who are pregnant

4.0 THERAPEUTIC PROGRAM

This Phase III randomized study is designed to determine if patients with locally advanced cervical cancer have longer overall survivals with pretherapeutic paraaortic surgical staging when compared to radiologic staging.



All eligible patients in MD Anderson and Lyndon B. Johnson General Hospital (LBJ) will be required to sign an informed consent prior to randomization. Patients will be equally allocated between the 2 treatment groups.

Eligible patients will be randomized to either standard chemoradiation (standard-of-care arm) or pretherapeutic paraaortic lymphadenectomy followed by tailored chemoradiation (experimental arm). Pretherapeutic lymphadenectomy will be performed via the laparoscopic extraperitoneal approach using either traditional laparoscopy or robotically-assisted laparoscopy. Patient demographic and treatment information will be collected at time of enrollment and throughout initial definitive therapy (Appendix C).

Radiology Protocol and Definitions of Positive and Indeterminate Nodes

All scans will be performed on a dedicated Positron Emission Tomography/Computed Tomography (PET/CT) scanner that will allow fusion of PET and CT images. Standard imaging protocols for PET/CT will be followed with non-contrast CT used for attenuation correction.

The standard definition of abnormal lymph nodes in the abdomen and pelvis by cross sectional imaging is size greater than 10 mm. Therefore nodes greater than 10 mm in the abdomen or pelvis will be considered abnormal by CT.

PET/CT images will be evaluated qualitatively for focal areas of abnormally increased 18-fluorine fluorodeoxy glucose (FDG) uptake. A positive finding is defined as the presence of abnormal FDG uptake when accumulation of the tracer is moderately to markedly increased relative to the uptake in comparable normal structures or surrounding tissues, with the exclusion of physiologic bowel and urinary activity. A negative finding is defined as no detectable FDG uptake.

The FDG PET and PET/CT: EANM procedure guidelines for tumor PET imaging: version 1.0 (Appendix D) states that "it is impossible to give universal rules for [quantative] detection limits" for what should be considered a positive node of PET scan. It goes on to say "detection limits obviously depend on the degree of contrast between the tumor and its immediate surroundings. Sensitivity of FDG PET is much lower in diabetic patients. There is no single detection limit for FDG PET since it depends on many factors. The most significant of these are: histology (FDG avidity of the type of tumor), the volume of vital tumor cells, movement during acquisition (e.g. blurred signals in the case of pulmonary foci), and physiological uptake in the adjacent background." Therefore pelvic or paraaortic nodes that are focally more avid than background will be considered positive. Nodes with no detectable FDG uptake above background activity will be considered negative. Indeterminate nodes on CT which are non FDG avid should be followed with the follow up CT to determine stability. If further enlargement is noted, then biopsy may be considered if clinically indicated.

Pretherapeutic Paraaortic Lymphadenectomy:

Pretherapeutic paraaortic lymphadenectomy should be performed no later than 3 weeks after the PET/CT scan.

The staging surgery begins with a transumbilical diagnostic laparoscopy to assess the peritoneal cavity. If there is no evidence of intraperitoneal disease, an extraperitoneal paraaortic lymphadenectomy is performed through the left sided extraperitoneal approach. Lymph node bearing tissue from the aorta, aortocaval space, vena cava and bilateral common iliac vessels is completely removed from the left renal vein cranially to both common iliac artery bifurcations caudally, and to both psoas muscles laterally. This procedure may be completed via traditional laparoscopy or robotically assisted laparoscopy. If the surgeon encounters perforation of the peritoneum, an additional trocar may be added and a laparoscopic fan placed to attempt to elevate the peritoneum. If it is felt by the surgeon that the laparoscopic retroperitoneal approach is not feasible, a laparoscopic transperitoneal approach may be attempted to complete the procedure. If laparoscopic transperitoneal approach is not successful, the patient may undergo

an open retroperitoneal dissection, an open transperitoneal dissection, or discontinuation of the staging procedure at the surgeon's discretion.

