NRG ONCOLOGY

Radiation Therapy Oncology Group

RTOG 0724/GOG-0724

(ClinicalTrials.gov NCT #: 00980954)

PHASE III RANDOMIZED STUDY OF CONCURRENT CHEMOTHERAPY AND PELVIC RADIATION THERAPY WITH OR WITHOUT ADJUVANT CHEMOTHERAPY IN HIGH-RISK PATIENTS WITH EARLY-STAGE CERVICAL CARCINOMA FOLLOWING RADICAL HYSTERECTOMY

Amendment 7: September 21, 2022

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This trial is part of the national NCI Clinical Trials Network (NCTN) program which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance, ECOG-ACRIN, and SWOG

Study Chairs (21-SEP-2022)

Principal Investigator/Radiation Oncology
Anuja Jhingran, MD
M.D. Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
713-563-2347/FAX 713-563-2366
ajhingra@mdanderson.org

Gynecology Oncology
Heidi Gray, MD
University of Washington
Division of Gynecologic Oncology
Department of OB/GYN, Box 356460
Seattle, WA 98195
206-543-3669/206-543-3915
hgray@u.washington.edu

Translational Research
Joanne Weidhaas, MD, PhD
UCLA / Jonsson Comprehensive Cancer Center
Department of Radiation Oncology
200 UCLA Medical Plaza
Suite B265
Los Angeles, CA 90095-6951
310-825-5037
jweidhaas@mednet.ucla.edu

Quality of Life
Rachel Hirschey, MD
The University of North Carolina at Chapel Hill
School of Nursing
Carrington Hall, CB#7460
919-843-9468
hirschey@unc.edu

Medical Physics
Mohammad R. Salehpour, PhD
U.T. M.D. Anderson Cancer Center
Unit 1210
1155 Pressler Street
Houston, TX 77030
713-563-2636/FAX 713-563-6895
msalehpour@mdanderson.org

Senior Statistician
Kathryn Winter, MS
NRG Oncology
50 South 16th Street, Suite 2800
Philadelphia, PA 19102
215-574-3198/FAX 215-928-0153
winterk@nrgoncology.org

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Protocol Agent

Agent	Supply	NSC #	IND #
Carboplatin	Commercial	N/A	Exempt
Cisplatin	Commercial	N/A	Exempt
Paclitaxel	Commercial	N/A	Exempt

Participating Sites

☐ U.S. Only
☐ Canada Only
☒ U.S. and Canada
☒ Approved International Member Sites

Document History

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NRG Oncology
1-800-227-5463, ext. 4189

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CONTACT INFORMATION ((21-SEP2022)		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Submit data electronically via the NRG Oncology/RTOG web site, www.rtog.org Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For patient eligibility or treatment-related questions: Contact the Study PI of the Lead Protocol Organization".		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

For imaging data submission questions:
IROCimagearchive@acr.org; please include trial number in the email subject line

For TRIAD access and installation support:
TRIAD-Support@acr.org
Triadhelp.acr.org

TRIAD Software Installation:
https://triadinstall.acr.org/triadclient/

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SCHEMA (8/21/14)

S **T** **R** **A** **T** **I** **F** **Y**	Intention To Use Brachytherapy 1. No 2. Yes RT Modality 1. Standard RT 2. IMRT Radiation Therapy Dose 1. 45 Gy 2. 50.4 Gy	**R** **A** **N** **D** **O** **M** **I** **Z** **E**	**Arm 1** Concurrent weekly cisplatin and RT ± brachytherapy Versus **Arm 2** Concurrent weekly cisplatin and RT ± brachytherapy FOLLOWED BY Carboplatin and paclitaxel

See Section 5.0 for credentialing requirements for radiation therapy.
See Section 6.0 for radiation therapy details.
See Section 7.0 for drug regimen details.

Patient Population: (See Section 3.0 for Eligibility) (8/12/10)
Patients with clinical stage IA2, IB or IIA squamous, adenosquamous, or adenocarcinoma of the cervix who have any/all of the following high-risk features after surgery (this corresponds to surgical TNM staging of T1-T2, N1, M0):

- Positive pelvic nodes
- Positive parametrium
- Positive para-aortic nodes- completely resected, PET/CT negative (PET only required if positive para-aortic nodes during surgery)

Required Sample Size: 285 patients

ELIGIBILITY CHECKLIST (12/29/10)
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NRG Oncology Institution #
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____(Y) 1. Did the patient have a radical hysterectomy (open, laparoscopically, robotic) and staging including pelvic node sampling for cervical carcinoma within 70 days of study entry?
____ (Y/N) Did the patient undergo para-aortic lymph node sampling/dissection at the time of surgery?
____ (Y)/N) If no, did the patient have a dissection of the common iliac nodes and the nodes were negative?
____ Y) If no, did the patient have a negative para –aortic PET scan or PET-CT scan pre-or post-operatively?

____(Y) 2. Does the patient have histologic proof of squamous, adenocarcinoma or adenosquamous carcinoma of the cervix?

____(Y) 3. Is the FIGO stage IA2, Ib or IIA?

____(Y) 4. Does the patient have any/all of the following high-risk features post surgery: positive pelvic nodes; positive parametrium; or positive para-aortic nodes-completely resected and PET/CT negative (required if + PA nodes during surgery)

____(Y) 5. Is the Zubrod performance score 0-1?

____(Y) 6. Has the patient had a history and physical within 56 days of study entry?

____(Y) 7. Has the patient met all the lab requirements as described in Section 3.1.6 and 3.1.7.?

____(Y) 8. Has the patient had a chest x-ray, chest CT, or whole body PET-CT within 70 days of study entry?

____(Y) 9. Has the patient had a contrast-enhanced CT or MRI of the abdomen and pelvis OR whole-body PET-CT (with or without contrast) within 90 days of study entry?

____(Y/N) 10. Has the patient had a prior invasive malignancy (except non-melanomatous skin cancer)?

____(Y) 11. If yes, has the patient been disease free for a minimum of 3 years?

____(N) 12. Has the patient had prior systemic chemotherapy for the current cervical cancer?

____(N) 13. Has the patient had prior radiation therapy to the region of the study cancer that would result in overlap of radiation therapy fields?

____(N) 14. Does the patient have unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months?

____(N) 15. Has the patient had a transmural myocardial infarction within the last 6 months?

____(N) 16. Does the patient have an acute bacterial or fungal infection requiring intravenous antibiotics at the time of study entry?

ELIGIBILITY CHECKLIST (12/29/10)
(page 2 of 3)

NRG Oncology Institution #
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Case #

_____(N) 17. Does the patient have chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of study entry?

____(N) 18. Does the patient have known coagulation defects?

___(Y/N) 19. Is the patient known to be HIV positive? (NOTE: HIV testing is not required)

_____(Y/NA) If the patient is known to be HIV positive, has the patient had a CD4 cell count of ≥ 350 cells/mm^3 obtained within 14 days of study entry?

_____(N) 20. Has the patient had prior allergic reaction to carboplatin, paclitaxel, and/or cisplatin?

_____(N) 21. Does the patient have gross residual disease?

_____(N) 22. Does the patient have distant metastatic disease other then + PA nodes that were completely resected and PET/CT negative?

<u>The following questions will be asked at Study Registration</u>:

IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the patient provided study-specific consent prior to study entry

_____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 11. Gender

_____ 12. Patient's Country of Residence

ELIGIBILITY CHECKLIST (12/29/10)
(page 3 of 3)

NRG Oncology Institution #
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_____ 13. Zip Code (U.S. Residents)

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Calendar Base Date

_____ 17. Registration/randomization date: This date will be populated automatically.

_____ 18. Medical oncologist

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 23 Have you obtained the patient's consent to allow someone from this institution to contact

him or her in the future to take part in more research?

_____(Y/N) 24. Did the patient agree to participate in the quality of life component?"

_____ If no, please specify the reason from the following:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

_____(Y/N) 25. Is use of brachytherapy intended?

_____(Standard RT/IMRT) 26. Radiation modality to be used

_____(45 GY or 50.4GY) 27. Indicate prescribed EBRT dose to be used.

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by _____ Date _____

1.0 INTRODUCTION

Cervical carcinoma is the third most common gynecologic cancer in the United States, with a projected 11,150 cases and 3,670 deaths in 2007 (American Cancer Society 2007). The incidence of cervical carcinoma is higher in underdeveloped countries. It has been well documented that early-stage patients have survival rates of approximately 90%, whether treated with radical hysterectomy or radiation therapy alone. However, in 15% to 20% of patients with early-stage disease, the disease has either spread to nodes or there is involvement of the parametrium or surgical margins at the time of radical hysterectomy. When one or more of these factors is found, the 5-year survival rate drops to 50% to 70% (Delgado 1990). Patients who receive pelvic radiation therapy because of these risk factors still have an approximately 34% recurrence rate, with 17% of patients experiencing recurrence in the radiated field only and 4% experiencing recurrence in the radiated field along with distant metastasis (Peters 2000).

In 1999, after 5 positive trials, the NCI sent out an alert stating that concurrent cisplatin-based chemotherapy plus radiation therapy in patients with cervical cancer was better than radiation therapy alone (Peters 1990; Rose 1999; Morris 1999). In one of these trials (Peters 1990), patients with cervical carcinoma after a radical hysterectomy with positive nodes, parametrium, or surgical margins were randomized to concurrent cisplatin and 5-fluorouracil (5-FU) chemotherapy plus radiation versus radiation alone. In this trial concurrent chemotherapy and radiation therapy significantly improved progression-free and overall survival compared with radiation therapy alone. However, patients received different amounts of chemotherapy and, although not part of the randomization, the amount of chemotherapy was evaluated for recurrence rates. The patients were to receive 2 courses of chemotherapy with the radiation and 2 more courses of chemotherapy after the radiation. The investigators found that patients who received ≤ 2 courses of chemotherapy had a 31% recurrence rate compared with 13% of patients who received 3 or 4 courses of chemotherapy. This trial suggests that adjuvant chemotherapy in addition to concurrent chemotherapy may be beneficial. The update of this trial, published in 2005, continued to show improvement with chemotherapy. However, there was a smaller absolute benefit when only one node was positive or when the tumor size was < 2 cm (Monk 2005).

In addition to platinum, there are other chemotherapy agents that have demonstrated activity in cervical cancer. In the Peters trial (1990), cisplatin and 5-FU were used. However, another Gynecologic Oncology Group (GOG) trial found greater toxicity with concurrent cisplatin and 5-FU versus cisplatin alone; therefore, concurrent weekly cisplatin is the considered standard in the United States. Paclitaxel is a biologically active agent in gynecologic malignancies, used most abundantly in ovarian cancer. In other primary squamous malignancies such as head and neck cancer, paclitaxel has demonstrated activity (Forsatiere 1993). In cervical cancer, single-agent paclitaxel has demonstrated a 17% to 25% response rate in recurrent and advanced tumors (McGuire 1996; Kudelka 1997).

The recently closed protocol GOG 204 is evaluating multiple arms of chemotherapy regimens, including paclitaxel and cisplatin in one arm, in patients with advanced or recurrent cervical cancer. The results were recently presented at ASCO. The investigators found no significant advantage of any arm over the control arm of cisplatin and paclitaxel (Monk, 2008). The quality of life data of this study was also presented. The investigators found that no doublet was clinically or statistically different from cisplatin and paclitaxel in quality of life or pain. The conclusions stated that there may be a clinical advantage to cisplatin and gemcitabine and cisplatin and topotecan in regards to neurotoxicity over the other two arms. However, the power was too low to detect a significant advantage (Wenzel,2008). Because of the concern of toxicity, especially neurotoxicity, with cisplatin, there has been interest in using carboplatin as a less toxic regimen. A trial published in 2005 looked at the combination of carboplatin and paclitaxel in advanced and recurrent cervical carcinomas and found a 20% partial response rate and a 20% complete response rate in 25 patients. They investigators concluded that carboplatin-paclitaxel is an active combination in advanced and recurrent cervical cancer (Tinker, 2005).

Recently, a multi-institutional retrospective study reported on experience with paclitaxel and carboplatin versus paclitaxel and cisplatin in advanced-stage or recurrent cervix cancer. Moore et al (2007) found objective responses of 53% in the carboplatin group compared with 29% in the cisplatin group, with significantly less toxicity. Internationally, there has been a trend towards using carboplatin in cervical cancer, especially in patients previously treated with radiosensitizing cisplatin. Therefore, there is mounting evidence that the combination of paclitaxel and carboplatin is an effective and less toxic regimen in cervical cancer. The added benefit of ease of administration as an outpatient treatment makes this regimen an ideal choice to study in this population.

Preliminary data from the ongoing protocol GOG 209, treating advanced or recurrent endometrial cancer with either paclitaxel, doxorubicin and cisplatin or paclitaxel and carboplatin, showed increased hematologic toxicities when patients were previously irradiated. This finding led to a protocol dose reduction to paclitaxel 135 mg/m^2 and carboplatin AUC 5 for women who have previously undergone pelvic irradiation. Consequently, we have modeled our starting doses in the treatment arm of paclitaxel and carboplatin to reflect these data.

The goal of the current study is to evaluate the addition of systemic adjuvant therapy with paclitaxel and carboplatin following radical surgery and chemoradiation in early-stage, high-risk patients for the reduction in recurrence risk and improvement in disease-free survival and overall survival. Toxicity will also be evaluated, and the trial will include a quality of life (See Section 1.1) and transitional research component (see Sections 10.2 and 10.3.)

Radiation therapy will be the standard in both arms. Intensity modulated radiation therapy will be allowed at the discretion of the treated radiation oncologist. In 2002, Mell et al. performed a nationwide survey and found that 15% of the IMRT users in the United States had treated at least one gynecologic patient with IMRT (Mell,2003). In the follow-up survey done in 2004, this percentage had increased to 35%, making gynecology the fourth most common site treated with IMRT and the most rapidly growing IMRT site overall in the United States (Mell,2005). RTOG recently completed a phase II trial evaluating the transportability of IMRT to multiple institutions in the post-operative setting in patients with both cervical and endometrial cancer. The results for the endometrial arm were recently presented at ASTRO in Boston and found IMRT was feasible across multiple institutions in the post-operative setting (Jhingran, 2008). Vaginal brachytherapy also will be allowed at the discretion of the treating physician which was not done in the Peters trial. Several retrospective studies have shown that vaginal brachytherapy in addition to external beam radiation therapy is safe and effective and the addition of it may reduce vaginal recurrence further than external beam therapy alone.

