SUMMARY OF CHANGES
Protocol Amendment #7 to: GOG-0263

NCI Protocol #: GOG-0263
Local Protocol #: GOG-0263

NCI Version Date: March 14, 2022
Protocol Date: March 14, 2022

| # | Section | Change |
|---|---|---|
| 1 | Title Page(s) | NCI Version Date has been updated |
| 2 | 11.1 | Administratively edited "post surgical" to hyphenated form "post-surgical" |
| 3 | 11.4 | • Accrual description has been revised, justification added to support closing the study.<br>• Figure added to reflect current data as of 1/7/2022 |
| 4 | 11.52 | Revised accrual section to support plans for study closure. |
| 5 | 11.82 | Administratively edited the words "one sided" to hyphenated form "one-sided" |
| 6 | 11.84 | • Added sub-section 11.84 to describe updated analysis plan titled "Suspending Follow-up for the Final Analysis (1/2022)"<br>• Updated RFS analysis table added. |
| 7 | ICF | • NCI Version Date updated. No other changes were made. |

# PROTOCOL GOG-0263

RANDOMIZED PHASE III CLINICAL TRIAL OF ADJUVANT RADIATION VERSUS CHEMORADIATION IN INTERMEDIATE RISK, STAGE I/IIA CERVICAL CANCER TREATED WITH INITIAL RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY (NCT #01101451) **(05/12/2014)**

*NCI Version: March 14, 2022*

Includes Revisions 1-7

POINTS:
PER CAPITA – 20
MEMBERSHIP – 6
TR PER CAPITA – Award based on specimen submission with 1.0 point for whole blood **(05/12/2014)**.

**Lead Organization: NRG / NRG Oncology (05/12/2014)**

**Participating Organizations (05/12/2014)**

**ALLIANCE** / Alliance for Clinical Trials in Oncology
**ECOG-ACRIN** / ECOG-ACRIN Cancer Research Group
**SWOG** / SWOG

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OPEN TO PATIENT ENTRY APRIL 12, 2010; REVISED MAY 25, 2010; REVISED JUNE 13, 2011; REVISED MAY 12, 2014; REVISED MARCH 5, 2018; REVISED APRIL 23, 2018; REVISED MAY 12, 2020; **REVISED MARCH 14, 2022**.

PROTOCOL GOG-0263

RANDOMIZED PHASE III CLINICAL TRIAL OF ADJUVANT RADIATION VERSUS CHEMORADIATION IN INTERMEDIATE RISK, STAGE I/IIA CERVICAL CANCER TREATED WITH INITIAL RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY

*NCI Version: March 14, 2022*

| **CONTACT INFORMATION (05/12/2014)(05/12/2020)** | | |
|---|---|---|
| **For regulatory requirements:** | **For patient enrollments:** | **For data submission** |
| Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.)<br><br>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.<br><br>Contact the CTSU Regulatory Help Desk at 1-866-651-2878 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.<br><br>Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923 or ctsucontact@westat.com. | Use the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page, to view and print a copy of each form along with instructions, and to submit forms electronically. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC.<br><br>GOG Statistical and Data Center<br>Roswell Park Cancer Institute, Carlton and Elm Streets, Buffalo, New York, 14263-0001<br>716-845-5702<br>FAX: 716-845-8393<br><br>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 Web page of the CTSU Member Web site located at 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 user 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 RSS. | | |
| **For clinical questions (i.e. patient eligibility or treatment-related)** 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:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |

OPEN TO PATIENT ENTRY APRIL 12, 2010; REVISED MAY 25, 2010; REVISED JUNE 13, 2011; REVISED MAY 12, 2014; REVISED MARCH 5, 2018; REVISED APRIL 23, 2018; REVISED MAY 12, 2020, **REVISED MARCH 14, 2022**.

## SCHEMA

- Post-operative Stage I-IIA cancer of cervix with intermediate risk factors (IRF)
- Squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma histology
- GOG performance status 0-2

↓

- Baseline Quality of Life Assessment
- Smoking History Questionnaire

↓

RANDOMIZE
Stratification factors: IRF, performance status, radiation modality, cooperative group

↙ ↘

**Regimen I (control arm)**
Radiation Therapy:
(External pelvic standard radiation or IMRT)

**Regimen II (CRT arm)**
Concurrent Cisplatin and Radiation Therapy
(External pelvic standard radiation or IMRT)

Cisplatin 40mg/m$^2$ (max=70mg) IV over 1-2 hours weekly x 6 cycles with radiation therapy (see Regimen II Schedule below)

**Regimen II (CRT arm) Schedule**

| **Cycle** | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| **Day** | 1 | 8 | 15 | 22 | 29 | 36 |
| **Cisplatin** | X | X | X | X | X | X** |
| **Radiation** | → | | | | | |

** The 6$^{th}$ cycle of cisplatin may be omitted if all radiotherapy has been completed.

Brachytherapy boost is NOT allowed on this protocol

Pathology Requirements to Confirm Eligibility: see sections 4.2, 7.2 and 10.2 for a description of the H&E stained pathology slides and reports that are required for this research study.

Quality of Life Research: see Sections 4.5, 4.6, 7.4 and 10.2 for a description of the quality of life assessments and time points for data collection for this research study.

Translational Research: see sections 7.3 and 10.2 as well as Appendix II for a description of the specimen requirements and laboratory testing for this research study.

CT of chest/abdomen/pelvis or PET/CT is required within 30 days of documentation of any site of relapse.

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# 1.0 OBJECTIVES

## 1.1 Primary Objectives

### 1.11 
To determine if post-operative adjuvant chemo-radiation therapy (CRT) can significantly improve recurrence-free survival (RFS) when compared to radiation therapy (RT) alone in Stage I-IIA cervical cancer patients with intermediate risk factors after treatment with radical hysterectomy.

## 1.2 Secondary Objectives

### 1.21 
To determine whether post-operative adjuvant CRT can improve overall survival (OS) when compared to RT alone in Stage I-IIA cervical cancer patients with intermediate risk factors after treatment with radical hysterectomy.

### 1.22 
To assess differences (across treatment arms) in incidence and severity of therapy attributed adverse events utilizing the active version of CTCAE.

### 1.23 
To provide assessment of patient risk vs. benefit (positive study only).

## 1.3 Quality Of Life Objectives

### 1.31 
To determine whether post-operative adjuvant CRT improves the health related Quality of Life (QOL) (compared to RT alone) as measured by FACT-Cx TOI and produce favorable toxicity profiles (with particular focus on treatment related genitourinary, gastrointestinal, neurological, pain and sexual adverse events).

## 1.4 Translational Research Objectives

### 1.41 
To bank archival tumor tissue for research including studies that evaluate the association between biomarkers and RFS, OS, and clinical-surgical-pathologic characteristics in patients randomized to post-operative adjuvant CRT compared to RT alone.

### 1.42 
To bank DNA from whole blood for research including studies that evaluate associations between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including RFS, OS, and adverse events in patients randomized to post-operative adjuvant CRT compared to RT alone.