Upon completion of the procedure, clips are placed on the inferior and superior borders of the dissection to guide radiation therapy treatment planning. All specimens are removed in endoscopic bags. If pathologically confirmed fixed or enlarged (> 2 cm) lymph nodes are encountered, attempts will be made to debulk them laparoscopically. Failing this, either clips will applied to demarcate the area for boost of radiotherapy or the procedure will be converted to an extraperitoneal laparotomy with open debulking. Similarly, although a pelvic node dissection is not part of the procedure as they are already in the radiation field, an open extraperitoneal debulking will be considered to debulk isolated enlarged pelvic nodes at the surgeon's discretion. To avoid the development of postoperative symptomatic retroperitoneal lymphocysts, we will create a transperitoneal opening of the left paracolic gutter to allow the abdominal reabsorption of the retroperitoneal lymph. This step is called "preventive marsupialization." Preventive marsupialization will not be done if a grossly positive node is encountered, resected and the rest of the paraaortic node dissection is abandoned.

In an effort to determine site of metastasis, nodal specimens removed from the inferior mesenteric artery to the renal vessels and labeled "supramesenteric lymph nodes" while nodal specimens removed from the inferior mesenteric artery to the bifurcation of the great vessels will be labeled "inframesenteric lymph nodes."

Pathologic Processing of Lymph Nodes:

The lymph nodes will be serially sectioned perpendicular to the long axis at 2 mm intervals in a "bread loaf" fashion. Lymph nodes 0.5 cm and smaller may be bisected; the node, if bisected, should be cut from hilum to periphery if possible. The lymph node blocks will be submitted for routine sections (1 slide per block).

Radiation Treatment Plan:

For women in the experimental arm, further management of the primary cervical cancer will be tailored to the results of the pretherapeutic staging procedure. Patients with negative paraaortic lymph nodes will be managed with external beam radiotherapy to the pelvis (as defined by the surgical clips applied at the lower limit of the paraaortic node dissection) at a usual dose of 45 Gy. Limited boosts will be indicated individually on clinically involved parametria or pelvic nodes. The external beam radiation therapy will be followed by intracavitary brachytherapy (HDR,LDR or PDR) with intent to cure. Patients with metastatic disease to paraaortic lymph nodes will receive extended-field external beam radiotherapy followed by intracavitary brachytherapy with intent to cure. Patients who complete both external beam radiation and intracavitary radiotherapy will receive a total dose of 80–90 Gy low-dose equivalent to Point A. Concurrent platinum-based chemotherapy will be given with definitive radiation therapy. Chemotherapy will be administered according to each participating institution's standard practice. Patients with carcinomatosis will be given platinum-based chemotherapy along with palliative radiotherapy if indicated.

For women in the standard of care arm, patients with negative paraaortic lymph nodes on PET imaging will be managed with external beam radiotherapy to the pelvis at a usual dose of 45 Gy. Limited boosts will be indicated individually on clinically involved parametria or pelvic nodes. The external beam radiation therapy will be followed by intracavitary brachytherapy with intent to cure (HDR, LDR or PDR). Patients who complete both external beam radiation and intracavitary radiotherapy will receive a total dose of 80–90 Gy low-dose equivalent to Point A. Concurrent platinum-based chemotherapy will be given with definitive radiation therapy.

IMRT may be used for the treatment of the paraaortic nodes. The nodal PTV will receive either 45 Gy in 25 fractions or 50.4 Gy in 28 fractions. Treatment will be delivered once daily, 5 fractions per week, over 5 to 5.5 weeks. Breaks in treatment should be minimized. Positive nodes may be boosted to 60-66 Gy after the initial treatment with IMRT or 3-D conformal treatment at 1.8 Gy or 2.0 Gy per fraction. The dose is prescribed to cover 97% nodal PTV. A volume of at least 0.03 cc within any PTV should not receive > 110% of the prescribed dose. No volume within the PTV that is 0.03 cc or larger can receive a dose that is < 93% of its prescribed dose. Any contiguous volume of 0.03 cc or larger of the tissue outside the PTVs must not receive > 110% of the dose prescribed to the composite PTV

Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. The use of custom made compensators or partial transmission blocks are also acceptable as long as dose specifications and constraints are satisfied. A megavoltage beam of 6 MV or greater must be used, with a minimum source-axis distance of 100 cm. The exception is the use of the Tomotherapy unit that uses 80 cm.