1.1 Assessments for Quality of Life, Neuropathy, and Diarrhea

A meta-analysis of 19 randomized controlled trials totaling 4,580 patients verified that the addition of chemotherapy to radiation therapy improved progression-free and overall survival. Five large randomized clinical trials demonstrated a significant survival benefit for patients treated with concurrent chemoradiotherapy, using a cisplatin (CDDP)-based regimen, with a 28%-50% relative reduction in the risk of death. In addition, the results of a meta-analysis of 19 randomized controlled trials of concurrent chemoradiotherapy (1981-2000) involving 4580 patients showed that concurrent chemoradiotherapy significantly improved overall survival [hazard ratio (HR) 0.71; P < 0.0001], as well as progression-free survival (HR 0.61; P < 0.0001). In line with these results, concurrent chemoradiotherapy is currently recommended as standard therapy for advanced cancer (stage III/IVA) in the United States. However, much less is known about the toxicity and quality of life impacts of chemoradiation. (Goonatillake 2009)

The Southwest Oncology Group (SWOG) Protocol 8797/Gynecologic Oncology Group (GOG) Protocol 109 addressed the role of adjuvant radiation and chemotherapy after radical hysterectomy and lymphadenectomy. This study evaluated women found to have positive pelvic lymph nodes (as in the current case) and/or microscopic involvement of the parametrium and/or positive surgical margins, who were randomly allocated to

receive either pelvic radiation alone or radiation in combination with chemotherapy (intravenous bolus cisplatin 70 mg/m^2 and a 96-hour infusion of fluorouracil 1,000 mg/m^2 every 3 weeks for 4 cycles). However, in another study by the GOG, it was felt that the combination of cisplatin and 5-FU was equally effective as weekly cisplatin and more toxic; therefore, weekly cisplatin has become the standard chemotherapy regime with radiation therapy. Additionally, the recently closed protocol GOG 204 is currently evaluating multiple combinations of chemotherapy, including cisplatin and paclitaxel, in the treatment of locally advanced cervical cancer. The combination of paclitaxel and cisplatin was generally felt to be the most active regimen of these three choices, increasing the response rate to 37% as well as prolonging the progression-free survival). However, because of the lack of a clear survival advantage, increased neuropathy, increased cytopenia, and associated alopecia, this combination can not be routinely recommended. (Monk 2007)

An additional study explored the role of carboplatin in the treatment of cervical cancer patients. Forty-three patients staged as IB2–IIIB were treated with three 21-day courses of carboplatin (area under the time–concentration curve 6 mg•min/ml) and paclitaxel at 175 mg/m^2 by 3-h infusion both on day 1 followed by radical type III hysterectomy and adjuvant radiation concurrent with 6-weekly doses of cisplatin at 40 mg/m^2. Response rate, resectability, toxicity, and survival were evaluated. Induction chemotherapy was well tolerated. A total of 129 cycles were administered, of which only two were delayed for 1 week. The most common toxicities were nausea/vomiting and neuropathy and occurred in 48% and 38%, respectively. There were no cases of leukopenia, but neutropenia was present in 12% and 3% of courses, respectively. Other toxicities were mild and uncommon. (Dueñas-Gonzales 2003)

A meta-analysis of 18 trials was conducted to assess effects of chemoradiation therapy and chemoradiotherapy plus chemotherapy. Chemotherapy use was also sub-divided by platinum-based and non-platinum. This meta-analysis differed from others in that it was conducted using individual patient data and examined both acute and late toxicity data (Meta-Analysis Group, 2008). Gastrointestinal and acute hematologic toxicities were the most commonly reported toxicities, with a significant increase in gastrointestinal toxicities for groups using both platinum-based chemoradiation plus chemotherapy and additional radiotherapy (control arm). Gastrointestinal toxicities were not noted in trials using non-platinum-based chemotherapy. Other data (Nagy 2007; Tormo Ferrero 2009) further validate the presence of gastrointestinal toxicities in platinum-based chemoradiation treatment for cervical cancer. These data corroborate the gap in knowledge for adverse profiles of diarrhea in cervical cancer patients receiving concurrent cisplatin and 5-fluorouracil chemotherapy plus radiation versus radiation alone. The exploration of these adverse event profiles will provide an investigation of the quality of life for this patient population and allow for the development of appropriate treatment protocols. Missing from these analyses were data on neuropathy, further underscoring the need for the current trial.

Quality of life, chemotherapy-induced neuropathy, and diarrhea will be assessed using the FACT-Cx, FACT-GOG/NTX4, and the FACIT-D respectively, all of which are patient-reported questionnaires. The FACT-Cx version 4 is comprised of 27 general items including the four domains of physical well-being, social and family well-being, emotional well-being, and functional well-being, as well as 15 additional items specific for symptoms and problems related to cervical cancer. The FACT-GOG/NTX4 is a patient-reported tool developed by the GOG to assess neuropathy. It is comprised of 4 items related to numbness or tingling in patients' extremities. The diarrhea-specific portion of the FACIT-D is comprised of 11 items. For all patients participating in this portion of the trial, these tools will be collected at the following time points: baseline; end of concurrent chemoradiation; and 6, 12, and 24 months after the end of chemoradiation.

The FACT-Cx, FACT-GOG/NTX4 and FACIT-D are derivatives of the FACT, a family of measures first developed in the early 1990's. The core portion of the FACT, referred to as FACT-G, is comprised of four components of quality of life measured across 27 items. The FACT-Cx includes 15 additional items specific to cervical cancer; the FACT-GOG/NTX4 has an additional 4 items specific to peripheral neuropathy; and the FACIT-D has an additional 11 items specific to diarrhea.

The FACT-CX has been translated into 14 languages; the FACT-GOG/NTX has been translated into 40 languages; and the FACIT-D is available in 17 languages. All are available free of charge to institutions with the completion of an agreement to share data, accessible http://www.facit.org/translation/licensure.aspx.

2.0 OBJECTIVES

2.1 Primary (8/12/10)

To determine if adjuvant systemic chemotherapy following chemoradiation therapy will improve disease-free survival compared to chemoradiation therapy alone in patients with high-risk early-stage cervical carcinoma found to have positive nodes and/or positive parametria after a radical hysterectomy.

2.2 Secondary

2.2.1 To evaluate adverse events

2.2.2 To evaluate overall survival

2.2.3 To evaluate quality of life

2.2.4 To evaluate chemotherapy-induced neuropathy

2.2.5 To perform a post-hoc dose-volume evaluation between cases treated with standard RT and cases treated with IMRT with respect to toxicity and local control

2.2.6 To collect fixed tissue to identify tumor molecular signatures that may be associated with patient outcomes, such as adverse events, disease-free survival, and overall survival

2.2.7 To collect blood to:

- Identify secreted factors from serum and plasma that may be associated with adverse events or outcome, and
- Identify SNPs in genes from buffy coat that may be associated with a genetic predisposition to tumor formation itself or a response to cytotoxic therapy

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (8/21/14)

For questions concerning eligibility, please contact the study data manager.

3.1.1 Patients must have undergone radical hysterectomy (open, laparoscopically or robotic) and staging including pelvic node sampling or dissection for cervical carcinoma within 70 days prior to study entry. [**NOTE**: If the patient did not have a para-aortic lymph node sampling/dissection, but had common iliac node dissection that was negative, a PET-CT is recommended, but not required. A negative pre or post-operative PET scan or PET-CT scan of the para–aortic nodes is required if the patient did not undergo para-aortic **or** common iliac nodal sampling/dissection]

3.1.2 Patients with clinical stage IA2, IB or IIA squamous, adenosquamous, or adenocarcinoma of the cervix who have any/all of the following high-risk features after surgery:

- Positive pelvic nodes
- Positive parametrium
- Positive para-aortic nodes- completely resected, PET/CT negative (PET only required if positive para-aortic nodes during surgery)

3.1.3 No distant metastases, based upon the following minimum diagnostic workup [**NOTE**: Patients with positive para-aortic nodes- completely resected, PET/CT negative are eligible]:

- History/physical examination within 56 days prior to study entry
- Contrast-enhanced imaging of the abdomen and pelvis by either CT, MRI, or whole body PET-CT (with or without contrast) within 90 days prior to registration. (NOTE: whole body PET-CT is preferred)
- Chest x-ray (PA and lateral) or chest CT within 70 days prior to study entry (except for those who have had whole body PET-CT per Section 3.1.3.).

3.1.4 Zubrod performance status 0-1.

3.1.5 Age ≥ 18

3.1.6 CBC/differential obtained 14 days prior to study entry, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.)
- White blood cell count ≥ 4000 cells/mm^3

3.1.7 Adequate hepatic and renal function defined as follows:

- Serum creatinine ≤ 1.5 mg/dL within 14 days prior to study entry
- Bilirubin ≤ 1.5 times normal 14 days prior to study entry
- Alkaline phosphatase within upper limits of institutional normal within 14 days prior to study entry
- ALT/SGPT and/or AST/SGOT within upper limits of institutional normal within 14 days prior to study entry
- Patients with known HIV positive must have a CD4 cell count be ≥ 350 cells/mm^3 within 14 days prior to study entry (note, however, that HIV testing is not required for entry into this protocol.) Excluding HIV positive patients with invasive cervical cancer and low CD4 cell counts is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

3.1.8 Patient must provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible)

3.2.2 Patients can not have any neuroendocrine histology in pathology.

3.2.3 Prior systemic chemotherapy for the current cervical cancer; note that prior chemotherapy for a different cancer is allowable. See section 3.2.1.

3.2.4 Prior radiation therapy to the pelvis that would result in overlap of radiation therapy fields

3.2.5 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of study entry
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of study entry
- Coagulation defects; note, however, that coagulation parameters are not required for entry into this protocol.

3.2.6 Prior allergic reaction to carboplatin, paclitaxel, and/or cisplatin.

3.2.7 Patients who have gross residual disease or distant metastatic disease.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

4.1.1 Serum calcium, magnesium, sodium, potassium, chloride, CO2, BUN, and glucose.

4.1.2 Audiogram when there is a history of hearing loss.

5.0 REGISTRATION PROCEDURES (8/21/14)

Access requirements for OPEN and TRIAD

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam

NOTE: Only physicians who have completed the Knowledge Assessment Questionnaire (for ALL radiation treatment modalities) available from the Imaging and Radiation Oncology Core(IROC) Houston website (http://irochouston.mdanderson.org) may enter patients onto this study.

NOTE: See below for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

5.1 Pre-Registration Requirements for IMRT Treatment Approach (8/21/14)

In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the IROC Houston web site. Visit http://irochouston.mdanderson.org and select "Credentialing" and "Credentialing Status Inquiry".

5.1.1 An IMRT phantom study with the IROC Houston must be successfully completed (if the institution has not previously met this credentialing requirement using IMRT on a Head and Neck or Pelvis phantom). Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the IROC Houston will notify both the registering institution and IROC Philadelphia that the institution has completed this requirement. Subsequently, IROC Houston will notify the institution that the site can enroll patients on the study. IROC Philadelphia will notify CTSU that the institution is credentialed.

5.1.2 The institution or investigator must complete a Facility Questionnaire and Credentialing Status Inquiry Form found on the IROC Houston website: http://irochouston.mdanderson.org and must set up a TRIAD account for digital data submission.

5.2 Pre-Registration Requirements for Standard RT Treatment Approach (8/21/14)

The Facility Questionnaire and Credentialing Status Inquiry Form must be completed it is available on the IROC Houston web site at http//irochouston.mdanderson.org Institutions must set up a TRIAD account for digital data submission. IROC Houston will notify the institution when all requirements have been met. IROC Philadelphia will notify CTSU that the institution is credentialed.

5.3 Pre-Registration Requirements for Brachytherapy Treatment Approach (8/21/14)

Upon review and successful completion of brachytherapy requirements per the IROC Houston website (http://irochouston.mdanderson.org) IROC Houston will notify both the registering institution and IROC Philadelphia. IROC Houston will then notify the institution. IROC Philadelphia will notify CTSU when all requirements have been met.

5.4 Digital Radiation Therapy Data Submission Using Transfer of Images and Data (21-SEP-2022)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) (CTEP-IAM) account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

5.5 Registration, Study Entry Procedures (21-SEP-2022)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr . RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave,acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, must be rostered at the enrolling site with a participating organization.

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

5.5.1 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s)record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).
- IRB/REB Approved Informed Consent (International sites only: English and native language versions*)

*Note: International and Canadian Institutions must provide certification/verification of IRB/REB IEC consent translation to NRG Oncology (described below).

Protocol Specific Requirements for RTOG 0724 site registration:

- CTSU RT Facilities Inventory Form (if applicable)

Non-English Speaking Canadian and Non-North American Institutions:
*Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Site must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory Support System (RSS) to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

5.5.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG* and protocol number *[NCI Protocol #]*.

Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go:
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
In addition to the requirements above, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) or e-mail (CTSURegulatory@ctsu.coccg.org) the following forms:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.5.3 *Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS*
*For institutions that **do not have an approved LOI** for this protocol:*
International sites must submit an LOI to NRG Oncology to receive approval to participate in this trial. For more details see link below: http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx

*For institutions that **have an approved LOI** for this protocol:*
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.6 Patient Enrollment (21-SEP-2022)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com

5.6.1 OPEN Registration Instructions

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:

- See Section 5.0 for obtaining a CTEP-IAM account.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.

- To perform registrations on protocols for which you are a member of NRG Oncology, you must have an equivalent 'Registrar' role on the NRG Oncology roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY (8/21/14)

***PRIOR TO ENROLLING PATIENTS*, please see Section 5.4 for information on installing TRIAD for submission of digital RT data.**

Note: Intensity Modulated RT (IMRT) Is Allowed (See Section 6.2)
Treatment planning CT scans with treatment planning dose information will be required for both IMRT and standard RT, and must be digitally submitted to TRIAD. The CT scans should be scans from at least L3 to mid femur. The thickness of the slices depends on the type of treatment: For IMRT, the slice thickness should not be more than 3 mm; for standard RT, slice thickness up to 5 mm is allowed. For standard RT, no contouring is required; for IMRT requirements are per section 6.2**.**

A rapid review of first enrolled case from each site will be conducted prior to RT treatment (see section 6.5)

Protocol treatment must begin within 70 days after surgery.