# 2.0 BACKGROUND AND RATIONALE

## 2.1 Rationale for Chemo-Radiation

Early cervical cancer has a relatively favorable prognosis with more than an 80% survival rate.[1] However, there are still high mortality rates and poor prognoses in cases of recurrent disease. Several clinico-pathologic risk factors for recurrence have been identified and investigated the clinical significance in cervical cancers.[2-5]

High risk factors, such as lymph node metastasis, parametrial invasion and positive resection margins increase the recurrence rate up to 40% after surgery in early cervical cancer patients.[5-8] In this high-risk group, concurrent chemotherapy with RT reduces recurrences and improves survival. In an earlier study, Peter et al. showed that adjuvant CRT in post-operative cervical cancer with high risk factors increased progression free survival from 63% to 80%, and the overall survival rate from 71% to 81%.[6] Several randomized clinical trials also consistently showed that the addition of concurrent chemotherapy to RT reduces the relative risk of death from cervical cancer by approximately 50% by decreasing local failure and distant metastasis. Based on these clinical trials, weekly intravenous cisplatin at 40mg/m$^2$ in combination with concurrent RT was established as a new standard treatment for the locally advanced cervical cancers.[6, 9-13]

However, the role of intermediate factors, such as deep stromal invasion, large tumor size, and lympho-vascular space involvement still remains controversial.[14-16] Worrying about over-treatment, many physicians are reluctant to treat the patients who have intermediate risk factors with CRT. This reluctance is understandable, given that patients with intermediate risk factors have a favorable prognosis: five-year survival without any adjuvant treatment for 85-90% of this population.[1] However, those who have two or more intermediate risk factors showed approximately a 30% recurrence rate, which is similar to that of patients with one high-risk factor; thus implying the need for adjuvant treatment. A Gynecologic Oncology Group (GOG) study confirmed that such intermediate risk factors existed in 25% of all Stage IB cervical cancers and that these factors increase the risk of recurrence from 2% to 31% at 3 years.[14-20]

Currently, the standard regimen for the patients with two or more intermediate-risk factors is adjuvant RT, which is based on GOG-0092.[17, 18] In GOG-0092, 277 cervical cancer patients with two or more intermediate risk factors after radical hysterectomy were randomized to either a “no further treatment” (NFT) group or a RT group. Even though the improvement of overall survival with RT did not reach statistical significance at two years, the RT arm showed a statistically significant reduction in risk of recurrence (HR=0.54, p=0.007) and an increase of two-year recurrence-free interval from 79 to 88% at the cost of low toxicity.[17] The recently published outcomes of GOG-0092 have shown that the use of

adjuvant RT was associated with a hazard ratio of 0.54 for recurrence (p=.007), hazard ratio of 0.58 for progression or death (p=0.009), and hazard ratio of 0.70 for overall survival (p=0.74). There was a greater decrease of recurrence among patients with adenocarcinomas and adenosquamous carcinomas than among those with squamous carcinomas. Women randomized to the RT arm did experience an increased rate of Grades 3 and 4 toxicity compared to those who did not undergo RT.[18]

Recently, we retrospectively investigated whether weekly cisplatin-based concurrent CRT increases three-year recurrence-free intervals in cervical cancer patients with two or more intermediate risk factors.[21] Of the 735 patients with post-operative cervical cancers included in this retrospective study, 172 were identified as having had intermediate risk factors. These 172 patients were then categorized into the following groups: no further treatment group (NFT, n=34), RT group (RT, n=49), and concurrent CRT group (CRT, n=89). The three-year recurrence-free interval increased to 90.5% (RT) from 72.5% (NFT), and further increased to 98.7% (CRT), making the disease almost curable by adding weekly cisplatin at 40mg/$m^2$.

Based on these results and previous clinical trials that have consistently shown the benefit of concurrent chemotherapy, we suggest that the addition of concurrent chemotherapy to RT may increase recurrence-free survival in cervical cancer patients with intermediate risk factors.

This study is to investigate whether there is any improvement of three-year recurrence- free interval in post-operative cervical cancer patients with intermediate risk factors through the addition of weekly cisplatin chemotherapy to RT. We expect at least a 6% increase (from 87 to 93%) of three-year recurrence-free interval in patients receiving concurrent chemotherapy compared to the RT alone group.

Our study will provide more sophisticated treatment for patients with cervical cancer with intermediate risk factors, who comprise 20-25% of all post-operative cervical cancers.

Table 1. GOG-0092 showed that the recurrence rate reduced from 27.9% to 15.3% by adjuvant RT in patients with cervical cancer with intermediate risk factors.

**Recurrences by Treatment Regimen**

| Site of Recurrence | RT (N=137) | No further therapy (N=140) |
|---|---|---|
| No Evidence of Disease | 116(84.7%) | 101(72.1%) |
| Recurrences | 21(15.3%) | 39(27.9%) |
| Local | 18(13.1%) | 27(19.3%) |
| Vagina | 2 | 8 |
| Pelvis | 15 | 17 |
| Vagina and pelvis | 1 | 2 |
| Distal | 3(2.2%) | 10(7.1%) |
| Abdomen | 0 | 3 |
| Abdomen and pelvis | 0 | 1 |
| Lung | 2 | 2 |
| Lung and pelvis | 0 | 2 |
| Lung and brain | 0 | 1 |
| Bone and supraclavicular lymph node | 1 | 1 |
| Unknown | 0(0%) | 2(1.4%) |

GOG-0092 showed that those who have two or more intermediate risk factors had a 27% recurrence rate without any treatment, which was reduced to 15% by adjuvant RT (Table 1). Interestingly, not only local recurrences, but also distant recurrences were reduced by RT, for reasons that are not yet clearly understood. The two-year disease-free interval was 79% in the NFT group and 88% in the RT group, which provides the basis for the 88% recurrence-free interval in the control arm (RT arm) of our protocol (Figure 1).

Most “pattern of failure” analyses in previous GOG trials have been limited to initial sites of failure. For example, if a local recurrence is documented, it is recorded as the site of failure, and further documentation of other sites of potential relapse is no longer required. Accurate and complete pattern of failure analysis is important to clearly delineate ALL sites of relapse, and will be important in helping to determine future strategies in addressing these sites of risk. Current widely available ‘total body’ tomographic imaging techniques (CT of the chest/abdomen/pelvis, or PET/CT) should be used, at the time of first documented recurrence in any given location, to fully assess for other sites of disease relapse.

Figure 1. GOG-0092 showed that adjuvant RT increased 2-year disease free survival in patients with cervical cancer with intermediate risk factors.

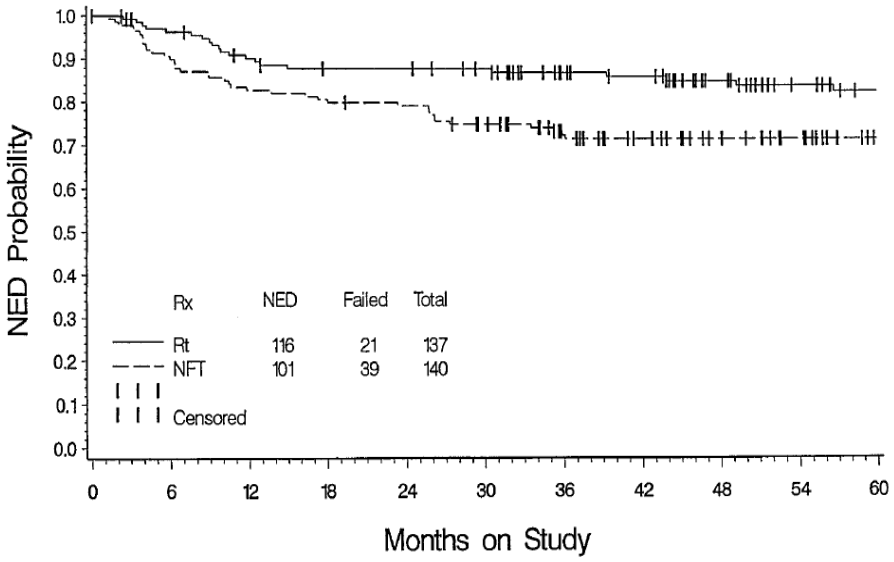
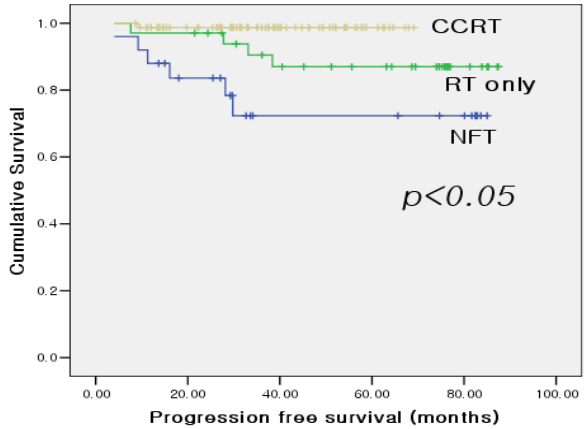



FIG. 1. Recurrence-free interval by treatment.