Patients will be immobilized in the supine position in an immobilization device. Patients should, at least, be immobilized in a cradle that fixes the position of the upper body, trunk and proximal legs. Patients will be treated in the immobilization device. Treatment planning CT scans will be required to define tumor, clinical and planning target volumes. The treatment planning CT scan should be acquired with the patient in the same position and immobilization device as for treatment IV contrast may be used during simulation to help better define the vessels; however, it is not required. Oral or rectal contrast is not allowed, because it will interfere with the planning process and may possibly cause anatomical distortion. Contrast may be used during simulation to help better define the vessels; however, it is not required. Oral or rectal contrast is not allowed, because it will interfere with the planning process and may possibly cause anatomical distortion.

If the paraaortic nodes for patients with positive common iliacs are treated, then PTV must end at the top of L2; for patients with positive paraaortic nodes, the PTV must end at the top of T12 (therefore, the CTV must end several slices below these endpoints). The top of the field should be at least one vertebra above the highest positive node. Bowel – will be outlined on every slice, including up to 2 cm above the planning target volume and no more. It includes the volume surrounding loops of small bowel out to the edge of the peritoneum because the bowel may lie within this space at any time throughout the course of treatment.

The dose constraints for critical structures are as follows:

- Bowel: ≤ 30% to receive > 40 Gy
- Rectum: ≤ 60% to receive > 45 Gy
- Bladder: ≤ 35% to receive > 45 Gy
- Kidneys: 2/3 of each kidney to receive ≤18 Gy
- Spinal cord: no more than 45 Gy at any point with a volume of 0.03 cc or greater

Follow-Up/Surveillance:

A PET scan will be obtained at 3 months after completion of chemoradiation therapy. CT scans will be obtained every 6 months for the next three years thereafter. Follow-up surveillance of patients will consist of serial clinical examinations by an oncologist every 3 months for the first 2 years, every 6 months for the next 3 years and annually thereafter. Patients will come off study at 5 years after completion of initial chemoradiation therapy or at time of death.

5.0 STATISTICAL CONSIDERATIONS

Sample Size Estimation

Based on data collected in the recently completed phase II study at MD Anderson which enrolled 65 women (60 evaluable) with locally advanced, approximately 32% will have PET imaging showing tumor metastasis to the pelvic nodes with negative paraaortic lymph nodes. Of these women, approximately 79% will truly have negative paraaortic lymph nodes. For them, 3 year overall survival with whole pelvis radiotherapy and concurrent chemotherapy is 75%. For the approximately 21% of women with false negative imaging (i.e. pathologically positive paraaortic lymph nodes with negative imaging), the 3 year overall survival with whole pelvis radiotherapy and concurrent chemotherapy is only 10%. If these metastases were known, however, and the radiation field was extended to cover the paraaortic basins, the 3 year overall survival improves to 50%. Thus, the expected overall survival without surgical staging would be approximately 61% and with preoperative paraaortic surgical evaluation would be 70%.

Assuming an accrual rate of 10 patients per month a sample size of 600 patients will yield 80% power with a 2-sided 0.05 significance level to detect a difference in 3-year overall survival of 61% and 70% between the patients without preoperative paraaortic surgical staging and the patients with preoperative paraaortic surgical staging. Accrual would take 5 years, and the study would be expected to take 7.6 years to complete, with a maximum 348 expected deaths. The accrual at LBJ will be 15 patients.

This sample size calculation includes an interim analysis for efficacy and futility once 174 deaths have been observed. The nominal p-value for the interim analysis of efficacy is 0.0031 and the nominal p-value for the interim analysis for futility is 0.3217. The nominal p-value for the final analysis is 0.049. The spending function approach of Lan and DeMets [16] with an O'Brien-Fleming [17] boundary for the interim analysis of efficacy and a Pocock [18] boundary for the interim analysis of futility were used in the sample size estimation. East 5.0 (Copyright © 2007, Cytel Inc., Cambridge, MA) was used to estimate the sample size and plan the interim analyses.