6.1 Standard External Beam Radiation Therapy (See Section 6.2. for IMRT) (8/21/14)

6.1.1 Dose Specifications

All patients will be treated with external beam radiation therapy with standard therapy or IMRT treatment plans. If using IMRT, please see Section 6.2 for dose specifications and requirements. All patients will be treated to either 45 Gy in 25 fractions or 50.4 Gy in 28 fractions (1.8 Gy/fraction). Patients will be treated once per day, 5 days per week. If using 6 MV or 10 MV photon energy, the patient must be treated with a 4-field technique using anterior/posterior and 2 lateral fields.
The specification of the target dose is in terms of a dose to a point at or near the center of the target volume. For all field arrangements the dose specification point is the common isocenter of all beams.

Radiation Treatment Interruption

If interruption of 7 consecutive days or fewer occurs, radiation should be completed to the prescribed total dose.

When therapy interruptions of more than 7 consecutive days occur, resumption of therapy will be at the discretion of the radiation oncologist but will be considered a deviation unacceptable. (See Section 6.1.8 for compliance criteria.) Follow-up must continue regardless of radiation treatment received.

6.1.2 Technical Factors

A megavoltage beam of 6 MV or greater must be used, with a minimum source-axis distance of 100 cm.

6.1.3 Localization, Simulation, and Immobilization

Treatment planning CT is required and must be digitally submitted to TRIAD All fields treated require simulation and portal verification on the treatment unit. Contouring of normal tissues as well as tissues at risk are not required; fields may be drawn using boney landmarks.

6.1.4 Whenever possible, patient should be treated with full bladder daily to reduce the amount of small bowel in the field. The patient should be instructed to drink 32 oz starting 30 to 60 minutes before each treatment.

6.1.5 Radiation Treatment Fields

Pelvic Portal (AP-PA)

- Superior border: A transverse line between L4-L5.
- Lateral border: 1-2 cm lateral to the widest true pelvic diameter.
- Inferior border: A transverse line below the obturator foramen and at least 4 cm beyond the vaginal cuff. A radio-opaque marker in the vagina to mark the vaginal cuff will help to facilitate proper placement of the lower border.
- Custom blocking to shield small bowel and femoral heads should maintain a margin of at least 1 cm from common iliac nodes and should not shield the obturator foramina However, contouring of nodes and normal structures is not required; fields may be drawn using boney landmarks.

Pelvic Portal (lateral fields)

- Superior border: Identical to AP/PA fields.
- Anterior border: A line drawn through the symphysis pubis and at least 1 cm anterior to common iliac nodes at L4/L5
- Posterior border: Care should be taken to include at S3-S4.
- Inferior border: Identical to AP/PA fields.
- Custom blocking should be used to shield anterior small bowel if possible, maintaining a margin of at least 1 cm from common and external iliac nodes. Blocking may split the L4/L5 vertebral body to shield posterior soft tissue and split the sacrum to provide adequate margin for pre-sacral nodes. Posterior rectum may be blocked.

Para-aortic Field (only if positive common iliac nodes or para-aortic nodes –AP/PA)

- Superior border: If common iliac nodes only positive and definitive negative para-aortic nodes – L1/L2 interspace; if positive para-aortic nodes – T11/T12 interspace.
- Inferior border: Identical to pelvic field.
- Lateral border: Just outside the transverse processes.
- Custom blocking to shield the kidneys and bowels, and in the pelvic area, should be identical to pelvic portal.

Para-aortic Field (lateral fields)

- Superior border: Identical to AP/PA fields
- Anterior border: At least 2 cm anterior to the vertebral body and/or 1 cm anterior to the para-aortic nodes region contoured.
- Posterior border: At least 1 cm posterior to contoured para-aortic nodal region and/or 1-1.5 into the vertebral body.

- Inferior border: Identical to pelvic fields.
- Custom blocking should block the small bowel and kidneys. Kidneys and spinal cord should be contoured, and doses to the kidneys and spinal cord need to be determined.

6.1.6 Documentation Requirements

Field outlines are required for all treatment fields. This information should be displayed on Digitally Reconstructed Radiographs (DRRs) produced with the institution's treatment planning computer. The images should include an outline of the field shape for each treatment portal, and must be obtained as a "screen capture" in standard jpg format. These images must be sent to TRIAD along with corresponding portal images obtained before the start of the first day's treatment. The portal images can be obtained with either EPID or film. Radiographic film images must be converted to a digital format by the institution using a film scanner so that jpg images can be sent via TRIAD. The portal imaging process should be repeated every five days. One set of portal images should be sent from the middle of the patient's fractionated treatment, and images from the final portal imaging process should also be forwarded TRIAD using the jpg image format. For data submission, please refer to Section 12.2.

6.1.7 Critical Structures

- The dose to kidneys and spinal cord should be considered when doing extended field radiation therapy; these structures should be contoured on the CT scan and dose should be calculated. The following dose criterion should be observed:
- Kidneys: 2/3 of each kidney should not receive more than 18 Gy
- Spinal cord: no more than 0.03 cc of spinal cord should receive a dose higher than 45 Gy

6.1.8 Compliance Criteria for Standard Radiation Therapy

Per Protocol: See Section 6.1.

Variation Acceptable

- Interruption of external beam RT of less than 7 consecutive days
- The minimum dose to the dose specification point is greater than or equal to 43.2 Gy for those patients for whom the intended dose was 45 Gy and greater than or equal to 48.6 Gy for those patients for whom the intended dose was 50.4 Gy.
- Maximum dose to a volume of ≥0.03 cc of tissue within the convergence of the treatment fields should not exceed 107% of the prescription dose

Deviation Unacceptable

- Field of RT is other than what is outlined in protocol
- Interruption of external beam RT of more than 7 consecutive days
- The minimum delivered dose to the dose specification point is less than 43.2 Gy for patients for whom the intended dose was 45 Gy or less than 48.6 Gy for patients for whom the intended dose was 50.4 Gy
- Maximum dose to a volume of ≥0.03 cc of tissue within the convergence of the treatment fields exceeds 107% of the prescription dose

6.2 IMRT (8/21/14)

Please refer to the Gynecological Atlas for volume specifications. The Atlas may be accessed at: http://www.rtog.org./CoreLab/ContouringAtlases/GYN.aspx

6.2.1 Dose Specifications

Prescription dose will be according to the following specifications:

The vaginal planning target volume (PTV) (ITV with 7.0 mm margin) and 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. All targets will be treated simultaneously with the same dose. Breaks in treatment should be minimized.

The dose is prescribed to cover 97% of the vaginal PTV and 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.

6.2.2 Technical Factors

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 is 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.

6.2.3 Localization, Simulation, and Immobilization

Prior to simulation, it is recommended that small radiopaque marker seeds be inserted into the vaginal apex to help identify the vaginal apex on the CT scan.

Radiopaque markers that distend or otherwise alter the vaginal anatomy should not be used.

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

6.2.4 Treatment Planning/Target Volumes

Two separate treatment planning CT scans (full bladder and empty bladder CT scans, as described below) are required (must be submitted) and then should be fused together prior to outlining target volumes. If two CT scans can not be performed, then IMRT will not be allowed and the patient must be treated with standard radiation therapy. The patient will be instructed to drink 32 ounces of fluid 30-60 minutes before simulation:

- A CT scan simulation will be performed with the full bladder, and
- A second CT will be performed after the patient has voided for the empty bladder scan.
- Both CT scans must be submitted (see Section 12.2)

In this study, which is used for post-operative patients with no gross disease, there should not be a GTV.

The Clinical Target Volume (CTV) is defined as areas considered to contain potential microscopic disease, delineated by the treating physician. The overall CTV includes both the vaginal/parametrial ITV and the nodal CTV. Please refer to Section 6.2.4.
for details.

Internal Target Volume (ITV) is defined as the volume of the vagina that is in both the empty and full bladder CT scans that are done at the time of simulation and fused together (the combined volume). This volume accounts for internal organ motion. Institutions who are unable to do an ITV will not be allowed to do IMRT and should treat their patients with standard radiation therapy. Institutions that can not acquire two CT scans (full and empty bladder scans) should treat the patient with

standard RT and not IMRT. It will be considered deviation unacceptable if the institution is unable to do two scans but uses IMRT.

The Planning Target Volume (PTV) will provide a margin around the ITV to compensate for the variability of treatment setup. Careful consideration should be made when defining the superior and inferior margins in three dimensions.

Planning of the IMRT will be done on the full bladder scan with full heterogeneity correction enabled in the treatment planning system.

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose volume histogram (DVH) analyses of the PTV (CTV with a 7 mm margin) and critical normal structures. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of non-involved tissues.

Planning Priorities

- Dose to nodal PTV and vaginal ITV are the most important planning priorities, followed by the dose to critical structures prescription goals.
- The priorities in addressing the protocol aims and constraints are in Critical Structures (See Section 6.2.5).

The nodal CTV should include lymph nodes that drain the involved site and adjacent perinodal soft tissue. This should include the internal (hypogastric and obturator), external, and common iliac lymph nodes; presacral lymph nodes and soft tissues should be included as well, down to the level of S3. Identification of the CTV usually begins with the identification of the iliac vessels. The nodal CTV will include the vessel , perinodal tissue (on the pelvic wall side, the margin will exclude psoas and piriformis muscle) and pertinent clips. The average margin will be 7 mm. Bone and intraperitoneal small bowel should be excluded from the CTV; also, iliopsoas muscle that lies adjacent to clinically negative lymph nodes should also be excluded from the CTV. Approximately 1-2 cm of tissue anterior to the S1, S2 and S3 sacral segments is usually added to the CTV for patients with cervical carcinoma in order to include the presacral lymph nodes and uterosacral ligaments. The most antero-lateral external iliac lymph nodes that lie just proximal to the inguinal canal should be excluded from the CTV (i.e., nodal CTV should stop right at the level of the femoral head). The CTV of the nodes should end 7 mm from L4/L5 interspace to account for the PTV. The PTV for nodes to stop at L4/L5 interspace. If the para-aortic nodes for patients with positive common iliacs are treated, then PTV must end at the top of L2; for patients with positive para-aortic nodes, the PTV must end at the top of T12 (therefore, the CTV must end several slices below these endpoints). (See GYN atlas for examples: http://www.rtog.org./CoreLab/ContouringAtlases/GYN.aspx.)

The vaginal and parametrial CTV should actually be an ITV, which will account for internal organ motion. The ITV is drawn after the full and empty bladder scans are fused together, and it should encompass the vagina and paravaginal soft tissues from both scans. This is because patients are not able to maintain constant levels of bladder filling, despite careful counseling. Patients should, however, be treated with a full bladder, because full bladder pushes the small bowel up and out of the field. The inferior limit is usually around the level of the upper third of the symphysis pubis but can be individualized based on inferior spread of the patient's tumor on prior pre-operative physical examination and post-operative pathology reports. The lateral margin of the vaginal PTV should be to the obturator muscle. However, at least 3 cm of the vagina needs to be treated or at least 1 cm below the obturator foramen.

PTV will provide a 7-mm margin (anteriorly, posteriorly, laterally, as well as in the superior and inferior directions) around the nodal CTV. The vaginal PTV will be 7.0 mm around the vaginal ITV anteriorly, superiorly, inferiorly, laterally, and posteriorly.

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing Recording and Reporting Photon Beam Therapy and 1999 ICRU Report #62: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50).

6.2.5 Critical Structures

Normal structures will be contoured using the full-bladder CT scan.

Bladder – will be outlined on every slice, including the portion inferior to the planning target volume. The contour includes the bladder contents.

Rectum – will be outlined on every slice, including the portion inferior to the planning target volume and superior to the level that it leaves the posterior pelvis around the region of the rectosigmoid. The contour includes the rectum contents.

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 femoral heads and the sacrum should be contoured in all slices.

The dose constraints for critical structures are as follows:

- Bowel: no more than 30% of the volume of the bowel to receive a dose that is greater than 40 Gy
- Rectum: no more than 60% of the volume of the rectum to receive a dose that is greater than 45 Gy
- Bladder: no more than 35% of the volume of the bladder to receive a dose that is greater than 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

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.

All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 3 mm or smaller through the region that contains the primary target volumes plus critical structures requiring Dose-Volume Histogram analysis. Anatomy inferior and superior to this region, can be imaged with a greater slice thickness that does not exceed 5 mm. The superior limit will be at least at the T10 interspace and inferior limit will be below the perineum.

The ITV and CTV and normal tissues must be outlined on all CT slices in which the structures exist on the full-bladder scan. ITV contours will be drawn to include the excursion of target tissues as demonstrated on the empty bladder scan (ITV). Using the full bladder scan, all normal tissues will be outlined on all CT slices in which the CTV and ITV exist and on at least 7 slices (21 mm) above and below the target. (See Section 6.2.4 for more detailed definitions.)

Lymph node groups at risk including the following:

- The lower common iliac nodes – the superior limit of the contoured common iliac will be at the top of L5 vertebral body – the PTV should be at the top of L5; therefore, the CTV should be contoured up to 7 mm from the top of L5
- Internal iliac (obturator and hypogastric) nodes
- External iliac nodes up to the level of the top of the femoral heads
- The presacral nodes down to the level of S3

- The obturator nodes – inferiorly to upper 1/3 of the obturator fossa
- If positive common iliacs: PTV must be to top of L2; if positive para-aortic nodes: PTV must be to top of T12

6.2.6 Documentation Requirements

Verification orthogonal films or images are required. For all forms of IMRT dose delivery, orthogonal films or images that localize the isocenter placement shall be obtained. The length of the treatment field shall be indicated on these films (images). These films (images) will not be collected but should be held by the institution and available for review if requested. For data submission, please refer to Section 12.2.