Our retrospective study showed that concurrent CRT increased three-year recurrence-free interval 8% more than the adjuvant RT, which supports the favorable role of CRT in cervical cancers with intermediate risk factors.[21] In this retrospective study, three-year recurrence-free interval increased to 90.5% by adjuvant RT (RT arm, n=49) from 72.5% of control (NFT arm, n=34), and further increased to 98.7% (CRT arm, n=89), thus making the disease highly curable with the addition of weekly cisplatin at 40m/m$^2$ to pelvic RT. (Figure 2).

Figure 2. A retrospective study showed that concurrent CRT increased three-year recurrence-free interval from 72% (NFT), 90% (RT) to 98% (CRT) in patients with cervical cancer with two or more intermediate risk factors.



## 2.2 Rationale of Intensity Modulated Radiation Therapy (IMRT)

In an attempt to potentially decrease both acute and late radiation-related toxicities, Intensity Modulated Radiation Therapy (IMRT) has been increasingly used by many practitioners in the post-hysterectomy setting. IMRT will be allowed at the discretion of the treating radiation oncologist, subject to appropriate physician and facility credentialing. 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.[22] 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.[23] 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.[24]

## 2.3 Rationale for Quality of Life Assessment

The results of GOG-0092 demonstrated a significant decrease in the recurrence rate with an increase in Grade 3/4 adverse events in women treated with adjuvant pelvic radiotherapy following radical hysterectomy versus women who received no further treatment.[17] Nine (7.0%) of the 128 women who received radiotherapy had 11 episodes of Grade 3 or 4 adverse events compared with three (2.1%) in the group receiving no further treatment. The addition of cisplatin in this protocol is anticipated to further increase three-year recurrence-free interval to 93%, although at the cost of increased toxicity.

Cisplatin neurotoxicity primarily affects sensory nerves; sensory neuropathy first appears about one month after initiation of therapy and can follow from total exposure as low as 200 mg/m$^2$. [25] Symptoms of neuropathy may start after cessation of therapy and can persist over the following months. [25, 26] Neurotoxicity scores of patients receiving cisplatin in GOG-0179 were not increased above pre-treatment levels prior to cycles 2 and 5; however, neurotoxicity scores were significantly higher 9 months post-random assignment than they were pre-5$^{th}$ cycle of chemotherapy.[27] It is not known to what extent the addition of cisplatin in this setting will result in symptoms that affect QOL. Given the estimated difference in rate of recurrence (87% versus 93%), the potential effect of cisplatin on neurotoxicity and QOL will be an important component of treatment decisions.

An additional factor that may affect the decision to include cisplatin is the effect of acute cisplatin toxicities on completion of all 6 cycles of therapy. Cisplatin chemotherapy is associated with nausea, vomiting, and diarrhea.[28-30] RT may also

be associated with nausea, vomiting, abdominal cramping and diarrhea.[28] However, cisplatin-induced toxicities added to RT toxicities may result in treatment delays and/or fewer women completing the 6 cycles of therapy. QOL assessments will provide information on the extent to which the addition of cisplatin affects treatment completion.

2.4 Translational Research Component:

2.41 Background and rationale for banking archival tumor for research

The GOG has a number of studies in cervical cancer that indicate the importance of markers of angiogenesis and hypoxia in this disease site. GOG-9911 evaluated whether markers of tumor angiogenesis were associated with progression-free survival (PFS) and overall survival (OS) in women with high-risk, early-stage cervical cancer treated on the multi-center randomized Phase III trial (SWOG 8797/GOG-0109/RTOG 91-12). One hundred seventy-three tumor specimens were analyzed by semi-quantitative immunohistochemical (IHC) staining for vascular-endothelial growth factor (VEGF, pro-angiogenesis factor), thrombospondin-1 (TSP-1, anti-angiogenesis factor), CD31 (non-specific endothelial marker), and CD105 (tumor-specific endothelial marker). Tumoral histoscores (HS) were calculated for VEGF using the formula: [% cells positive x (intensity +1)]. TSP-1 specimens were categorized as negative or positive. CD31 and CD105 microvessel density (MVD) "hotspots" were counted in three 20X high-power fields. Associations between angiogenesis markers and survival were evaluated. TSP-1 expression was observed in 65% of cases while 66% expressed high VEGF ($\geq 200$), 34% exhibited high CD31 (CD31 $\geq 110$) and 66% displayed high CD105 (CD105 $\geq 28$). In univariate analyses, CD31 MVD, but not tumor TSP-1, was associated with improved PFS (HR=0.37; 95% CI=0.18-0.76; p=0.007) and OS (HR=0.37; 95% CI=0.17-0.79; p=0.010). After adjusting for prognostic clinical covariates, high CD31 MVD, but not TSP-1,VEGF or CD105 MVD, was an independent prognostic factor for PFS (HR=0.36; 95% CI=0.17-0.75; p=0.006) and OS (HR=0.36; 95% CI=0.17-0.79; p=0.010). In conclusion, tumor angiogenesis measured by CD31 MVD is an independent prognostic factor for both PFS and OS in high-risk, early-stage cervical cancer. We hypothesize this finding may be explained by improved treatment response in well-vascularized, well-oxygenated tumors. These results were recently accepted for publication in Gynecologic Oncology in 2009.

GOG-9911 was then used to determine whether carbonic anhydrase-IX (CA-IX), a marker of hypoxia, was associated with progression-free survival (PFS) and overall survival (OS) in this cohort of women with high-risk, early-stage cervical cancer treated with adjuvant pelvic radiotherapy with or without radio-sensitizing chemotherapy on a multi-

center randomized Phase III trial (SWOG 8797/GOG-0109/RTOG 91-12). CA-IX expression was detected using an immunohistochemistry assay and categorized as low when ≤ 80% of tumor cells exhibited CA-IX staining and high when >80% tumor cells display CA-IX staining. Associations between CA-IX expression and clinical characteristics, angiogenesis marker expression and clinical outcome were evaluated. High CA-IX expression was observed in 35/166 (21.1%) of cases. CA-IX expression was not associated with age, race, stage, cell type, grade, positive margins, parametrial extensions, positive lymph nodes or lymphovascular space invasion but was correlated with tumor size categorized as <2 cm, 2-2.9 cm, or ≥3 cm (r=0.233, p=0.001) and cervical invasion confined to the inner two-thirds compared with the outer third of the cervix (r=0.176, p=0.003). CA-IX expression was not associated with immunohistochemical expression of p53, CD-31, CD-105, thrombospondin-1 or vascular endothelial growth factor. Women with high versus low CA-IX expression had slightly worse PFS (p=0.053) and significantly worse OS (p=0.044). After adjusting for prognostic clinical covariates, high CA-IX expression was an independent prognostic factor for PFS (hazard ratio [HR]=1.996; 95% confidence interval [CI]=1.072-3.715; p=0.029) and OS (HR=2.575; 95% CI=1.314-5.049; p=0.006). In conclusion, tumor hypoxia as measured by immunohistochemical expression of CA-IX appears to be an independent prognostic factor for both PFS and OS in high-risk, early-stage cervical cancer.