Analysis

We will use descriptive statistics to summarize patient demographic and clinical characteristics by treatment group.

We will estimate overall survival (OS) with the product limit estimator of Kaplan and Meier [19], and we will estimate the 3-year OS with a 95% confidence interval. We will also estimate the median OS with a 95% confidence interval. We will use the log-rank test to compare the 2 treatment groups with respect to OS.

We will also use the log-rank test for the interim analysis of OS, which will take place after 131 deaths have been observed. If the p-value from this test is < 0.0031 the study will be stopped for efficacy, and if the p-value from this test is > 0.3217 the study will be stopped for futility.

We will use Cox [20] proportional hazards regression to model OS as a function of treatment and other well-known and potential prognostic factors such as clinical stage, histology, and grade. We will estimate the hazard ratio for treatment (preoperative paraaortic surgical staging vs not) and other potential prognostic factors with 95% confidence intervals.

We will perform similar analyses for disease-free survival (DFS) as for OS.

We will tabulate the numbers of patients with particular short- and long-term morbidities including intraoperative and postoperative complications and treatment delay for each treatment group, and we will use the chi-square test to compare treatment groups with respect to the incidence of these morbidities.

For the treatment arm with pretreatment paraaortic surgical staging we will estimate the sensitivity of pretreatment radiologic staging examinations to detect metastatic disease with a 95% confidence interval. The findings of the pretreatment paraaortic surgical staging will be considered the true diagnosis of metastatic disease.

5.1 Recruitment Plan

This study seeks a sample size of 600 patients. In order to accomplish this target the investigators plan to convert this study into a multicenter project, enlisting sites worldwide. At that time we anticipate we will have enough funding to cover the monitoring costs and thus anticipate accrual will increase as sites are added. In the meantime we plan to open the study at MDACC and LBJ and work toward our ultimate goal of an international, multicenter study.

6.0 REGISTRATION AND RANDOMIZATION

All eligible patients in MD Anderson and LBJ will be required to provide informed signed consent before randomization. Randomization will be performed using the method with an equal allocation between the two treatment groups.

7.0 ADVERSE EVENTS

7.1 Definitions

The Investigator is responsible for reporting only common AEs (section 7.2) that are observed or reported during the study, regardless of their relationship to treatment or their clinical significance. Hematological and nonhematological AEs related to chemoradiation will not be collected due to the expectedness of the attribution (ie diarrhea, nausea, vomiting,etc.)

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment.

A treatment-emergent AE is defined as any event not present prior to surgery or any event already present that worsens in either intensity or frequency following surgery.

All common AEs(section 7.2) that occur after surgery during the study must be reported in detail in the patient's source/chart and followed to satisfactory resolution or until the local Principal Investigator or Co-Investigator deems the event to be chronic or the patient to be stable. The description of the AE will include the onset date, date of resolution, severity, seriousness, , and the likelihood of relationship of the AE to study treatment.

Severity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTC-AE v4.0),

If an adverse event occurs which is not contained in the CTC-AE v4.0, the five-point scale below will be used:

1. Mild: discomfort noticed but no disruption of normal daily activity.
2. Moderate: discomfort sufficient to reduce or affect daily activity.
3. Severe: inability to work or perform normal daily activity
4. Life Threatening: represents an immediate threat to life
5. Death

7.2 Common Adverse Events

The most common postoperative adverse events from study treatment include:

- Intraoperative injury (bowel, bladder, ureter, nerves or blood vessels)
- Wound complication (vault or pelvic hematoma or collection)
- Infectious complications (bladder, chest, septicemia)
- Postoperative hemorrhage/ bleeding, thromboembolic events (DVT, pulmonary embolus)
- Prolonged Ileus > 7 days, fistula formation (any) or hernia formation
- Cardiac, pulmonary renal or cerebrovascular complications
- Returned to theatre in same admission (re-operation)
- Bladder dysfunction
- Lymphoedema

7.3 Laboratory Test Abnormalities

Laboratory test value abnormalities will not be reported as AEs, unless there is an associated clinical condition for which the patient is given treatment, concomitant treatment is altered or the event is considered a serious adverse event.