6.2.7 Compliance Criteria

- Per Protocol: Interruption of 0 days
- Variation Acceptable: Interruption of 1-7 consecutive days
- Deviation Unacceptable: Interruption of ≥ 8 consecutive days

Volumes

PTV vagina 45 or 50.4 Gy

- Per protocol: The prescription criteria in Section 6.2.1 are fulfilled.
- Variation Acceptable: The 0.03cc volume of overdose for the PTV exceeds 110% of the prescribed dose but remains below 115%. No volume within this PTV that is 0.03 cc or larger receives a dose that is < 91% of its prescribed dose.
- Deviation Unacceptable: A total of 0.03 cc of the PTV receives a dose that is over 115% of the prescribed dose. A volume within this PTV that is 0.03 cc or larger does receive a dose that is < 91% of its prescribed dose.

PTV nodal

- Per Protocol: The prescription criteria in section 6.2.1 are fulfilled.
- Variation Acceptable: The 0.03 cc volume of overdose for the PTV exceeds 110% of the prescribed dose but remains below 115%.No volume within this PTV that is 0.03 cc or larger receives a dose that is < 91% of its prescribed dose.
- Deviation Unacceptable: A total of 0.03 cc of the PTV receives a dose that is over 115% of the prescribed dose. A volume within this PTV that is 0.03 cc or larger does receive a dose that is < 91% of its prescribed dose.

6.2.8 Critical Structures

Per Protocol

- Bowel: no more than 30% of the volume of the bowel to receive a dose that is greater than 40 Gy. No volume within bowel that is 0.03 cc or larger receives a dose that is > 110% of the prescription dose.
- Rectum: no more than 60% of the volume of the rectum to receive a dose that is greater than 45 Gy. No volume within rectum that is 0.03 cc or larger receives a dose that is > 110% of the prescription dose.
- Bladder: no more than 35% of the volume of the bladder to receive a dose that is greater than 45 Gy. No volume within bladder that is 0.03 cc or larger receives a dose that is > 110% of the prescription dose.
- 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

Variation Acceptable

- Bowel: A volume of 30% of the bowel does receive a dose that exceeds 40 Gy but does not exceed 45 Gy. A volume of 0.03 cc or larger of bowel exceeds 110% of the prescribed dose but remains at or below 115%.
- Rectum: A volume of 60% of the rectum does receive a dose that exceeds 45 Gy but does not exceed 50 Gy. A volume of 0.03 cc or larger of rectum exceeds 110% of the prescribed dose but remains at or below 115%.
- Bladder: A volume of 35% of the bladder does receive a dose that exceeds 45 Gy but does not exceed 50 Gy. A volume of 0.03 cc or larger of bladder exceeds 110% of the prescribed dose but remains at or below 115%.

Deviation Unacceptable

- Bowel: A volume of 30% of the bowel does receive a dose that is > 45 Gy. A volume of 0.03 cc or larger of bowel exceeds 115% of the prescribed dose.
- Rectum: A volume of 60% of the bowel does receive a dose that is > 50 Gy. A volume of 0.03 cc or larger of rectum exceeds 115% of the prescribed dose.
- Bladder: A volume of 35% of the bladder does receive a dose that is > 50 Gy. A volume of 0.03 cc or larger of bladder exceeds 115% of the prescribed dose.

Note: All required structures must be labeled for digital RT data submission as listed in the table below. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

The following table outlines the naming of normal and critical structures for submission to **TRIAD.**

STANDARD

Structure	DICOM name	Description
ITV	ITV	The volume of the vagina that is in both the empty and full bladder CT scans that are done at the time of simulation and fused together (the combined volume).
CTVLN	CTVn	Nodal CTV
PTVLN	PTVn	
CTV VAG	CTVp	Vaginal CTV

STRUCTURE NAMES for TRIAD SUBMISSION

PTV VAG	PTVp	Vaginal PTV
Bladder	Bladder	
Rectum	Rectum	
Left Femur	Femur_L	
Right Femur	Femur_R	
Small Bowel	BowelSpace	It includes the volume surrounding loops of small bowel out to the edge of the peritoneum
Left Kidney	Kidney_L	
Right Kidney	Kidney_R	
Spinal Cord	SpinalCord	
Unspecified Tissue	External	

6.3 Intracavitary Radiotherapy Technique and Dose Specifications (optional treatment)

6.3.1 If vaginal brachytherapy boost is given, it must follow the external beam irradiation and be started within 7 days of completion of the pelvic irradiation. If high-dose rate applications are to be used, the insertions should be given in such a way to allow completion of the insertion prior to the beginning chemotherapy. More than one insertion may be performed per week. External beam radiation and intracavitary treatment should not be given on the same day. Iridium or cesium sources are to be used for intracavitary application with vaginal applicators for the after-loading applicator system.

6.3.2 It is preferable to treat the vaginal cuff only (treatment of the entire length of the vagina is discouraged and may increase morbidity). Not more than 2/3 of the vagina should be included in the treatment volume. Colpostats/ovoids or cylinders may be used.

6.3.3 For low-dose rate applications, 20-25 Gy (depending on the final external beam dose) to the vaginal surface in a single application will be given. For high-dose rate applications, 12-18 Gy to the vaginal surface in 2 to 3 applications (depending on the final external beam dose as described below) will be given.

For low-dose rate applications: A dose of 20-25 Gy will be prescribed to the vaginal surface at a dose rate of 0.8 to 1.2 Gy per hour (see Appendix IV). Final dose is determined by the final dose of the external beam; if 45 Gy if given, then 25 Gy to the vaginal surface should be delivered and if 50.4 Gy is given, then the dose delivered should be 20 Gy. Colpostats or cylinders may be used. The largest possible cylinder diameter should be selected. Colpostats should be secured with maximal packing to minimize dose to the adjacent bladder and rectum.

For high-dose rate applications: Two to three applications of 6 Gy each will be prescribed to the vaginal surface, for a total of 12-18 Gy. Dose will be prescribed at

the vaginal surface (see Appendix IV). If treating to a pelvic dose of 45 Gy, the dose to the vaginal surface should be 18 Gy in 3 fractions; if treating to a dose of 50.4, the dose to the vaginal surface should be 12 Gy in 2 fractions.

6.3.4 A Gynecological Brachytheraphy Protocol Compliance Form report on the source specifications, strengths, spacing relative to the applicators, size of applicator, and dosimetry calculations for all points is MANDATORY. The source employed must be in the directory used by IROC Houston. Dwell times and dwell positions for all HDR insertions are also required. For all films that are submitted, the points of dose calculations should be marked on the film (vaginal surface points) as well as bladder and rectal points if calculated. If cylinders are used and source specification and applicator size does not change, dose distributions may be made on only the first cylinder if desired. Dose to the vaginal surface from ovoid (colpostat) should include contribution from both ovoids.

- Vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the ovoid or cylinder. See Appendix IV.
- If a cylinder is used, the dose at the apex of the cylinder should be calculated to be as close as possible (within +/- 25%) to the lateral vaginal surface dose. Dose points 0.5 cm posterior and anterior to the cylinder or colpostat should be calculated.

6.4 Compliance Criteria for Brachytherapy

6.4.1 Per Protocol: See Section 6.3.1

6.4.2 Variation Acceptable: Brachytherapy starting within 7 days from the completion of external beam RT.

6.4.3 Deviation Unacceptable: Brachytherapy starting after 14 days from the completion of external beam RT.

6.5 R.T. Quality Assurance Reviews (8/21/14)

The Radiation Oncology Chair, Anuja Jhingran, MD (or NRG Oncology approved designee), will perform RT Quality Assurance Rapid Reviews on the first case from each site before the start of treatment. The next four cases submitted within one-week of RT planning will be performed as "Timely Reviews" (RT may begin and accrual continue before review feedback on these timely reviews). The remaining cases will be reviewed on an ongoing basis.

6.6 Radiation Therapy Adverse Events

Adverse effects expected from radiotherapy include tiredness near the end of treatment, diarrhea, nausea and vomiting, rectal irritation, urinary frequency and dysuria, loss of pubic hair, reddening and irritation of the skin in the irradiated field, and depression of blood counts. Long-term side effects, although uncommon, may include chronic malabsorption, rectal ulcer, bleeding, or stricture, dysuria, hematuria, bowel obstruction, shortening of the vagina, dyspareunia, vaginal vault necrosis and fistula formation between pelvic tissues. If the para-aortic nodes are treated, additional side effects include possible long-term kidney damage leading to dialysis and spinal cord damage leading to paralysis.

6.7 Radiation Therapy Adverse Event Reporting

See Section 7.0.

6.8 Weekly Portal Images

All participating institutions in either IMRT or Standard arm of the trial must digitally submit the first set of weekly portal images (every five treatment fractions) of all treatment films, a set taken in the middle of the external beam course, and the final set of weekly portal images in JPEG format. These images can come either from EPIDs or scanned Portal films. For data submission please refer to section 12.2

7.0 DRUG THERAPY

Protocol treatment must begin within 70 days after surgery.

7.1 Treatment (8/21/14)

All patients will receive concurrent chemotherapy with weekly cisplatin intravenously during external beam radiation therapy for a total of 6 cycles. Patients randomized to the chemotherapy treatment arm (Arm 2) will receive paclitaxel and carboplatin once every 21 days for 4 cycles, to start 4 to 6 weeks following completion of chemoradiation.

7.1.1 Concurrent Chemoradiation

	Drug	Dose	Schedule
Arm 1	Cisplatin	40 mg/m^2, maximum dose 70 mg	IV weekly over 1 hour, during external beam radiation x 5-6 weeks (see Section 7.1.1.3 for administration details)
Arm 2	Cisplatin	40 mg/m^2, maximum dose 70 mg	IV weekly over 1 hour, during external beam radiation x 5-6 weeks (see Section 7.1.1.3 for administration details)

Dose Calculation: The dose will be calculated using actual body weight. The dose will be recalculated if there is a weight change of >10% from baseline.
Preparation: Patients will receive pre- and post-hydration per institutional guidelines. Pre-medications can be given at the discretion of the treating physician. Cisplatin injection should be further diluted in 0.9% sodium chloride or 5% dextrose and 0.25% to 0.5% sodium chloride injection (Do not dilute in just 5% Dextrose Injection) and administered within 24 hours.

Administration: Cisplatin will be administered once a week (starting on Monday or Tuesday, day 1 or 2) during external beam therapy (days 1, 8, 15, 22, 29, 36 or days 2, 9, 16, 23, 30, 37). Cisplatin can be given before or after radiation.

7.1.2 Adjuvant Chemotherapy

Patients randomized to the chemotherapy arm should start chemotherapy 4-6 weeks following completion of radiation therapy.

	Drug	Dose	Schedule
Arm 1	No treatment	No treatment	No treatment
Arm 2	Paclitaxel	135 mg/m^2, maximum dose at BSA 2.0 m^2	IV over 3 hours, every 21 days x 4 (see Section 7.1.2. for administration details)
	Carboplatin	AUC 5	IV over 30 mins, every 21 days x 4 (see Section 7.1.2. for administration details)

Paclitaxel

Dose Definition

The dose of paclitaxel is 135 mg/m^2, with maximum body surface area (BSA) of 2.0 m^2. The dose will be recalculated if there is a weight change of ≥10% from baseline.

Preparation

The regimen can be administered in an outpatient setting. Paclitaxel will be administered in a 3-hour infusion followed by carboplatin over 30 minutes. Paclitaxel will be administered via an infusion control device (pump) using non-

PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin)which are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered. An antiemetic regimen is recommended. The antiemetic regimen used should be based on peer-reviewed consensus guidelines per institutional protocol. It is recommended that a preparative regimen be employed to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine) given prior to administration of paclitaxel.

Administration

Paclitaxel 135 mg/m^2, 3-hour infusion, Day 1, q 21 days, administered prior to carboplatin

Patients randomized to the chemotherapy arm should start treatment within 4, but no longer than 6, weeks following completion of radiation therapy.

Carboplatin

Dose Definition

The dose of carboplatin is area under the curve (AUC) 5. The dose will be calculated to reach a target area under the curve (AUC) of concentration x time according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

The initial dose of carboplatin must be calculated using GFR. In the absence of new renal obstruction or other renal toxicity greater than or equal to CTCAE v. 4.0 grade 2 (serum creatinine >1.5 x ULN), the dose of carboplatin **will not** be recalculated for subsequent cycles, but will be subject to dose modification as noted.

Carboplatin doses will be based on the subject's weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of ≥ 10% from baseline.

In patients with an abnormally low serum creatinine (less than or equal to 0.7 mg/dl), due to reduced protein intake and/or low muscle mass, the creatinine clearance should be estimated using a minimum value of 0.7 mg/dl. If a more appropriate baseline creatinine value is available within 4 weeks of treatment that may also be used for the initial estimation of GFR. When concerned about the safety in a specific patient, measure GFR.

Calvert Formula: Carboplatin dose (mg) = target AUC × (GFR +25).

Note: the GFR in the Calvert formula should not exceed 125ml/min

Maximum carboplatin dose (mg) = target AUC (mg/ml) x 150 ml/min.

The maximum allowed doses of carboplatin in the study are:

AUC 5 = 750 mg
AUC 4 = 600mg

For the purposes of this protocol, the GFR is considered equivalent to the creatinine clearance. The creatinine clearance (Ccr) is estimated by the method of Cockcroft-Gault using the following formula:

Creatinine Clearance (mL/min) = [140-Age(years)] x Weight (kg) x 0.85
72 x serum creatinine (mg/dl)

NOTES:

1).Weight in kilograms:
In general, actual weight should be used for estimation of GFR. However it is also acceptable to utilize ideal weight, when concerned about safety in a specific patient, in accordance with local institutional policy. An example of a commonly employed ideal weight calculation is:
Ideal weight (kg) = (Height (cm)/2.54) – 60) x 2.3) + 45.5
2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor)
3) Conversion of IDMS creatinine levels to "non-IDMS" values will no longer be performed.

Preparation
Carboplatin will be reconstituted in 5% dextrose in water or 0.9% sodium chloride to produce a carboplatin concentration of 10 mg/ml.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.
Administration
Carboplatin AUC of 5 over 30 minutes, Day 1, q 21 days for 4 cycles, administered after paclitaxel.