In follow up to these findings, an analysis was then performed to explore the relationship between CD31-MVD and CA-IX as part of the GOG-9911 protocol. Although categorized CD31-MVD and CA-IX are not themselves correlated, these biomarkers appear to have an independent inverse association with prognosis in the cervical cancer patients treated with adjuvant pelvic radiotherapy with or without radio-sensitizing chemotherapy. Women who have tumors with high CD31-MVD (high angiogenesis) and low CA-IX (low hypoxia) had the best PFS and OS, those with low CD31-MVD (low angiogenesis) and low CA-IX (low hypoxia) had intermediate PFS and OS, and those with low CD31-MVD (low angiogenesis) and high CA-IX (high hypoxia) had the worst PFS and OS. This finding supports our hypothesis that improved treatment response is observed in the well-vascularized and well-oxygenated tumors with high CD31-MVD and low CA-IX expression. These results were presented at a Plenary Presentation at the 2009 Society of Gynecologic Oncologists (SGO) meeting in San Antonio, TX.[31]

Translational research objectives were prospectively embedded in a series of randomized Phase III treatment protocols in women with cervical cancer, including GOG-0191, GOG-0219 and GOG-0240. The GOG programmatically incorporated the same objective into each of these trials to determine definitely which markers of angiogenesis and hypoxia are

associated with PFS, OS and clinicopathologic characteristics. The immunohistochemistry assays for CD31-MVD, CD105-MVD, VEGF, TSP-1 and CA-IX in the GOG-191 cohort are currently underway. GOG-219 is still accruing patients and specimens, and GOG-240 was opened to patient accrual in April 2009.

The GOG proposes to bank archival tumor specimens (block or 5 to 15 unstained slides depending on the quantity of available material) from cervical cancer patients participating in this phase III treatment protocols to expand the resource of well-annotated tumor specimens linked with detailed clinical, surgicopathologic, treatment and outcome data from patients enrolled at multiple institutions in North America and Korea. This resource will enable the research community to not only study cervical cancer biology, progression and factors that either positively or negatively impact treatment response and therapeutic efficacy but moreover to identify and validate biomarkers with predictive, prognostic and/or therapeutic value in this disease site. This will be an **optional but high priority effort** for GOG Institutions outside the United States.

2.42 Background and rationale for banking DNA from whole blood for research

The National Cancer Institute is encouraging cooperative clinical trial groups, including the Gynecologic Oncology Group, to bank whole blood from women participating in Phase III clinical trials such that the blood specimens will be linked to clinical outcome data (recurrence-free survival, progression-free survival, overall survival, response, and adverse effects) and information regarding treatment. The purpose of this effort is to support research, including pharmacogenomic and pharmacogenetic research. Specifically, it is well known that individual single nucleotide polymorphisms (SNPs) and SNP profiles are associated with many clinical aspects of cancer. This includes risk of developing invasive cancer, risk of recurrence of cancer, patient survival, and adverse events. We propose to bank DNA from whole blood to enable researchers to use genome-wide SNP and individual SNP analyses to identify SNPs that correlate with a variety of clinical measures, including but not limited to patient survival, recurrence of disease, response, and adverse events.

Women who are candidates for this clinical trial will be asked to give permission for 10 ml of their blood to be collected for research. No matter what the women decide to do, it will not affect their care. The women can still participate in this GOG study even if they do not allow their blood to be collected and used for research. For financial, practical and logical reasons this will be an **optional, but high priority effort** for women enrolled at GOG institutions within the United States.

## 2.5 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire stage I-IIA cervical cancer population treated by participating institutions.

# 3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

## 3.1 Eligible Patients

3.11 Pathologically proven primary cervical cancer I-IIA with squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma initially treated with a standard radical hysterectomy with pelvic lymphadenectomy.

3.12 Patients with the following characteristics (depth of stromal invasion and lymphovascular space involvement to be pathologically confirmed):

3.121 Positive capillary-lymphovascular space involvement and one of the following:

- Deep third penetration
- Middle third penetration, clinical tumor ≥ 2 cm
- Superficial third penetration, clinical tumor ≥ 5 cm

3.122 Negative capillary-lymphatic space involvement:

- Middle or deep third penetration, clinical tumor ≥ 4

3.13 Patients must have adequate:

3.131 Hematologic function: ANC ≥ 1,500/mcl, platelets ≥ 100,000/mcl

3.132 Renal function: creatinine ≤ ULN or calculated creatinine clearance ≥ 60 Ml/min

3.133 Hepatic function: bilirubin ≤ 1.5 x normal, alkaline phosphate and SGOT ≤ 3 x normal

3.14 GOG performance status 0, 1, 2.

3.15 Patients should not be randomized less than 3 weeks post-surgery but will not be acceptable for randomization more than 8 weeks post-surgery.

3.16 Patients who have met the pre-entry requirements specified in Section 7.0.

3.17 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.18 Patients must be ≥ 18 years of age. **(06/13/2011)**

## 3.2 Ineligible Patients

3.21 Patients with tumor in the parametria, pelvic lymph nodes or any other extra uterine site or with positive surgical margins.

3.22 Patients with septicemia or severe infection.

3.23 Patients with intestinal obstruction or gastrointestinal bleeding.

3.24 Patients with postoperative fistula.

3.25 Patients with cervix cancer who have received any previous radiation or chemotherapy.

3.26 Patients whose circumstances do not permit completion of the study or the required follow-up.

3.27 Patients with renal abnormalities requiring modification of radiation field (pelvic kidney, renal transplant, etc).

3.28 Patients with GOG Performance Status of 3 or 4.

3.29 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the last five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

# 4.0 STUDY MODALITIES

## 4.1 Surgery

All patients will have had a radical hysterectomy and pelvic lymphadenectomy trans-abdominally or laparoscopically. Para-aortic lymphadenectomy is not required.

## 4.2 Pathology Requirements

4.21 Eligible Patients: Patients must have a histologic diagnosis of primary invasive cervical cancer Stage I-IIA (squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma) with histologically-documented depth of cervical stromal invasion and/or capillary-lymphatic space involvement.

4.22 Ineligible Patients: Patients with a gynecologic malignancy other than invasive cervical cancer Stage I-IIA or lacking histologically-documented depth of cervical stromal invasion or capillary-lymphatic space involvement

4.23 Requirements and Instructions: H&E stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility and to confirm depth of cervical invasion and capillary-lymphatic space involvement for the protocol. See Sections 7.2 and 10.2 for specific requirements and instructions for the stained pathology slides, pathology reports, and forms.

## 4.3 Radiation Therapy

****Brachytherapy boost is not allowed in this protocol. IMRT is allowed in this protocol ****

4.31 NOTE: Patients will receive external beam radiotherapy using 4-field 'standard' radiotherapy or Intensity Modulated Radiation Therapy (IMRT) techniques. Megavoltage equipment with ≥ 6 MV photons and a minimum of 100 cm SAD is required. Before ANY patient is enrolled on this study, the treating radiation oncologist must complete online a Knowledge Assessment Questionnaire found on the IROC Houston (formerly the Radiological Physics Center [RPC]) website (http://irochouston.mdanderson.org).

Prior to use of IMRT on study, credentialing through IROC Houston, including an IMRT phantom study, must be completed (see Section 5.2). The treatment plan for the first patient to be treated at that institution on this protocol must be digitally submitted via TRIAD ;it will be processed

in preparation for rapid review. A rapid review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The rapid review will be conducted by IROC Houston in collaboration with a radiation oncologist and suggestions regarding protocol compliance will be forwarded to the participating institution's radiation oncologist. The treatment plans for subsequent patients enrolled at a site will not be required to be reviewed prior to treatment, but documentation will still need to be submitted for post-therapy central review. Once data has been submitted to TRIAD, complete a DDSI contact information form at http://www.rtog.org/CoreLab/TRIAD.aspx. **(05/12/2014)**

For IMRT details, see Section 4.33.

All patients should be sufficiently healed from surgery before beginning RT; they are to begin no sooner than 3 weeks and no later than 8 weeks post-operatively.