7.4 Serious Adverse Events

An SAE is defined as any event that:

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Reporting requirements:
Any AE considered serious or which meets the previous criteria must be reported to the study chair within one business day from the time that study personnel first become aware of the serious adverse event.

All reported SAEs (related or not to the surgery) will be followed until satisfactory resolution or until the attending physician deems the event to be chronic or the patient to be stable. SAEs will be reported till 30 days from completion of primary therapy.

7.5 Adverse Event Reporting

Information regarding AEs will be collected from the time the patient signs the informed consent form up to 6 months post treatment.

All AEs reported or observed during the study will be recorded as an AE in the patient's source/chart. Information to be collected includes:

- Type of event
- Onset
- Investigator-specified assessment of severity and relationship to treatment
- Resolution of the event
- Grade
- Any required treatment or evaluations

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be recorded. All AEs will be followed to adequate resolution. Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be

reported as an AE. However, if it deteriorates at any time during the study it should be recorded as an AE.

7.6 Obtaining Adverse Event Information

At every study visit, patients will be asked a standard non-leading question to obtain any medically related changes in their wellbeing. In addition to patient or Investigator observations, AEs as defined in section 7.0 and 7.2 will be documented from any data collected (e.g., laboratory values, physical examination findings), or other documents that are relevant to patient safety.

7.7 Assessment of Causality

The Investigator's assessment of an AE's relationship to treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

- **Unrelated:** This relationship suggests that there is no association between the surgery and the reported event.
- **Possible:** This relationship suggests that treatment caused or contributed to the AE, i.e. the event follows a reasonable temporal sequence from the time of surgery and/or follows a known response pattern to the surgery, but could also have been produced by other factors.
- **Probable:** This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and the likely association of the event with the surgery. This will be based upon the known or previously reported complications to the surgery, or judgment based on the Investigator's clinical experience.
- **Definite:** This relationship suggests that a definite causal relationship exists between the surgery and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

7.8 Assessment of Severity

Adverse Event severity will be rated by the Investigator as mild, moderate, or severe using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events

characterized as intermittent require documentation of onset and duration of each episode.

8.0 PATIENT WITHDRAWAL

Patients will be advised that they may voluntarily withdraw from the study at anytime, for any reason and it will not affect their medical care. However, in such cases, appropriate effort will be made by the Investigator to determine the reason for voluntary withdrawal from the study and to document reason for withdrawal in the medical record, if known.

The last known status of these patients will be reported with the study results and all attempts to locate patients lost to follow up will also be documented.

Patients will be informed that, should they withdraw from the study, they should remain under the care of an appropriately experienced physician until the physician deems further follow-up unnecessary.

The following are circumstances for which a patient would be identified as not continuing her participation in the study:

- Study Completed / Terminated
- Death
- Voluntary Withdrawal
- Unable to Return
- Physician discretion
- No recurrence of cervical cancer at 5 years after completion of initial chemoradiation therapy
- Failure to complete treatment due to toxicity

If a patient relocates to another geographic area, which requires a change of physician, reasonable attempts will be made to locate and request cooperation from that physician in order to complete follow-up.

In many instances patient withdrawal from the study constitutes a cessation of treatment. In these cases, permission should be obtained from patients by study staff to continue monitoring their disease state (relapse, survival, toxicity etc) via patient records as this is a crucial component of the study for which consent was originally obtained.

9.0 STUDY COMMITTEES

9.1 Trial Safety Committee (TSC)

An independent Trial Safety Committee (TSC) will be assembled to review the safety and efficacy data collected during the study. They will be composed of individuals who

are independent of the study and are not involved (either directly or indirectly) in the management of this study. The membership includes the following:

- 3 gynecological oncologists who are otherwise not related to the trial;
- 2 Statisticians who are otherwise not related to the trial;
- 1 public member

The TSC will be responsible for monitoring, on an ongoing basis, any of the following events:

- General Toxicity (NCI-CTC AE, v4.0): grade 3 and grade 4 adverse events, serious adverse events
- A patient death (grade 5)

The first safety analysis will be performed after 20 patients have completed treatment. All further TSC reviews should take place twice per year and the committee will review all safety data collected during the study.