Patients randomized to the chemotherapy arm should start treatment within 4, but no longer than 6, weeks following completion of radiation therapy.

7.2 Cisplatin Agent Information

Refer to the package insert for comprehensive pharmacologic and safety information.

7.2.1 Description, Packaging, and Storage

Cis-diamminedichloroplatinum (cisplatin) is a heavy metal complex and is water soluble. It mechanism of action is a bifunctional alkylating agent. Cisplatin is packaged as a sterile aqueous solution, each mL containing 1 mg cisplatin and 9 mg sodium chloride. Cisplatin is supplied in multidose vials with 50 mg and 100 mg of cisplatin. Store at 15-20°C. Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

NOTE: Aluminum reacts with cisplatin causing precipitation formation and loss of potency; therefore, needles, or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

7.2.2 Supply

Commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.2.3 Adverse Effects

Allergy: Allergic reactions
Gastrointestinal: Nausea and vomiting
Hematologic: Myelosuppression, anemia, thrombocytopenia

Metabolic: Electrolyte imbalance, hypocalcemia, hypomagnesemia
Neurologic: Peripheral neuropathy
Ocular/Visual: Ocular toxicity
Ototoxicity: Aminoglycoside ototoxicity

(Infrequent)
Acute myeloid leukemia
Dermatologic: Rash
Gastrointestinal: Anorexia
Hepatic: Elevated SGOT
Renal: hemolytic uremic syndrome
Other: Alopecia, Metallic taste

Severe renal toxicity can be largely avoided by induction of a diuresis before, during, and after treatment. Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy if BUN > 30 mg/dl or creatinine > 2.0 mg/dl develop. Mild or severe electrolyte abnormalities may occur *(5%)* as acute or chronic complications, especially hypokalemia or hypomagnesemia. Monitoring of electrolytes and electrolyte replacement will usually correct these abnormalities. Rarely, severe hypomagnesemia and hypocalcemia may require replacement therapy and discontinuation of treatment with cisplatin. Allergic reactions are rare. If accompanied by respiratory symptoms, allergic reactions require discontinuation of treatment. Patch or skin tests are recommended for patients with suspected allergy to cisplatin. An emergency set for the treatment of allergic reactions should be available in the treatment area. Local necrosis and thrombophlebitis can be avoided by careful administration. Neurotoxicity is related to cumulative dose and severe toxicity can be largely avoided by careful monitoring for evidence of paresthesias and timely discontinuation of treatment. Ataxia has been described. Ototoxicity may occur.
NOTE: Eighth *(VIII)* nerve toxicity resulting in hearing loss and *(less commonly)* vestibular symptoms, is a well-documented complication of cisplatin treatment and is usually related to total cumulative dose. It is advised that patients placed on cisplatin, whether as a single agent therapy or combination, be questioned concerning hearing loss. Patients with a history of hearing loss should be considered for pre-treatment audiometry with follow-up audiometry as clinically indicated. It is recommended that patients be queried concerning hearing loss before each course of cisplatin.

7.3 Carboplatin Agent Information

Refer to the package insert for comprehensive pharmacologic and safety information.

7.3.1 Description, Packaging, and Storage

Carboplatin is supplied as a sterile lyophilized powder available in single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol. Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, carboplatin solutions are stable for eight hours at room temperature, since no antibacterial preservation is contained in the formulation it is recommended that carboplatin solutions be discarded eight hours after dilution.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles, or intravenous sets containing aluminum parts that may

come in contact with the drug must not be used for the preparation or administration of carboplatin. Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

7.3.2 Supply

Commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.3.3 Adverse Effects

Allergy: Allergic reaction
Gastrointestinal: Nausea and vomiting
Hematologic: Myelosuppression
Hepatic toxicity: Mild elevations in bilirubin, SGOT, and alkaline phosphatase levels.
Metabolic: Electrolyte imbalance, hypomagnesemia, hypocalcemia
Neurologic: Peripheral neuropathy
Ototoxicity
Ocular/Visual: Ocular toxicity

7.4 Paclitaxel Agent Information

7.4.1 *Refer to the package insert for comprehensive pharmacologic and safety information.*
Description, Packaging, and Storage

Paclitaxel is a poorly soluble plant product from western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. It is also available in 100 and 300mg vials. Paclitaxel, at the appropriate dose, will be diluted in 500-1000 cc of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D5W) (500 cc's is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of Taxol. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic microporous filter of pore size not greater than 0.22 microns (e.g. IVEX-II, IVEXHP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used. The intact vials can be stored in a temperature range between 2-25oC (36-77°F). Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

7.4.2 Supply

Commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.4.3 Adverse Effects

Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
Blood pressure: Hypotension, hypertension (possibly related to concomitant medication--dexamethasone)
Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis
Heart: arrhythmia, heart block, ventricular tachycardia, myocardial infarction(MI), bradycardia, atrial arrhythmia
Hematologic: Myelosuppression

Liver: Increased SGOT, SGPT, bilirubin and alkaline phosphatase, hepatic failure, hepatic necrosis
Neurologic: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy
Pulmonary: Pneumonitis
Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, radiation recall reactions
Other: Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy
Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata

7.5 Dose Modifications (8/30/12)

7.5.1 Chemoradiation Therapy with Weekly Cisplatin

No chemotherapy will be given until all drug-related toxicities, except anemia, > grade 2 have resolved to grade 1. There will be no dose escalations in this study. Chemotherapy will not be administered during a radiation therapy delay. Radiotherapy will not be omitted or delayed for chemotherapy-related toxicities unless the investigator considers the patient too ill to be treated.

Initial treatment modifications will consist of cycle delay and/or dose reduction as directed. Treatment decision will be based on absolute neutrophil count (ANC) not total white blood cell count (WBC). No cisplatin will be administered or resume until ANC is ≥1500 cells/m^3 and/or platelet count is ≥ 75,000 cells/m^3. Chemotherapy will be delayed week-by-week until these levels are exceeded. External radiation should continue while cisplatin is being held. Patients who fail to recover from toxicities within 21 days will not receive further protocol-directed therapy. Only one dose reduction is allowed for cisplatin.

Table A. Dose Level Modifications

Drug	Starting dose level	Dose level -1
Cisplatin	40 mg/m^2 (70 mg maximum)	30mg/m^2 (60 mg maximum)

CONCURRENT TREATMENT

TOXICITY	PARAMETER	MODIFICATION
Febrile neutropenia/ANC	1st occurrence febrile neutropenia (≥ grade 3) or ANC <500 mm^3 lasting >7 days	Hold for that week. Repeat CBC. If ANC resolves to grade 1, resume at 1 dose level reduction. If ANC does not resolve to grade 1, discontinue chemotherapy.
Febrile neutropenia/ANC	2nd occurrence	Discontinue cisplatin.
ANC	Uncomplicated (no fever/infection) <500 mm^3 lasting <7 days	No dose reduction.
Platelets	1st occurrence grade 4 thrombocytopenia or bleeding associates w/ grade 3 thrombocytopenia	Hold for that week. Repeat blood work. If platelets >75,000 cells/mm^3, resume at 1 dose level reduction. If platelets do not resolve to grade 1, discontinue cisplatin.
	2nd occurrence	Discontinue cisplatin.
	Grade 3 – uncomplicated	Hold until platelets > 75,000 cells/mm^3.

	(absence of associated bleeding)	Resume at current dose level (no dose modification).
Nausea/vomiting	Grade 4	Once resolved to grade 1 with supportive therapy, resume and reduce by 1 dose level.
	2nd occurrence	Discontinue cisplatin.
Serum creatinine	>2.0 mg/dl	Hold 1 week. Repeat blood work. Resume if creatinine resolves to less than institutional ULN within 1 week. Discontinue if not recovered after 1 week.
Neurotoxicity-peripheral neuropathy	Grade 2	Hold cisplatin until neuropathy resolves to grade 1, then resume at 1 dose level reduction. If neuropathy does not resolve to grade 1, discontinue chemotherapy.
	≥ Grade 3	Hold until grade 1. Resume at 1 dose level reduction.
Hearing loss	Symptomatic	Discontinue cisplatin.
Fatigue	Any grade	No dose reduction.
Other non-hematologic toxicity	≥ Grade 3	Hold until grade 1. If delayed >21 days, discontinue cisplatin.

7.5.2 Adjuvant Chemotherapy with Paclitaxel and Carboplatin

The adjuvant treatment course will not begin until all toxicities, except anemia, ≥ grade 2 have resolved to grade 0 or 1. There will be no dose escalations in this study.

Initial treatment modifications will consist of cycle delay and/or dose reduction as directed. Treatment decisions will be based on absolute neutrophil count (ANC) not the total white blood cell count (WBC). No treatment course will begin or resume until ANC is ≥ 1500 cells/mm^3 (CTCAE grade 1) and platelet count is ≥ 100,000/mm^3. Treatment will be delayed for a maximum of 21 days until values are achieved. A patient who fails to recover adequate counts in the 21-day period will not receive protocol-directed chemotherapy. Exceptions to the above statement are patients who received G-CSF prior to the current cycle; these patients will be allowed to receive chemotherapy with ANC ≥ 1000 cells/mm^3. Also, patients who are delayed more than 7 days for hematologic toxicity may begin with ANC ≥1000 cells/mm^3, as they will receive G-CSF during the subsequent therapy (See Section 9).

Delayed Hematologic Recovery

If ANC is less than 1,500 cells/mm^3 (CTCAE grade 2 or worse) within 24 hours prior to chemotherapy, or 1000 cells/mm^3 if the patient received G-CSF during the previous cycle, therapy will be delayed. If platelet count is less than 100,000 cells/mm^3 within 24 hours prior to chemotherapy, therapy will be delayed. Patients who have a >7 day delay in recovery of ANC to greater than 1000 cells/m^3 will receive G-CSF with the next cycle. Treatment will be delayed for a maximum of 21

days until values are achieved. Patients who fail to recover adequate counts in the 21-day period will not receive protocol-directed chemotherapy.

Paclitaxel Hypersensitivity Reaction

Hypersensitivity reactions during administration of paclitaxel usually occur in the first few minutes of infusion. Appropriate symptomatic therapy should be given per the treating physician institution's protocol. Consideration for continued treatment should be given if the reaction is not considered life threatening. If the patient decides to continue treatment, it is preferable to re-treat that same day. A suggested re-treatment would be to administer the drug first with 1 cc of the original IV solution diluted in 100 cc over 1 hour, then 5 cc in 100 cc over 1 hour, then 10 cc in 100 cc over 1 hour and finally the original solution at the normal speed. Patients who elect not to have immediate (same day) re-treatment of paclitaxel may be given just carboplatin only that day, but they would be candidates for paclitaxel hypersensitivity rechallenge at the next cycle per their institution's protocol.

Table B. Dose Level Modifications

Drug	Starting dose level	Dose Level -1
Paclitaxel	135 mg/m^2	110 mg/m^2
Carboplatin	AUC 5 (750 mg or less)	AUC 4 (600 mg or less)

ADJUVANT TREATMENT

TOXICITY	PARAMETERS	MODIFICATION Refer to Section 7.5.2 for resumption details
Febrile neutropenia/ ANC and platelets	1st febrile neutropenia or ANC <500 mm^3 lasting >7 days AND grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding	Reduce carboplatin 1 dose level
	2nd	Reduce paclitaxel 1 dose level and add G-CSF
	3rd	Discontinue protocol therapy.
Febrile neutropenia/ ANC only	1st occurrence febrile neutropenia or ANC<500 mm^3 lasting >7 days	Reduce carboplatin 1 dose level
	2nd occurrence	Reduce paclitaxel 1 dose level and add G-CSF
	3rd occurrence	Discontinue protocol therapy.
Neutropenia	Grade 4 uncomplicated (no fever/infection) lasting <7 days	No dose modifications.
Platelets only	1st occurrence grade 4	Reduce carboplatin 1 dose level
	2nd	Reduce paclitaxel 1 dose level
	3rd	Discontinue protocol therapy.
	1st occurrence grade 3	Reduce carboplatin 1 dose level

	associated with bleeding	
	2nd	Reduce paclitaxel 1 dose level
	3rd	Discontinue protocol therapy.
	Grade 3 uncomplicated (absence of associated bleeding)	No dose modifications.
GI	Any grade	No dose modifications.
Serum creatinine	≥Grade 2 (less than 2.0 mg/dl)	Hold treatment; when recovered to grade 1, resume, reducing carboplatin 1 dose level. If not recovered to ≤grade 1 within 21 days, discontinue protocol therapy.
	>2.0 mg/dl	Hold treatment. Calculated creatinine clearance must be obtained. If <50 ml/min, hold treatment and get weekly CalCcr until level is >50 ml/min. Then resume treatment, reducing carboplatin 1 dose level. If after 21 days the CalCcr is still <50 ml/min or serum creatinine is >2.0 mg/dl, discontinue protocol therapy and notify study chair.
	≥Grade 3	Notify study chair.
Neurotoxicity-peripheral neuropathy	≥Grade 3	Reduce paclitaxel and carboplatin 1 dose level and delay subsequent therapy for up to 21 days until recovered to grade 1. If not recovered within 21 days, discontinue protocol therapy.
	2nd occurrence	Discontinue protocol therapy.
SGOT/SGPT/alkaline phosphatase	≥Grade 3	Hold treatment; when recovered to ≤grade 1 resume, reducing paclitaxel 1 dose level. If not recovered to ≤grade 1 within 21 days, discontinue protocol therapy.
Bilirubin	≥Grade 3	Hold treatment; when recovered to ≤grade 1 resume, reducing paclitaxel 1 dose level. If not recovered within 21 days, discontinue protocol therapy.
Alopecia, fatigue, myalgias	Any grade	No modification.
Other non-hematologic toxicity	≥Grade 3	Hold treatment until recovered to grade 1. If not recovered to ≤grade

		1 within 21 days, discontinue protocol therapy.

7.6 Modality Review

The Medical Oncology Co-Chair, Heidi Gray, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Gray will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology. Dr. Gray will perform the next review after complete data for the next 20 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.

7.7 Adverse Events (8/21/14)

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.
Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via either the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the RTOG Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.7.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.7.2 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.8 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table. Contact the CTEP-AERS Help Desk if assistance is required.