4.311 Radiation Therapy Quality Control and Documentation:

All participating institutions are required to be monitored by IROC Houston through the remote auditing program. IROC Houston is funded by the NCI to support clinical trials employing RT and will supervise the dosimetry quality control for this clinical trial. **(05/12/2014)**

## 4.32 Standard Radiation Therapy:

4.321 Dose specifications:

4.3211 External beam pelvic radiotherapy will be given to a dose of 50.4 Gy in 28 fractions (1.8 Gy/fraction). (If using IMRT, please see Section 4.33 for dose specification and requirements.). Treatment will be delivered once daily, 5 fractions per week, over 5.5 weeks. All prescribed fields treated daily.

4.3212 For standard radiotherapy, 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.

4.322 Technical factors
RT will be delivered by means of mega-voltage equipment with ≥ 6 MV photons, and a minimum of 100 cm SAD.

4.323 Standard Radiotherapy Localization and Simulation: (see Section 4.33 below for IMRT specifications)

For standard radiotherapy, all fields require simulation on a dedicated simulator and portal verification on the RT unit. CT-based treatment planning is required. For standard RT, CT scan slice thickness of up to 5 mm is permitted. The intended target volume includes the upper half of the vagina, the parvaginal and parametrial tissues, and the first echelon nodal chains (obturator, internal iliacs, and external iliacs). Customized blocking of the femoral heads, bowel, and iliac crests should be carefully performed to avoid under-coverage of the obturator foramen, parametria, and iliac nodal chains.

4.3231 AP-PA pelvic field set-up:

*Superior* - To include at least L5-S1 interspace, but not more cephalad than the superior aspect of the L5 vertebral body.

*Inferior* - At least down to the mid obturator foramen (a temporary vaginal marker, such as a tampon or OB-Gyn applicator/swab, should be placed at the time of simulation to mark the vaginal apex, and assure that at least the upper 3 cm of the **non-distended** vagina is included).

*Lateral* - At least 1cm beyond the lateral margins of the bony pelvis at the widest plane through the pelvis

4.3232 Lateral pelvic field set-up:

*Superior and inferior borders:* same as above

*Anterior border:* transverse line through anterior portion of the pubic symphysis

*Posterior border:* to include at least the S3-S4 interspace, with adequate margin (3 cm) on the temporary vaginal marker and sufficient coverage of the parametria and uterosacral ligaments

4.324 Documentation requirements for standard radiotherapy:

All fields treated require simulation and beam verification films. For standard 4-field radiation treatments, simulation or digital reconstructed radiographs (DRR) of each of the treatment fields, are to be obtained and submitted for evaluation. For non-IMRT plans, contouring of the vagina, parametria and nodal volumes are optional. However, if CTVs are defined for standard 4-field radiation treatment planning, 3-D reconstruction of these volumes should also be submitted for review.

For patients treated with standard 4-field radiotherapy, full dosimetry plans, including multi-plane and multi-view isodose distributions will be obtained and submitted.

4.325 Compliance Criteria for Standard Radiation Therapy

4.3251 Per protocol: See section 4.3211

4.3252 Variation acceptable:
- Interruption of external beam RT of less than 7 consecutive days.
- The minimum dose to the dose specification point is greater or equal to 48.6 Gy
- Maximum dose to a volume of at least 0.03 cc of tissue within the convergence of the treatment fields should not exceed 107% of the prescription dose

4.3253 Deviation Unacceptable
- Field of RT is other than what is outlined in the protocol.
- Interruption of external beam RT of more than 7 consecutive days
- The minimum delivered dose to the dose specification point is less than 48.6 Gy.
-Maximum dose to a volume of at least 0.03 cc of tissue within the convergence of the treatment fields exceed 107% of the prescription dose.

## 4.33 IMRT

Credentialing by IROC Houston is required for IMRT treatments (see Section 5.2). Please refer to the RTOG Gynecological Atlas for volume specifications. The Atlas may be accessed on the RTOG website: http://www.rtog.org/atlases/gynatlas/main.html. **(05/12/2014)**

4.331 Dose Specifications
Prescription dose will be according to the following specifications:

4.3311 The vaginal/parametrial planning target volume (PTV) (ITV – see section 4.3344 - with 7.0 mm margin) and nodal PTV will receive 50.4 Gy in 28 fractions. Treatment will be delivered once daily, 5 fractions per week, over 5.5 weeks. All targets will be treated simultaneously. Breaks in treatment should be minimized.

4.3312 The dose is prescribed to cover 97% of the vaginal/parametrial PTV and the 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 PTV's must not receive > 110% of the dose prescribed to the composite PTV.

4.332 Technical Factors

4.3321 Megavoltage equipment capable of delivering static intensity modulation with a multi-leaf collimator or dynamic intensity modulation (using a multi-leaf collimator or tomotherapy) is required. The use of three-dimensional conformal radiotherapy (3D-CRT) using forward-planned IMRT treatment planning methods is acceptable. The use of compensators or partial transmission blocks is also acceptable as long as dose specifications and constraints are satisfied.

4.3322 Recognizing that higher energies with higher monitor units increase neutron contamination, a 6-10 MV energy photon beam is recommended.

4.333 Localization, Simulation, and Immobilization

4.3331 Prior to simulation, it is recommended that a temporary non-distending vaginal marker 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.

4.3332 Patients will be immobilized in the supine position in an immobilization device. Patients should, at least, be immobilized in a device that fixes the position of the trunk

and proximal legs. Patients will be treated daily in the immobilization device.

4.3333 Treatment planning CT scans will be required to define tumor and clinical and planning target volumes. The maximal thickness of the CT scan slices should be no more than 3 mm for IMRT planning. The treatment planning CT scan should be acquired with the patient in the same position and immobilization device as for treatment

4.334 Treatment Planning/Target Volumes

4.3341 Two separate treatment planning CT scans (full bladder and empty bladder CT scans, as described below) are required and then should be fused together prior to outlining target volumes. 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.

4.3342 In this study, which is used for post-operative patients with no gross disease, there should not be a gross tumor volume GTV.

4.3343 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.

4.3344 Internal Target Volume (ITV) is defined as the combined volume of the vagina and parametria that is in **both** the empty and full bladder CT scans that are done at the time of simulation and fused together. This volume accounts for internal organ motion.

4.3345 The Planning Target Volume (PTV) will provide a margin around the CTV/ITV to compensate for the variability of treatment setup. Careful consideration should be made when defining the superior and inferior margins in three dimensions.

4.3346 Planning of the IMRT will be done on the full bladder scan with full heterogeneity correction enabled in the treatment planning system.

4.3347 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/ITV with a 7 mm margin) and critical normal structures. The treatment aim will be the delivery of RT to the PTVs and the exclusion of non-involved tissues.

4.335 Planning Priorities:

Dose to nodal PTV and vaginal/parametrial ITV/PTV 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 4.336).

4.3351 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, to fully include the attachments of the uterosacral ligaments. Identification of the CTV usually begins with the identification of the iliac vessels. The nodal CTV will include the vessel, residual nodal or 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 around the blood vessels, any perivascular clips, or any residual radiologically identified nodal tissue. 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 pre-sacral lymph nodes and uterosacral ligament attachments. 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 7mm below the level of the sacral promontory (or no higher than the bifurcation of the common iliac vessels), and the PTV for nodes will stop at the axial level of the sacral promontory. (See GYN atlas for examples: http://www.rtog.org/gynatlas/main.html.)