Following each meeting, the committee will recommend that the study continues according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases the committee may recommend stopping the study due to safety reasons.

9.2 Trial Management Committee (TMC)

A Trials Management Committee (TMC) will be assembled to review and manage the trial's progress. The TMC will consist of the study chair, the co-chairs, two study coordinators, and the study statistician. The TMC will meet/confer every four months.

Following each meeting, the committee will recommend that the study continues according to the protocol or may suggest changes to the protocol based on the outcome of the data review.

10.0 DATA HANDLING AND QUALITY ASSURANCE

10.1 Data Management

Participating Investigators must agree to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate source documentation as part of the patient's case history.

10.2 Data Security

Access to the study data base will be by username and password and will be restricted to trial personnel.

10.3 Data Quality Assurance

Accurate and reliable data collection will be assured by verification and cross–check of the collected data against the patients' medical record. The data collected will be entered directly onto a secure electronic database with access limited to study personnel. A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the investigator.

11.0 ADMINISTRATIVE CONSIDERATIONS

The following administrative items are intended to guide the conduct of the trial.

11.1 Confidentiality

All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient or the patient's guardian, except as necessary for monitoring by CDMU or its representative, regulatory authorities, or the IRB.

The Investigator and all employees and co-workers involved with this study shall not disclose or use for any purpose, other than performance of the study, any data, records or other unpublished, confidential information disclosed to those individuals for the purpose of the study.

11.2 Modification of the Protocol

The TMC must review and approve any changes in this research activity. Amendments to the protocol must be submitted in writing to the Investigator's IRB/HREC for approval prior to patients being enrolled into an amended protocol.

11.3 Informed Consent

A written informed consent shall be obtained from each patient prior to the patient's entrance into the study. Before recruitment and enrolment, each prospective patient will be given a full explanation of the study and be allowed to read the approved informed consent form. The Investigator will inform the patient of the purpose of the study, randomization of study groups and the follow-up schedule. The Investigator will discuss foreseeable risks involved, as well as potential benefits that result from the use of the new surgical technique. The Investigator will inform the patient that her medical records will be subject to review by government authorities, members of TSC and by the IRB.

The patients will be informed by the Investigator that they are free to refuse participation in this study and, if they choose to participate, that they may withdraw from the study at any time without compromising further medical care.

Once the Investigator is assured that the individual understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the informed consent form. The Investigator shall provide a copy of the signed informed consent to the patient.

11.4 Protocol Violations and Deviations

The Investigator or designee should document and explain any deviation from the approved protocol. The Investigator may deviate from the protocol to eliminate an immediate hazard to trial patients without prior IRB approval. As soon as possible after such an occurrence, the Investigator should submit the implemented deviation or change, the reasons for it to the site IRB to CDMU, if required.

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the IRB and agreed to by the Investigator. Deviations usually impact individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is non-adherence to the protocol that results in a significant added risk to the patient, when the patient or Investigator has failed to adhere to major protocol requirements, or when there is non-adherence to regulatory authorities' regulations and/or ICH Good Clinical Practice (GCP) guidelines.

CDMU or its representative will review the protocol violations and deviations during the monitoring visit and will notify the Investigator of violations and deviations verbally or in writing of their findings. The Investigator should notify the IRB/HREC of protocol violations and deviations in accordance with the IRB requirements.

12.0 STUDY CONDUCT

The study will be conducted according to the principles of the ICH E6 Guideline on GCP and the principles of the World Medical Association Declaration of Helsinki. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

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Addendum:

Definition of common iliac nodes – or the highest positive nodes allowed on protocol: In order to be eligible for the study, all FDG avid lymph must lie inferior to the midpoint of the SI joint. To define this point, the superior and inferior aspect of the SI joint should be marked to determine the mid-SI point (Figure). The most superior PET positive lymph node must lie inferior to the mid-SI point for the patient to be eligible for enrollment.