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;

- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- 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 medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.7.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.8 CTEP-AERS Expedited Reporting Requirements (8/21/14)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP web site,
https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet

connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the Additional Information section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Oncology dedicated SAE FAX, 215-717-0990.
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as "expedited reporting NOT required" must still be reported to fulfill RTOG safety reporting obligations. Sites must bypass the "NOT Required" assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies utilizing a Commercial Agent within 30 Days of the Last Administration of the Commercial Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the commercial agent (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:
None

8.0 SURGERY

All patients will undergo surgery for their cancer prior to enrolling in this protocol

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.2 Antiemetics should be given prior to and immediately after chemotherapy per the treating institution's protocol.

9.1.3 Anticoagulants: Patients may receive anticoagulation therapy as a prophylaxis treatment for venous thromboembolism.

9.1.4 Antidiarrheals may be administered per the treating institution's protocol.

9.1.5 Analgesics may be administered per the treating institution's protocol.

9.1.6 Hematopoietic Growth Factors and Protective Agents: *(**NOTE**: See Section 9.2.2 for non-permitted hematopoietic growth factors and protective agents)*
Patients may receive erythropoietin (EPO) for management of anemia AFTER documentation of hemoglobin less than 10g/dl (CTCAE grade 2). Patients may receive transfusion or iron supplements as clinically indicated. Patients may receive filgrastim (G-CSF) or PEG-filgrastim (Neulasta) if they demonstrate hematologic toxicity as outlined in Section 7.6.

9.1.7 Herbal Products: may be administered per the treating institution's protocol.
9.1.8 Nutritional Supplementation: may be administered per the treating institution's protocol.

9.2 Non-Permitted Supportive Therapy

9.2.1 Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible.

9.2.2 Hematopoietic Growth Factors and Protective Agents: (***NOTE**: See Section 9.1.6 for permitted hematopoietic growth factors and protective agents*)
Patients will NOT receive prophylactic filgrastim (G-CSF), PEG –filgrastim (Neulasta), or sargramostim (GM-CSF). Patients will NOT receive prophylactic thrombopoietic agents. Patients will NOT receive amifostine or other protective agents. [**NOTE**: If patients experience delays due to hematologic toxicity, hematopoietic growth factors are allowed as indicated as outlined in Section 7.6.]

9.3 Additional Considerations

Please see Section 7.2.3 for additional supportive care considerations related to cisplatin administration.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the tissue/specimen submission portion of the protocol. If the patient consents to participate in this component of the study, the site is required to submit the patient's specimens as specified below.

Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 General Information

The NRG Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The NRG Biospecimen Bank also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the NRG Biospecimen Bank for the purpose of tissue banking and translational research (recommended but not mandatory).

10.2 Fixed Tissue Specimen Collection for Banking and Translational Research (8/21/14)

For patients who have consented to participate in the tissue/blood component of the study

In this study, from FFPE tumor tissue we will isolate RNA and DNA to allow us to perform tumor tissue microarrays. We will also obtain FFPE tumor cores and create tissue arrays to allow us to perform immunohistochemistry for gene expression. Evaluation of tumor specimens and the possibility of creating a tissue array allows for easy simultaneous staining for proteins of interest and TUNEL staining for apoptosis. MicroRNA and gene expression utilizing microarray technology has been evaluated in a wide variety of neoplasms. Microarray technology allows for the simultaneous evaluation of hundreds of microRNAs and thousands of genes, creating a "snap shot" of the pathways activated in the tumor. The ultimate goal of these studies will be to identify tumor signatures that predict for patient outcomes such as toxicity, disease-free survival and overall survival. Better predictors of these factors before the initiation of treatment in the future could help guide treatment and create a "genetically tailored' treatment approach.

The following must be provided in order for the case to be evaluable for the Biospecimen Bank:

10.2.1 One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide (block); it does not have to be the diagnostic slide itself)

10.2.2 A corresponding paraffin-embedded tissue block of the tumor the block must match the H&E being submitted) or three 2-mm diameter cores of tissue, punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punches, tubes, and instructions can be obtained free of charge from the NRG Oncology Biospecimen Bank. Block or core must be clearly labeled with the pathology identification number and block ID that corresponds to the Pathology Report.

10.2.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number.

10.3 Peripheral Blood Collection for Banking and Translational Research (8/30/12)

In this study from serum and plasma we will be able to measure levels of secreted factors, antibodies, microRNAs, tumor cells etc., giving insight into both initial levels of these factors as well as levels at the end of treatment, to determine if levels determine toxicity or outcome at either timepoint. Whole blood analysis will allow us to have the patient normal DNA to perform studies such as SNP (single nucleotide polymorphism) studies in each patient. SNPs are inherited differences in a person's DNA. There is mounting evidence that SNPs in genes important in DNA repair (oncogenes etc.) might either predict for a genetic predisposition to tumor formation itself or response to cytotoxic therapy.

Serum and plasma for consenting subjects will be taken prior to treatment and at completion of chemoradiotherapy. Whole blood for DNA can be taken prior to treatment **OR** at completion of treatment.

10.3.1 Serum

- Use a Red top blood tube for serum collection.
- Keep serum collection tubes at 4° C until processing (tubes may be on ice up to 2 hrs).
- Centrifuge specimens at 1000 x g (approximately 2500 RPM for standard clinical centrifuge) at 4°C for 10 minutes.
- Using sterile techniques to avoid contamination, aliquot 0.5 mL serum into 5-10 1.0 mL cryovials and freeze at -80° C until ready to ship on dry ice.
- Take great care to collect only serum and avoid collecting any solid particulate matter into the cryovials.

10.3.2 Plasma

- Collect blood into one 3–5 mL purple-topped tubes (containing EDTA), using a 19–21 gauge needle to minimize hemolysis.
- Store blood tubes vertically at 4°C, avoiding any kind of agitation. Ideally these should be processed within 30 minutes.
- Centrifuge specimens at 1000 x g (approximately 2500 RPM for standard clinical centrifuge) at 4°C for 10 minutes.
- Take the top two-thirds of supernatant and aliquot to a 0.5 mL/vial into 5-10 mL cryovials. The tip of the transfer pipette should be kept far away (at least 0.5 cm) from the buffy coat (this is very important in order to avoid platelet contamination).
- Label each aliquot with study protocol and case numbers, the date and time of collection, and the time point taken, before or after treatment.

- Place specimens in -80° C freezer until ready to ship on dry ice.

10.3.3 Whole Blood

- Collect blood into one 5 mL purple-topped tubes (containing EDTA), using a 19–21 gauge needle to minimize hemolysis.
- Invert tubes to mix the whole blood and aliquot 1.0mL into up to 3-5 1mL cryovials.
- Store at -80° C until ready to ship on dry ice.

10.3.4 The above materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date and time of collection of the specimen; the NRG Oncology protocol number, the patient's case number, and method of storage, for example, stored at -80° C, must be included.

Collection Kits may be requested from the Biospecimen Bank at RTOG@ucsf.edu

10.4 Storage Conditions (8/12/10)

Store at –80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada: Mon-Tues).
  OR:
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only- Canada: Mon-Tues).
  OR:
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only- Canada: Mon-Tues).

Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

10.5 Submission Address (8/21/14)

Submit materials for banking and translational research as follows:

Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter St, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Trackable FFPE and ALL Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter St, Room S341
San Francisco, CA 94115

Questions: 415-476- 7864/FAX 415-476-5271; RTOG@ucsf.edu

10.6 Specimen Collection Summary (8/21/14)

Specimens taken from patient:	Collected when:	Submitted as:	Shipped:
Representative H&E stained slide of the	At surgery	H&E stained slide	Slide shipped ambient

primary tumor			
A paraffin-embedded tissue block of the primary tumor or three 2 mm diameter core of tissue, punched from the tissue block with a punch tool	At surgery	Paraffin-embedded tissue block or punch biopsy (must match the H&E slide being submitted)	Block or punch shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-treatment and at completion of chemotherapy	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Pre-treatment and at completion of chemotherapy	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/ lavender top) and mix	Pre-treatment **OR** at completion of chemotherapy. **NOTE** if site missed the collection site may collect this specimen at any timepoint or follow-up but this must be noted on the ST.	Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (three to five).	Whole blood sent frozen on dry ice via overnight carrier

10.7 Reimbursement (8/21/14)

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

10.8 Confidentiality/Storage (8/30/12)

(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.8.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.8.2 Specimens will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, remaining material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS (12/29/10)

11.1 Study Parameters: See Appendix I for a summary of assessments and time frames. Details and exceptions appear below

11.1.1 Audiogram will be performed for patients with a history of hearing loss and for patients who start to complain about ringing in the ear or hearing loss during treatment.

11.1.2 Pap smear should be performed at least yearly during follow-up but should follow the standard guidelines of the institution.

11.1.3 Chest x-ray/chest CT will be performed yearly during follow-up unless there is reason to perform it sooner.

11.1.4 A PET Scan or PET-CT will be performed pre or post-operatively for patients who do not undergo para-aortic lymph node or common iliac lymph node sampling/dissection or who have positive common iliac nodes during surgery but no para-aortic sampling (See section 3.1.1 of the protocol for details).

11.2 Efficacy Outcome Definitions

11.2.1 Local Failure: Cervical cancer recurrence; **biopsy confirmation is required.**

11.2.2 Regional Failure: Appearance or recurrence of pelvic nodes; **biopsy confirmation is required.**

11.2.3 Para-Aortic Nodal Failure: Appearance or recurrence of para-aortic nodes; **biopsy confirmation is required.**

11.2.4 Distant Metastases Failure: Appearance of distant metastases other than para-aortic nodes.

11.2.5 Disease-Free Survival Failure: Local, regional, para-aortic, distant metastases failure, or death due to any cause.

11.2.6 Overall Survival Failure: Death due to any cause.

11.3 Criteria for Discontinuation of Protocol Treatment

11.3.1 Appearance of recurrent disease.

11.3.2 Adverse events that require discontinuation of protocol treatment per protocol-specified dose modifications.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

11.4 Assessments for Quality of Life, Neuropathy, and Diarrhea (8/12/10)

NOTE: Patients must be offered the opportunity to participate in the Quality of Life/Neuropathy/Diarrhea portion of the study. If the patient consents to participate in this component of the study, the site is required to submit the patient's specimens as specified below.

Sites are not permitted to delete the Quality of Life/Neuropathy/Diarrhea portion from the protocol or from the sample consent.

For all patients participating in this portion of the trial, these tools will be collected at the following time points: baseline; end of concurrent chemoradiation; and 6, 12, and 24 months after the end of chemoradiation.

The FACT-CX has been translated into 14 languages; the FACT-GOG/NTX has been translated into 40 languages; and the FACIT-D is available in 17 languages. All are available free of charge to institutions with the completion of an agreement to share data, accessible http://www.facit.org/translation/licensure.aspx.

If a non-English form is used, it must be transcribed onto the English version of the form and submitted to NRG Oncology per Section 12. Both copies must be kept in the patient's files.

11.4.1 FACT-GOG/NTX4

The FACT-GOG/NTX4 is a patient-reported tool developed by the GOG to assess neuropathy. It is comprised of 4 items related to numbness or tingling in patients' extremities.

11.4.2 FACT-Cx

The FACT-Cx version 4 combines the components of the FACT-G (27 general items including the four domains of physical well-being, social and family well-being, emotional well-being, and functional well-being), with 15 additional items specific for symptoms and problems related to cervical cancer.

11.4.3 FACIT-D

The diarrhea-specific portion of the FACIT-D is comprised of 11 items.

12.0 DATA COLLECTION (04-FEB-2022)

Data should be submitted to:

NRG Oncology*
50 South 16th Street, Suite 2800 Philadelphia, PA 19102

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (8/21/14)

Item	Due
Demographic Form **(A5)**	Within 2 weeks of study entry
Initial Evaluation Form **(I1)**	Within 2 weeks of study entry
Treatment Form **(TF)**	Within 1 week of Chemo/RT completion
Treatment Form **(SF)- ARM 2 Patients Only**	Within 1 week of Adjuvant Chemo completion
Follow-Up Form **(F1)**	Every 3 months for the first 2 years, then every 6 months for 3 years, then annually. Also at progression/relapse and at death.
Surgical Operative Report **(S2)**	Within 2 weeks of study entry
Surgical Pathology Report **(S5)**	Within 2 weeks of study entry
Autopsy Report **(D3)**	As applicable
Quality of Life **(QL)**	Pre-treatment, at the end of concurrent treatment, and then at 6,12 and 24 months after concurrent treatment
Final Dosimetry Information:	
Radiotherapy Form **(T1) (copy to HQ)**	1 week after RT
Complete Daily Treatment Record **(T5) (copy to HQ)**	

12.2 Summary of Dosimetry Digital Data Submission (Submit TRIAD; see **Section 5.0** for account access and installation instructions) **(8/21/14)**

Item	Due
Preliminary Dosimetry Information (DD)	
Digital Data Submission – Treatment Plan submitted to TRIAD via TRIAD in DICOM format exported from treatment planning machine by Physicist	Within 1 week of start of RT
Digital data submission includes the following:	
• DICOM CT data, • DICOM Structure critical normal structures, all GTV, CTV, and PTV contours	
• DICOM Plan	
• DICOM Doses	
• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan • All required structures **MUST** be labeled per the Table in Section 6.2. • *The "RTOG 0724 Datasheet" is available in the Forms section of the of the NRG Oncology/RTOG web* site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0724 Submit via TRIAD with the digital data listed above.	
Upon submission of the digital data via TRIAD, complete an online digital data transmission form (DT) located in the Forms section on the NRG Oncology/RTOG web site at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0724	
Final Dosimetry Information	Within 1 week of RT end
Radiotherapy Form **(T1) [copy to HQ]** Daily Treatment Record **(T5) [copy to HQ]** Modified digital patient data as required through consultation with Image-Guided Therapy QA Center NOTE: Three sets of portal or isocenter verification images (beginning, middle of fractionated treatment and end) should be sent via TRIAD in jpg format. Institutions using Tomotherapy or relying on IGRT are required to send "screen captures" of the images used for verifying the patient's position.	

***Optional Brachytherapy data (see section 6.3)**

Submit to IROC Houston: Complete brachytherapy treatment planning data including digital images or films INCLUDING AP and LATERAL views.