4.3352 The vaginal and parametrial CTV should actually be an ITV, which will account for an internal organ motion. It is recommended that a temporary non-distending vaginal marker 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. The ITV is drawn after the full and empty bladder scans are fused together, and it should encompass the vagina and parvaginal/parametrial 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. If gas/stool distends the rectum on the treatment planning CT, the ITV should be expanded to include the anterior half of the rectal circumference, to account for evacuation/variation of the rectal contents during the treatment course. The inferior limit should include at least 3 cm of the upper vaginal cuff, or at least down to the level of the mid-obturator foramen. The lateral margin of the vaginal/parametrial ITV should be to the obturator muscle. **(06/13/2011)**

4.3353 PTV Definition:
Nodal 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/parametrial PTV will provide a 7 mm margin (anteriorly, superiorly, inferiorly, laterally and posteriorly) around the vaginal/parametrial CTV/ ITV. The overall PTV will consist of the combined nodal and vaginal/parametrial PTVs

4.3354 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).

4.336 <u>Critical Structures</u>

4.3361 Normal structures will be contoured using the full-bladder CT scan.

4.33611 Bladder – will be outlined on every slice, including the portion inferior to the planning target volume. The contour includes the bladder contents.

4.33612 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, including the rectosigmoid. The rectum and rectosigmoid will be outlined to 2 cm superior to the PTV, and no more. The contour includes the rectum contents.

4.33613 Small bowel – will be outlined on every slice, including up to 2 cm above the PTV 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. Care must be taken to delineate the small bowel as precisely as possible (i.e., large bowel loops such as transverse colon, cecum, and rectosigmoid should NOT be included in the small bowel volume).

4.3362 The dose constraints for critical structures are as follows **(06/13/2011)**:

- Bowel: ≤ 30% to receive > 40 Gy
- Rectum: ≤ 80% to receive > 40 Gy, Dmax < 55 Gy
- Bladder: ≤ 35% to receive > 45 Gy

4.3363 IV contrast may be used during simulation to help better define the vessels; however, it is not required. Rectal contrast is not recommended because it may interfere with the planning process and may possibly cause anatomical distortion.

4.3364 All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 0.3 cm or smaller through the region that contains the primary target volumes and at least 4 cm above and below the target volumes. The superior limit of scanning will be at least at the L2-L3 interspace and inferior limit will be below the perineum.

4.3365 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 modified to include the excursion of target tissues as demonstrated on the empty bladder scan (ITV), and should be further modified if there is significant gas/stool distention of the rectum on the treatment planning CT (see Section 4.3352). Using the full

bladder scan, all normal tissues will be outlined on all CT slices in which the CTV and ITV exist and up to 2 cm superior the PTV. (See Section 4.334 for more detailed definitions.) **(06/13/2011)**

4.3366 Lymph node groups at risk including the following:

- Internal iliac (obturator and hypogastric) nodes
- External iliac nodes down 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

4.337 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. These films will not be collected but should be held by the institution and available for review if requested.

4.3371 For IMRT plans, all plans must be submitted electronically via TRIAD for review, in addition to what is required from IROC Houston in Section 10.2. **(05/12/2014)**

4.3372 For IMRT plans, Dose-Volume Histograms (DVHs) are to be obtained for each one of the target volumes defined above, as well as the critical surrounding structures, and need to be submitted for evaluation.

For submission to TRIAD, the structure names MUST be match exactly as listed below or resubmission may be required

| **Structure Name** | **Description** |
|---|---|
| ITV | Envelope of Vagina and Parametria in bull and empty bladder scans.<br>**Required** |
| CTVn | Nodal CTV<br>**Required** |
| CTV_5040 | ITV combined with Nodal CTV<br>**Required** |
| PTVp_5040 | ITV with a 7.0 mm margin<br>**Required** |
| PTVn_5040 | Nodal CTV with a 7 mm margin |

| | **Required** |
|---|---|
| PTV_5040 | Nodal PTV combined with vaginal/parametrial PTV<br>**Required** |
| Bladder | Bladder<br>**Required** |
| Rectum | Rectum<br>**Required** |
| BowelSpace | **Bowel**<br>**Required** |
| NonPTV | External minus PTVs<br>**Required** |
| External | External Skin<br>**Required** |

**(05/12/2014)**

4.338 Compliance Criteria for IMRT

Per protocol: Interruption of 0 days
Variation acceptable: Interruption of 1-7 consecutive days
Deviation unacceptable: Interruption of ≥ 8 consecutive days

4.3381 Target volumes (PTV)

Composite PTV to 50.4 Gy
- Per protocol: The prescription criteria in Section 4.331 are fulfilled.
- Variation acceptable: The 0.03 cc volume of overdose for the PTV exceeds 110% of the prescribed dose but remains at or 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 receives a dose that is < 91% of its prescribed dose.

4.3382 Critical normal structures

Bowel:

Per protocol: ≤ 30% receives > 40 Gy. No volume within bowel that is 0.03 cc or larger receives a dose that is > 110% of the prescription dose.

Variation acceptable: > 30% receives > 40 Gy, but ≤ 45 Gy. A volume of at least 0.03 cc of bowel exceeds 110% of the prescribed dose, but remains at or below 115%

Deviation unacceptable: > 30% receives > 45 Gy. A volume of at least 0.03 cc of bowel exceeds 115% of the prescribed dose.

Rectum **(06/13/2011)**:

Per protocol: ≤ 80% receives > 40 Gy. No volume within rectum that is 0.03 cc or larger receives a dose that is > 110% of the prescription dose.

Variation acceptable: > 80% receives > 40 Gy, but ≤ 50 Gy. A volume of at least 0.03 cc of rectum exceeds 110% of the prescribed dose, but remains at or below 115%

Deviation unacceptable: > 80% receives > 50 Gy. A volume of at least 0.03 cc of rectum exceeds 115% of the prescribed dose.

Bladder:

Per protocol: ≤ 35% receives > 45 Gy. No volume within bladder that is 0.03 cc or larger receives a dose that is > 110% of the prescription dose.

Variation acceptable: > 35% receives > 45 Gy, but ≤ 50 Gy. A volume of at least 0.03 cc of bladder exceeds 110% of the prescribed dose, but remains at or below 115%

Deviation unacceptable: > 35% receives > 50 Gy. A volume of at least 0.03 cc of bladder exceeds 115% of the prescribed dose.

4.4 Chemotherapy

4.41 Formulation: Cisplatin (Cis-diamminedichloroplatinum)
Cisplatin is available in aqueous solution in 50 mg and 100 mg vials with 9 mg/Ml of sodium chloride.

4.42 Preparation: 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.

4.43 Storage: The aqueous solution should be stored at room temperature and protected from light.

4.44 Adverse effects (please see package insert for more information):

4.441 Frequent: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, aminoglycoside ototoxicity, ocular toxicity, and allergic reactions.

4.442 Infrequent: Cardiac abnormalities, anorexia, elevated SGOT, rash, alopecia, and acute myeloid leukemia.

4.443 NOTE: Aminoglycoside antibiotics given before, with, or after Cisplatin may potentiate renal toxicity and should be avoided whenever possible.

4.444 Severe renal toxicity can be largely avoided by induction of a diuresis before, during, and after treatment.

4.445 Mild renal dysfunction is a common complication (10%) of chronic
therapy and may require discontinuation of therapy if creatinine > 1.5 x Institutional upper limit normal (ULN) develop.

4.446 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.

4.447 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.

4.448 Local necrosis and thrombophlebitis can be avoided by careful administration.

4.449 Neurotoxicity may be 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.

4.4410 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.

4.45 Drug Interactions
*Phenytoin:* cisplatin decreases the effect of phenytoin
*Aminoglycosides, amphotericin B***:** increased renal toxicity
*Loop Diuretics (furosemide):* increased risk of ototoxicity

4.46 Supplier: Commercially available.

4.47 Concurrent Cisplatin Administration **(06/13/2011)**
1,000 ml of normal saline should be infused intravenously one hour before cisplatin. Increased oral intake of water should be encouraged starting the day before treatment. Additional fluid may be given as needed for symptomatic support.

Patients enrolled will receive 40 mg/ $m^2$ of cisplatin (maximum total dose of 70 mg/week). Drug may be diluted in 250 ml 0.9% sodium chloride and administered over one or two hours. Alternatively, cisplatin may be diluted and administered per established institutional guidelines.

Details of pre- and post-hydration are left to the discretion of the treating physician, but at least 1,000 ml 0.9% sodium chloride prior to cisplatin and another 500-1,000 ml 0.9% sodium chloride after cisplatin are recommended.

**This is the minimum fluid administration recommendation and more fluid may be given at the discretion of the treating physician**.

Cisplatin will be given on the first day of external RT (Day 1), preferably approximately four hours prior to RT, cisplatin will be repeated as above on days 8, 15, 22, 29, and 36 (preferably Mondays) of external RT.

See Appendix V for General Chemotherapy Guidelines

The 6th cycle of cisplatin may be omitted if all radiotherapy has been completed.

4.5 Quality of Life Assessments (QOL)

4.51 The Functional Assessment of Cancer Therapy – (FACT-G, Version 4) is a brief, validated, sensitive 27-item measure for evaluating QOL in patients receiving treatment for cancer[32]. In addition to a total QOL score, subscale scores for physical, functional, social and emotional well being are produced. Utilization of this questionnaire will allow for a determination of the extent to which the addition of chemotherapy affects overall QOL as well as domain specific QOL (for example, functional well being).

4.52 The four sensory items from the FACT-Neurotoxicity (Ntx) subscale will be included to assess potential side effects from cisplatin chemotherapy (FACT-Ntx 1 through FACT-Ntx 4). A recent study examined the use of this subscale in patients with advanced endometrial cancer treated with doxorubicin/cisplatin doxorubicin/cisplatin/paclitaxel prior to 1-7 cycles of treatment.[33] The sensory items (Ntx1 though Ntx4) accounted for 80% of treatment differences and 63% of longitudinal changes in the subscale score. These four questions will therefore be included so that assessment of neurotoxicity is included, but response burden is minimized.

4.53 Response to a single question from the Brief Pain Inventory (BPI) will be included in order to obtain important information on pain levels, shown to be significant in other cervical cancer studies,[27] without significantly increasing response burden (Describe pain at its worst during the last 24 hours).[34]

4.54 In order to understand effects of the proposed treatments, the following patient-reported outcomes will also be measured:

4.541 The cervix subscale of the FACT-Cx, which consists of 15 questions developed from interviews with patients and clinicians involved with cervical cancer,[35] has been used to assess QOL in women with cervical cancer who are undergoing cisplatin chemotherapy.[27,35]

4.542 Acute toxicities associated with RT include nausea, vomiting, abdominal cramping and diarrhea.[28] Grade 3-4 adverse events in women receiving RT reported in GOG-0092 [17] were hematologic, gastrointestinal, and genitourinary. The FACT-Cx includes questions that directly address nausea, lack of appetite, side effects of treatment, pain, and control of urine.

4.543 Five additional questions that address control of bowels, cramping and diarrhea will be included. These questions are expected to more sensitively measure less severe grades of acute toxicity. The five additional questions are:

BL2. I urinate more frequently than usual.
C3. I have control of my bowels.
O3. I have cramps in my stomach area.
C4. I can digest my food well.
C5. I have diarrhea.

4.544 All questions will be combined into one Scantron form. Total number of questions will be 52: FACT-Cx (42), Neurotoxicity questions (4), additional toxicity questions (5), brief pain question (1).

4.55 Translation of the instruments into Korean.

The FACT-G, the Cervix subscale, the five additional questions, and the Neurotoxicity subscale have been translated into Korean and validated by the Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare, Evanston, IL. This translation involved a rigorous methodology, psychometric testing and cognitive interviewing to ensure that the resulting measure was both conceptually equivalent as well as cross-culturally valid utilizing the linguistic experience of the translation team and staff experienced with the outcome measures. Details of the methodology used for translation have been published.[36-38]

Yun et al [39] have published a validation study of the Korean version of the Brief Pain Inventory (BPI) that included a back translation. Korean versions of QOL instruments were used to further validate the translated BPI in 132 patients with recurrent or metastatic cancer.

4.6 Timing of Quality of Life Assessments:

Baseline: Longitudinal QOL scores are correlated [27] so that assessment of longitudinal QOL scores in this study will include a baseline measurement completed prior to randomization to control for effects influencing patients prior to treatment. The baseline QOL assessment will be completed prior to entry/randomization.

During treatment: To assess the effect of adding cisplatin chemotherapy to RT, QOL assessments will be made 3 weeks following the first day of treatment and 7 weeks following the first day of treatment. In women receiving cisplatin chemotherapy, the QOL assessment 3 weeks following the first day of treatment should be done prior to starting a cisplatin cycle.

Long term effects: QOL data will be collected at 9 months following the first day of treatment. This will allow for determination of the acute effects of cisplatin as well as effects that may appear following cessation of treatment.[25, 28] This will also allow for assessment of potentially additive toxicities due to surgery and RT with cisplatin therapy.

All QOL questionnaires are to be administered by the nurse/data manager or the physician. Patients should be told that they will be asked to complete the same questionnaire again at specific time intervals that coincide with appointments/treatment. If patients need assistance, they may be helped. Please record the reason for assistance. Patients should be instructed to answer all questions and report any symptoms even if they are not related to cancer or treatment. Family members should be asked to wait in another room while the patient completes the questionnaire.

Women Who Terminate Treatment or Experience Treatment Delays:

**QOL assessments are not tied to treatment so should be given at the specified time** (3 weeks following the first day of treatment, 7 weeks following the first day of treatment, 9 months following the first day of treatment), **even if women experience treatment delay or termination.**

# 5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE **(06/13/2011) (05/12/2014)**

## 5.1 Investigator and Research Associate Registration with CTEP **(05/12/2014) (05/12/2020)**

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and 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 Cancer Trials Support Unit (CTSU) 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; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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

## 5.11 Cancer Trials Support Unit Registration Procedures

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).

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

### 5.111 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 for Local Context (SSW) 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;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

**Additional Requirements**

Additional 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); and
- Compliance with all protocol-specific requirements (PSRs).

**Protocol-Specific Requirements for GOG-0263 Site Registration**

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. Sites 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 any roster is required to update 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.

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.

5.122 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 based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in 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 Oncology and protocol number GOG-0263
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

5.123 Requirements For GOG-0263 Site Registration:

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. Sites 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 any roster is required to update 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.

5.124 Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU 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 at 1-866-651-2878 in order to receive further instruction and support.

5.125 Checking Your 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 sites 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.

5.2 Patient Enrollment (05/12/2014)(05/12/2020)

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. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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 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.

5.3 Credentialing Requirements **(05/12/2014)(05/12/2020)**

5.31 Credentialing for this protocol will be handled by IROC Houston

(formerly the Radiological Physics Center [RPC[). All information regarding credentialing can be found on the IROC Houston website (http://irochouston.mdanderson.org ) by selecting "Credentialing", then "GOG."

5.32 Before ANY patient is enrolled on this study, the treating radiation oncologist must complete on-line a Knowledge Assessment Questionnaire found on the IROC Houston website.

Each institution must complete the Facility Questionnaire available on the IROC Houston web site by selecting "Protocol GOG-0263".

5.33 IMRT credentialing requirements when IMRT is planned:
Institutions must be credentialed for IMRT by IROC Houston for this protocol prior to enrolling patients into this study when IMRT is planned. Each institution must successfully irradiate a standardized phantom available from IROC Houston. Instructions for requesting and irradiating the phantom are available at the IROC Houston web site. Institutions that have been previously credentialed for IMRT by RTOG or GOG via the head and neck phantom or the pelvic phantom can determine what additional requirements must be completed by filling out the "Credentialing Status Inquiry" form on the IROC Houston website. IROC Houston will issue credentials for this protocol to the institution and notify the GOG Statistical and Data Center.