Send by mail or FedEx to:
IROC Houston QA Center
8060 El Rio Street
Houston, TX 77054

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

Disease-free Survival (DFS) *(failure: local, regional or distant metastases failure or death due to any cause)*

13.1.2 Secondary Endpoints

- Adverse events
- Overall survival
- Chemotherapy-induced neuropathy as measured by FACT-GOG/NTX4
- QOL as assessed by FACT-Cx & FACIT-D
- Associations between tumor molecular signatures, from fixed tissue, and outcomes such as adverse events, disease free survival and overall survival
- Associations between secreted factors from serum and plasma with adverse events or outcome
- Associations between SNPs in genes from buffy coat and a genetic predisposition to tumor formation itself or a response to cytotoxic therapy

13.2 Sample Size (04-FEB-2022)

13.2.1 Stratification

Patients will be stratified before randomization with respect to intention to use brachytherapy (no vs. yes) and radiation therapy modality (standard RT vs. IMRT), and radiation therapy dose (45 vs. 50.4 Gy). The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution. Patients will be randomized to radiation given concurrently with weekly cisplatin and optional brachytherapy $\pm$ 4 additional cycles of carboplatin and paclitaxel.

13.2.2 Sample Size Derivation

The sample size calculations are based on the primary hypothesis that the addition of 4 cycles of carboplatin and paclitaxel following concurrent radiation and weekly cisplatin will increase 4-year disease-free survival from 80% to 90% for patients with cervical carcinoma with positive nodes and/or positive margins after a radical hysterectomy. The 4-year disease-free survival rate of 80% for the control arm is based on the Peters et al study. (2000)

Previous studies' including GOG-0109 suggest a significant proportion of patients on this study will be cured. Therefore, the control arm is assumed to follow the Gompertz ~ (γ, θ) survival probability distribution with initial hazard γ and hazard dissipation θ [2-4]. Equations [1,] [2,] and [3] list survival, hazard, and cure rate functions respectively under the Gompertz ~ (γ, θ) survival probability distribution assumption.

$$S(t) = \begin{cases} \exp\left(\frac{\gamma}{\theta}\left[1-\exp(\theta t)\right]\right) & \text{for } t \geq 0 \\ 0 & \text{elsewhere} \end{cases} \qquad [1]$$

$$h(t) = \begin{cases} \gamma \exp(\theta t) & \text{for } t \geq 0 \\ 0 & \text{elsewhere} \end{cases} \qquad [2]$$

$$\pi = \exp\left(\frac{\gamma}{\theta}\right) \qquad [3]$$

The parameter estimates $\hat{\gamma}_{\text{MLE}}$ and $\hat{\theta}_{\text{MLE}}$ were derived using the outcome data of the

GOG-0109 CRT arm, since this historic information came from patients whose disease and treatment profiles best mimics the control arm. As a result, the anticipated performance (primary endpoint) of this study's control arm was estimated by substituting the calculated $\hat{\gamma}_{\text{MLE}}$ and $\hat{\theta}_{\text{MLE}}$ into equation [1] at several time points. Similarly, using equation [3] the expected cure rate ($\hat{\pi}_{\text{MLE}}$) for the control arm was deduced.

Derived parameter estimates and expected cumulative probability of recurrence (ECPR) for the control arm at 36, 48, and 60 months are listed in below:

Historic Data (GOG-0092 RT arm)			Control Arm					
			Time (months)	36	48	60	96	120
0.0072	-0.0212	0.7120	ECPR	0.1658	0.195	0.2169	0.2557	0.2687

Figure 1 shows superimposed plots of the expected and empirical cumulative probability of disease recurrence consistent with the estimated Gompertz model (solid curve) and the outcome data from GOG-0109 CRT arm (dash curve), respectively.

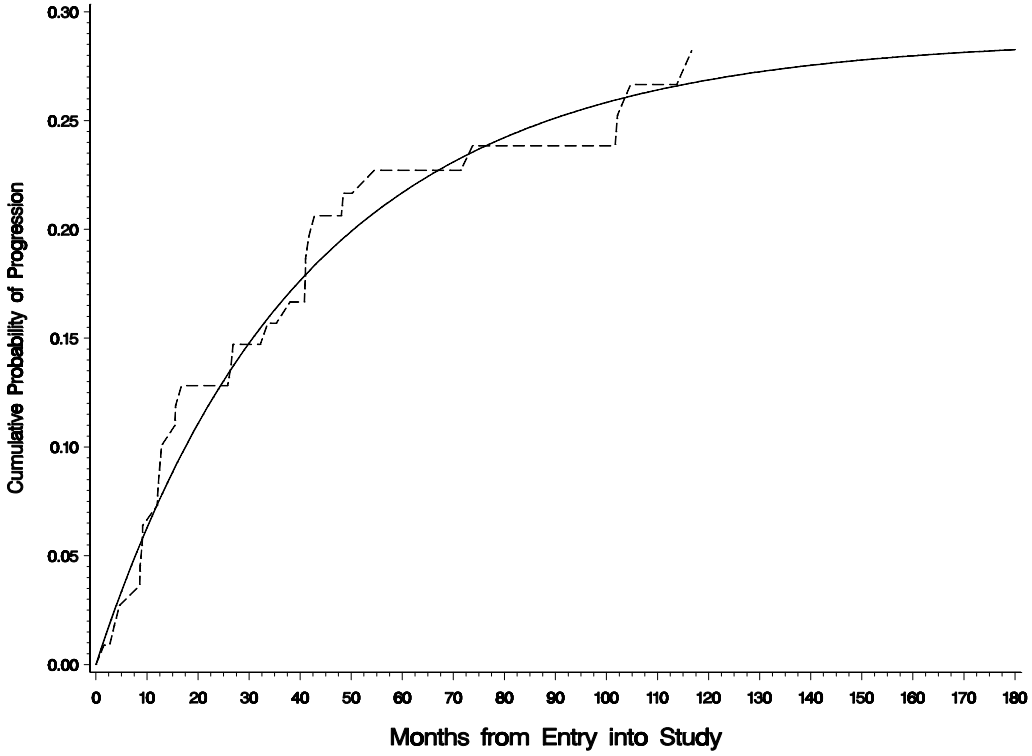

Figure 1

The required sample size for the primary endpoint of disease-free survival is based on the following conditions:

- Survival times follow the Gompertz distribution with (at least approximately) constant hazards in both treatment arms
- The control arm (Arm 1) will have a 4-year disease-free survival of 80%
- The experimental arm (Arm 2) will have a 4-year disease-free survival of 90%, which corresponds to a hazard ratio (λ_2/λ_1) = 0.4722

- 1-sided test at $\alpha = 0.05$
- Statistical power of 80%
- 5.5 years of accrual with 4 years of follow-up
- 2 interim significance tests and a final test are planned using the Lan-DeMets spending function (Lan 1983) for rejecting the null hypothesis (efficacy) and Rule C in Freidlin and Korn, (Freidlin 2002) for rejecting the alternative hypothesis (futility)

Using the group sequential design method (Pocock 1997) with 2 interim analyses, 50 disease-free survival failure events are required to detect an absolute disease-free survival benefit of 10%, translating into a hazard ratio of 0.47 (experimental/control). Given the conditions above, 272 evaluable patients will be required to be accrued uniformly over 5.5 years with an additional 4 years of follow-up. Guarding against an ineligibility or lack-of-data rate of up to 5%, **the final targeted accrual for this study will be 285 patients**.

Revised Targeted Accrual

Due to the slower than projected accrual, the required 50 DFS events will be able to be reached with a final targeted sample size of 235 patients. There are no changes being made to the parameters driving the primary statistical design.

13.2.3 Statistical Power Information for Secondary Endpoints

Overall Survival

The 4-year overall survival rate for the control arm is expected to be approximately 85%. The overall survival will be compared between the two arms. The final targeted sample size of 235 patients with the longer accrual time, will provide 64% and 78% power to detect an increase in overall survival to 92% and 93% respectively, with a 1- sided alpha of 0.05.

Patient-Reported Outcomes

Overall quality of life, chemotherapy-induced neuropathy, and diarrhea will be assessed using the FACT-Cx, FACT-GOG/NTX4, and the FACIT-D respectively, all of which are patient-reported questionnaires. The FACT-Cx version 4 is comprised of 27 general items including the four domains of physical well-being, social and family well-being, emotional well-being, and functional well-being, as well as 15 additional items specific for symptoms and problems related to cervical cancer. The FACT-GOG/NTX4 is a patient-reported tool developed by the GOG to assess neuropathy. It is comprised of 4 items related to numbness or tingling in patients' extremities. The diarrhea-specific portion of the FACIT-D is comprised of 11 items.

The FACT-Cx, FACT-GOG/NTX4, and the FACIT-D will be collected at 6, 12 and 24 months following completion of concurrent chemoradiation. While participation is strongly encouraged, patients are not required to participate in these endpoints. It is anticipated that at least 80% of patients will agree to participate . With 188 evaluable patients, there will be at least 85% power to address the hypotheses listed below.

FACT-Cx

The primary hypothesis for the FACT-Cx is that there is no difference between the treatment arms in cervical cancer–specific QOL at 12 months. Cervical cancer-specific QOL at 6 and 24 months after the end of chemoradiation will also be evaluated.

FACT-GOG/NTX4

The primary hypothesis for neuropathy is that four additional cycles of chemotherapy following concurrent chemoradiation will not significantly adversely affect the chemotherapy-induced neuropathy at 12 months after

the end of chemoradiation. Neuropathy at 6 and 24 months after the end of chemoradiation will also be evaluated.

FACIT-D

The primary hypothesis for the FACIT-D is that there is no a difference between the treatment arms in diarrhea at 12 months. Diarrhea at 6 and 24 months after the end of chemoradiation will also be evaluated.

13.3 Patient Accrual (8/21/14)

Given that there will not be any major phase III studies competing for this patient population and participation from other cooperative groups through the CTSU mechanism, the patient accrual is projected to be 6 cases per month, with 3 cases per month expected in the first 3 "ramp-up" months following activation. The accrual is projected to be complete in 5.5 years. The total duration of the study is expected to be 9 years from the time the first patient is entered to the overall survival analysis. If the average monthly accrual rate during months 12-18 following activation is below 2 cases per month, the study statistician will recommend closure of the study to the RTOG Data Monitoring Committee (DMC), per the NCI guidelines for slowly accruing trials.

Revised Accrual **(8/21/14)**

The projected monthly accrual is being reduced to 3 cases per month. This accrual rate will be monitored and reassessed with NCI 1 year after this amendment is released.

13.4 Analysis Plan (8/21/14)

13.4.1 Statistical Methods

Disease-Free Survival: FS will be estimated by the Kaplan-Meier method (Kaplan 1958). The distribution of DFS estimates between the two arms will be compared using the log rank test. (Mantel 1966) DFS time will be measured from the date of randomization to the first date of DFS failure (local, regional or distant metastases failure or death due to any cause) or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with DFS. (Cox 1972)

Overall Survival: OS will be estimated by the Kaplan-Meier method. (Kaplan 1958) The distribution of OS estimates between the two arms will be compared using the log rank test. (Mantel 1966) Survival time will be measured from the date of randomization to the date of death or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with OS. (Cox 1972)

13.4.2 Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice a year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date *(while the study is still accruing)*
- total patients accrued
- distributions of important pretreatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm.
- compliance rates of treatment delivery

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, DFS, or any secondary endpoints.

13.4.3 Significance Testing for Early Termination and/or Reporting

Primary Endpoint: Disease-Free Survival

A group sequential test with 2 planned interim analyses and a final analysis will be performed. The timing of the interim analyses will be based on primary endpoint events as defined in 13.1.1. The maximum number of DFS failure events required for the trial is 50. Under the alternative hypothesis that the an additional 4 cycles of

carboplatin and paclitaxel will increase disease-free survival from 80% to 90% at 4 years, the projected numbers of DFS failure events and the nominal significance levels for rejecting the H_0 or the H_1 at each of these interim analyses, along with the projected timing and accrual, are shown in the table below:

Table 1: Nominal Significance Levels for Interim Analyses

Interim Analysis	Efficacy: Reject H_0 if p (H_0) ≤	Futility: Reject H_1 if Z (H_1) ≤	# Events
#1	≤ 0.0.0056	-0.69	25
#2	≤ 0.0.0229	-0.26	38

At each planned interim analysis, the 1-sided p-value from the log-rank test assessing treatment efficacy with respect to disease-free survival will be compared to the nominal significance levels in Table 1. These levels are based on the Lan-DeMets alpha spending function (Lan 1983) that behaves like the O'Brien-Flemming boundary. (O'Brien 1979) If the computed p-value for efficacy is less than or equal to the nominal significance level boundary for rejecting the H_0 (efficacy), then accrual to the trial will be stopped (if applicable), it will be concluded that the DFS rate of the experimental arm (Arm 2) is higher than that of the control arm (Arm 1), and the results will be reported. For futility, the alternative hypothesis will be tested using Rule C from Freidlin and Korn (Freidlin 2002) at the critical values stated in the above table. If the critical value is less than or equal to the nominal value boundary for rejecting the H_1 (futility), then accrual to the trial will be stopped (if applicable) and it will be reported that it cannot be concluded that the disease-free survival rate of the experimental arm (Arm 2) is higher than that of the control arm (Arm 1). If neither of these boundaries is crossed, accrual (if applicable) and follow-up will continue until the next interim or final analysis.

In addition to reporting results as listed in Section 13.4.2, at the first NRG Oncology DMC meeting following the required number of disease-free survival events for each planned interim analysis, blinded efficacy results will be reported to the NRG DMC.

13.4.4 Analysis for Patient-Reported Outcome Endpoints

The distributions of quality of life data collection patterns over all collection points in each treatment arm will be described. To inspect the missing data mechanism for each tool, at least a graphical method will be used. A missing completely at random (MCAR) mechanism exists when missing values are randomly distributed across all observations. A missing at random (MAR) mechanism exists when values are not randomly distributed across all observations, rather than one or more sub-samples.

If the cause of missing data is MCAR, listwise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then an imputation method such as multiple imputation will be applied to impute missing data.

If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline quality of life score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted and an imputation method such as multiple imputation will be applied. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR (missing not at random) must be addressed by an explicit model for the missing data mechanism and then an imputation method such as multiple imputation will be applied. All results from the imputed analysis using the multiple imputation will be compared to the complete case analysis results to assess any potential biases.

FACT-Cx

The 15 cervical cancer specific items on the FACT-Cx are scored from 0 to 4. More than half of the items must be answered to provide a valid score. Analysis of covariance, using the baseline FACT-Cx cervical cancer–specific score as a covariate, will be used to determine if there is a difference in cervical cancer–specific quality of life between the treatment arms.

FACT-GOG/NTX4

If the neuropathy score for the 4 additional cycles of chemotherapy is at least 2 standard errors of measure higher than for the control arm, it will be considered to significantly adversely affect the chemotherapy-induced neuropathy. The 4 items on the FACT-GOG/NTX4 are scored from 0 (none) to 4 (quite a bit). At least 3 of the items must be answered to provide a valid score. Analysis of covariance, using the baseline FACT-GOG/NTX4 score as a covariate, will be used to determine if the chemotherapy-induced neuropathy is significantly worse for the patients on the 4 additional cycles of chemotherapy treatment arm.

FACIT-D

The 11 diarrhea-specific items on the FACIT-D are scored from 0 to 4. More than half of the items must be answered to provide a valid score. Analysis of covariance, using the baseline FACIT-D diarrhea-specific score as a covariate, will be used to determine if there is a difference in diarrhea between the treatment arms.

13.4.5 Analysis for Reporting the Initial Treatment Results

The primary objective of this study is to determine whether the addition of 4 cycles of carboplatin and paclitaxel following concurrent radiation therapy and weekly cisplatin will increase 4-year disease-free survival from 80% to 90% for patients with cervical carcinoma with positive nodes and/or positive margins after a radical hysterectomy. This major analysis will occur after at least 50 total failures have been observed, unless an early stopping rule is satisfied. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rate of treatment delivery
- observed results with respect to the primary and secondary endpoints

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit will be tested using the log-rank statistic with a 1-sided significance level of 0.0424, given that the 2 interim analyses were carried out per Section 13.4.3.. Additional analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factor of intention to use vaginal cuff boost included as a fixed covariate, as well as other possible modifying factors, such as age, gender, race, and other patient characteristics that are imbalanced between the treatment arms. If feasible, treatment comparisons with respect to the primary endpoint (disease-free survival) will be compared within each ethnic and racial category.

13.4.6 CDUS Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.7 Post-Hoc Dose-Volume Analysis

The collection of 3D volume data sets for all patients will allow for a central contouring of the vagina and pelvic lymph nodes. If the distribution of patients being treated with standard RT and IMRT allows, this data will then be used to perform a post-hoc dose-volume analysis comparing standard RT and IMRT with respect to toxicity and local control.

13.5 Inclusion of Minorities (21-SEP-2022)

Women of all races and ethnic groups are eligible for this study. In conformance with the national Institutes of Health *(NIH)* Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between race/ethnicity and treatment. Based on the Peters study (2000), it is projected that 14% will be of Hispanic or Latino ethnicity; racial distribution are projected to be 73% White, 23% are Black or African American and 4% Asian. The following table lists the projected accrual by ethnic and racial categories.

DOMESTIC

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	2	0	0	0	**2**
Asian	6	0	0	0	**6**
Native Hawaiian or other Pacific Islander	0	0	0	0	**0**
Black or African American	22	0	4	0	**26**
White	93	0	25	0	**118**
More than one race	1	0	2	0	**3**
TOTAL	**124**	**0**	**31**	**0**	**155**

FOREIGN

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	0	0	0	0	**0**
Asian	72	0	0	0	**72**
Native Hawaiian or other Pacific Islander	0	0	0	0	**0**
Black or African American	0	0	0	0	**0**
White	8	0	0	0	**8**
More than one race	0	0	0	0	**0**
Not Reported	0	0	0	0	**0**
TOTAL	**80**	**0**	**0**	**0**	**80**

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APPENDIX I (9/22/14)
STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS

Assessment	**Time Points**			
	≤ 90 days prior to study entry	**≤ 70 days prior to study entry**	**≤ 56 days prior to study entry**	**≤ 14 days prior to study entry**
Radical hysterectomy/ node sampling		X		
History/physical			X	
Height, weight, BSA			X	
Pelvic exam			X	
Performance status			X	
Contrast-enhanced CT or MRI of the abdomen and pelvis (if whole body PET-CT not done)	X See section 11.1			
Chest x-ray/CT (if whole body PET-CT not done)		X See section 11.1		
Whole-body PET-CT scan (optional)	X			
CBC w/ diff & ANC, plt, Hgb				X
Serum creatinine, bilirubin, alk phos plus AST/SGOT and/or ALT/SGPT				X
Serum calcium, magnesium, Na,K, CL, CO2, BUN, creatinine, glucose				X
Audiogram				X See section 11.1
CD4 count (for patients known to be HIV positive)				X
Informed Consent	Prior to study entry			
Quality of Life (for consenting patients)			X	
Tissue (for consenting patients)		X		
Blood for serum and plasma (for consenting patients)		X		
Whole Blood for DNA (for consenting patients)		X See section 10.6		

APPENDIX I
STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT

Assessment	**Time Points**			
	Day 1-56: Weekly	Day 57-140: q Course	≤ 14 days of patient-reported symptoms	At end of concurrent chemoRT
History/physical	X	X		X
Height, weight, BSA	X	X		
Pelvic exam				X
Performance status	X	X		
CBC w/ diff & ANC, plt, Hgb	X	X		
Serum calcium, magnesium, Na,K, CL, CO2, BUN, creatinine, glucose	X	X		
Audiogram			X See section 11.1	
Adverse event eval	X	X		
Quality of Life (for consenting patients)				X
Tissue (for consenting patients)				X
Blood for serum and plasma (for consenting patients)				X

APPENDIX I
STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP

Assessment	**Time Points**		
	q 3 mo X 2 yrs, q 6 mo x 3 yrs & then yrly from treatment start	**Yrly from treatment start**	**At 6, 12, & 24 mos from completion of concurrent chemoRT**
History/physical	X		
Height, weight, BSA	X		
Pelvic exam	X		
Performance status	X		
Contrast-enhanced CT or MRI of the abdomen and pelvis (if whole body PET-CT not done)		X	
Chest x-ray/CT (if whole body PET-CT not done)		X See section 11.1	
CBC w/ diff & ANC, plt, Hgb	X		
Serum calcium, magnesium, Na,K, CL, CO2, BUN, creatinine, glucose	X		
Audiogram	X		
Adverse event eval	X		
Quality of Life (for consenting patients)			X

APPENDIX II
ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction.**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work.**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed.**
5	**Death.**

APPENDIX III
STAGING FOR CERVICAL CANCER
(AJCC, 6th Edition, 2002)

Primary Tumor *(T)*

TNM Categories	FIGO Stages	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	0	Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are T1b/IB. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less*
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2/T1a2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Tumor invades beyond the uterus but not to pelvic wall or to lower third of the vagina
T2a	IIA	Without parametrial invasion
T2b	IIB	With parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumor involves lower third of vagina no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumor invades *mucosa* of bladder or rectum and/or extends beyond true pelvis*
M1		Distant metastasis

**Note: The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.*
**Note: The presence of bullous edema is not sufficient to classify a tumor as T4.*

Regional Lymph Nodes (*N*)
- NX – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastasis
- N1 – Regional lymph node metastasis

Distant Metastasis (*M*)
- MX – Distant metastasis cannot be assessed
- M0 – No distant metastasis
- M1 – Distant metastasis

(Continued on Next Page)

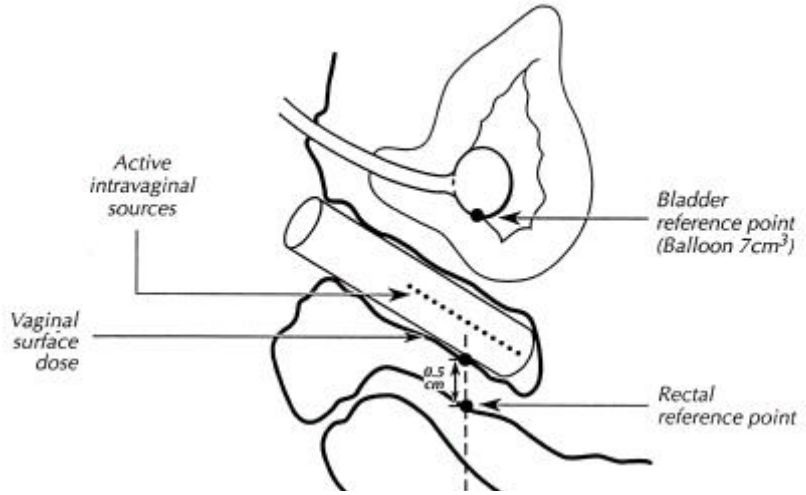
STAGE GROUPING

FIGO Stage	UICC		
	T	N	M
0	Tis	N0	M0
IA1	T1a1	N0	M0
IA2	T1a2	N0	M0
IB1	T1b1	N0	M0
IB2	T1b2	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIIA	T3a	N0	M0
IIIB	T1	N1	M0
	T2	N1	M0
	T3a	N1	M0
	T3b	Any N	M0
IVA	T4	Any N	M0

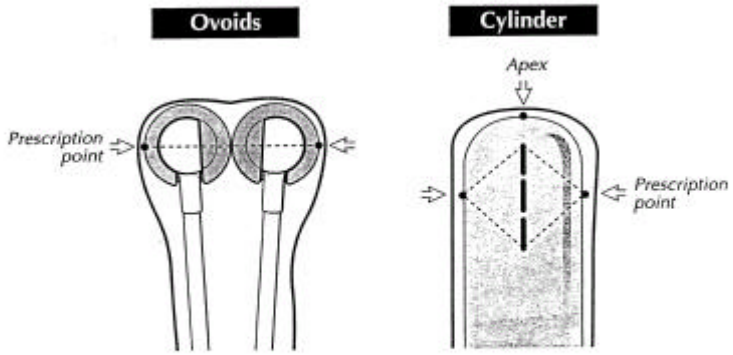
APPENDIX IV

DEFINITION OF BLADDER AND RECTAL POINTS

Vaginal Cylinder



Points of Calculation



APPENDIX V (8/21/14)

Appendices for NRG Oncology Biospecimen Collection *(as specified by the protocol)*.

NRG Oncology FFPE Specimen Plug Kit Collection
NRG Oncology Blood Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter St, room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For ALL Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (ST) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

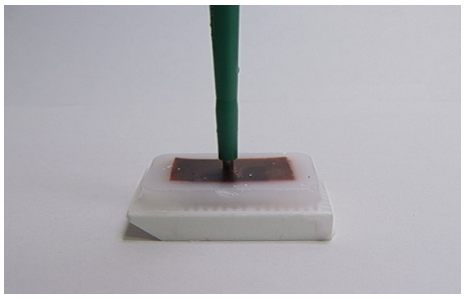
- ❑ **FFPE Specimens:**
  - ○ Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the block shaking it might break during shipping.
  - ○ Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - ○ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified. If possible keep Serum, Plasma and Whole Bloods in separate bags
  - ○ Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - ○ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - ○ Send frozen specimens on dry ice via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

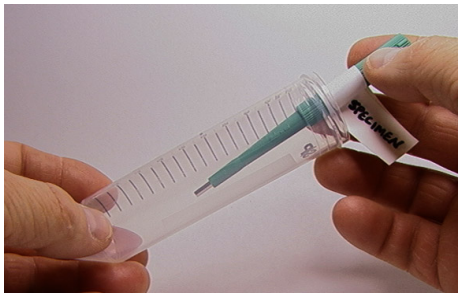
- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: RTOG@ucsf.edu or phone: 415-476- 7864or Fax: 415-476-5271.**

APPENDIX V (8/21/14)
NRG Oncology FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

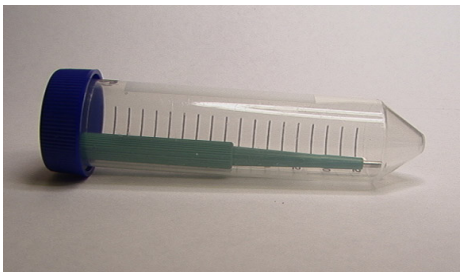


Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.



Step 2
Label punch tool with proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or email us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

*NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship: Specimen plug kit, specimen in punch tool, and all paperwork to the address below:

US Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter St, Room S341 San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For ALL Frozen Specimens or Trackable shipments
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter St, Room S341 San Francisco, CA 94115
Questions: 415-476- 7864/FAX 415-476-5271; RTOG@ucsf.edu

APPENDIX V (8/21/14)
NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS (continued)

This Kit is for collection, processing, storage, and shipping of <u>serum, plasma, or blood</u> (as specified by protocol):

Kit contents: (one collection timepoint)

- One Red Top for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal (ST) Form and Kit Instructions

(A) Serum (if requested): <u>Red Top Tube</u>

- ❑ Label as many 1ml cryovials (5-10) as serum collected. Label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "serum".

<u>Process:</u>

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. Aliquot **0.5 ml serum** into as many cryovials as are necessary for the serum collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form..

(B) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

<u>Process:</u>

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot **0.5 ml plasma** into each cryovial (5-10) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma".
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST.

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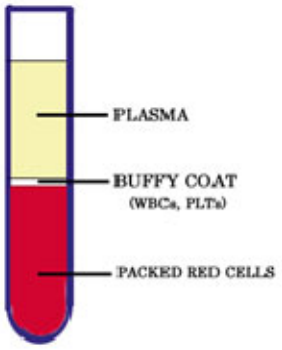
APPENDIX V (8/21/14)

NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS (continued)



(C) Whole Blood For DNA (if requested): Purple Top EDTA tube #2

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1**.0 ml blood** into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST.

Freezing and Storage

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.

- ❑ Include all NRG Oncology paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864

Shipping Address :

Courier Address (FedEx, UPS, etc.): For ALL Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864or e-mail: RTOG@ucsf.edu