Each Institution must complete the IMRT portion of the Facility Questionnaire available on the IROC Houston web site by selecting "Protocol GOG-0263". Each institution must submit the completed IMRT Facility Questionnaire online.

Institution and/or peer-reviewed documentation of target position reproducibility [planning treatment volume (PTV) and clinical target volume (CTV)] must be consistent with Section 4.334.

5.34 Digital Radiation Therapy Data Submission Using Transfer of Images and Data **(05/12/2014)(05/12/2020)**

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 CTEP-IAM account.
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician

Investigator (NPIVR), or Investigator (IVR) registration type. 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.

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## 5.4 Treatment Plan

Patients who meet the eligibility requirements according to Section 3.0 will be assigned randomly to one of the two regimens:

Arm I: Control Arm; RT alone (Section 4.3)

Arm II: CRT Arm; weekly Cisplatin 40mg/$m^2$ concurrent to RT (Section 4.4)

# 6.0 TREATMENT MODIFICATIONS

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and 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 CTEP Active Version of CTCAE.

## 6.1 Treatment Modification of Radiation Therapy

Treatment may be interrupted for up to a maximum 2 weeks for CTCAE Grade 3 or 4 gastrointestinal or hematologic toxicities, but every effort should be made to minimize treatment delays. In particular, those with Grade 3 toxicities who remain outpatients should receive maximal supportive care, including medications and IV fluid/electrolytes supplementation that would reduce or prevent treatment interruptions.

**The Study Chair should be notified of any Grade 4 toxicity.**

### 6.11 Expected Toxicity

#### 6.111 Blood/Bone Marrow (Hematologic)

Hematologic toxicity is seen infrequently unless pelvic RT is accompanied by chemotherapy. A CBC should be obtained weekly, and if the ANC is below 500/mcl or the platelet count drops below 50,000/mcl, counts should be obtained twice weekly. Even if chemotherapy is held for myelosuppression, radiotherapy should be continued as long as blood counts remain above critical values (See Section 6.12).

Every effort should be made to maintain hemoglobin $\geq$ 10g/Dl It is up to the individual investigator's discretion as to how best to achieve this.

#### 6.112 Gastrointestinal

Nausea and vomiting are rather unusual after pelvic RT. The use of prophylactic anti-emetics is strongly encouraged. Anti-emetic regimens are at the discretion of the investigator. Anti-emetics may be given when symptoms occur if not given prophylactically prior to treatment.

Intractable nausea or vomiting is rarely seen with pelvic RT alone and is usually the result of another process (i.e., bowel

obstruction). Increased bowel activity with diarrhea usually can be controlled with low-fiber, low-fat, bland diets and anti-diarrheal medications. Should GI toxicity become severe, hospitalization may be required at which time the treatment may be interrupted temporarily until the patient's condition improves. This interruption should be limited to < 1 week if possible, but no more than 2 weeks to remain on study.

6.113 Renal/Genitourinary

Acute toxicity of the urinary tract is manifested by cystitis. Maintaining high fluid intake is important. Bladder antispasmodics, analgesics and antibiotics are recommended. Gross hematuria is not usually seen with acute cystitis and suggests bladder invasion by tumor.

6.114 Dermatologic/Skin (Cutaneous)

With the use of megavoltage external beam RT skin reactions in the treatment field are infrequent. During RT, mild irritation and redness of the skin may occur within the radiation fields. Some patients may experience more intense skin reaction such as dry or moist desquamation depending upon the energy of the megavoltage beam, number of fields used per day, need to cover distal vagina and therefore flashing perineum and use of chemotherapy. Hair loss in the pubic area may occur which can be permanent. Late subcutaneous fibrosis, telangiectasia, and skin atrophy are uncommon sequelae.

Acute skin reactions may be treated according to the institutional preferences. Aquaphor or steroid creams may be used for CTCAE Grade 1-2 reactions, and it is not necessary to interrupt the RT. For CTCAE Grade 3-4 skin reactions when generalized macular, papular or vesicular eruptions have developed, or there is generalized exfoliative or ulcerative dermatitis in the treatment fields, RT may be interrupted, but maximal supportive care should be used to avoid treatment breaks.

Treatment may require symptomatic management of pain, use of warm saline soaks, vitamin A&D ointment, wearing loose clothing, and keeping the area dry. RT should be resumed as soon as the skin reactions have improved.

6.12 Radiation Dose Modifications

A maximum of up to 7 consecutive treatment days for RT break is allowed on protocol, but every effort should be made to minimize RT treatment delays and interruptions. **The radiation oncology study co-chair should be notified of any treatment break exceeding 7 days.**

6.121 Blood Bone Marrow (Hematologic) Adverse Effects
External RT may be delayed for ANC < 250/mcl or platelet count < 30,000/mcl. During an RT break for myelosuppresion, CBCs should be checked at least 2 times per week and RT restarted when counts exceed the threshold.

6.122 Gastrointestinal Adverse Effects
Patients will be treated with a low residue diet and anti-peristaltic drugs. External RT may be interrupted for CTCAE Grade 3 or 4 GI toxicity. **Use of prophylactic anti-emetics is strongly recommended.**

6.123 Renal/Genitourinary Adverse Effects
External RT may be delayed for CTCAE Grade 3 or 4 bladder toxicity.

6.124 Dermatologic/Skin (Cutaneous) Adverse Effects
RT will not be delayed for moist desquamation, but a treatment break may be required for cutaneous ulceration.

6.13 Patients who must take a break longer than 2 weeks during radiotherapy will be removed from the protocol directed therapy. However, they should re-start radiotherapy off-study as soon as the toxicities have improved to an acceptable level.

6.2 Treatment Modification of Concurrent Chemotherapy

Radiotherapy will not be omitted or delayed for chemotherapy-related toxicities unless the investigator considers that the patient is too unwell to be treated. Any interruption in radiotherapy due to toxicity requires a dose reduction of one level.

6.21 Cisplatin Modifications

6.211 Gastrointestinal Adverse Effects

6.2111 For nausea and vomiting, antiemetics should be used prophylactically.

6.2112 For nausea and vomiting requiring hospitalization or TPN >

24 hours, reduce cisplatin by one dose level.

6.212 Renal/Genitourinary Adverse Effects

6.2121 If creatinine rises to greater than 2.0 mg/Dl, discontinue cisplatin therapy.

6.2122 Selective renal tubular defects are sometimes observed: Hypocalcemia with hypomagnesemia and hypokalemia are common and potentially severe. Replacement of magnesium, calcium and potassium are usually effective. Severe tubular effects, although rare, may require chronic replacement therapy. Diagnostic tests for alternative mechanisms of hypocalcemia (e.g. GI or metabolic) should be considered.

6.213 Neurologic Adverse Effects

6.2131 CTCAE Grade 1 - No change

6.2132 CTCAE Grade 2 - Reduce cisplatin by one dose level

6.2133 CTCAE Grade 3 or 4 - Hold cisplatin until recovered to ≤ grade 2 and then resume at one dose level reduction

6.214 Blood/Bone Marrow (Hematologic) Adverse Effects

Cisplatin should be withheld from patients with an ANC less than 500/mcl or platelet count less than 50,000/mcl. Therapy should be delayed up to one week until these levels are exceeded.

**External RT should continue while drug is withheld, as long as thresholds for continued RT are met (see Section 6.12).**

6.215 Dose Modification Tables

| Dose Level | Cisplatin |
|---|---|
| Dose Level 1 | 40 mg/ $m^2$ (max = 70 mg*) |
| Dose Level -1 | 30 mg/ $m^2$ (max = 52.5 mg*) |
| Dose Level -2 | 20 mg/ $m^2$ (max = 35 mg*) |

* Max doses apply to those with BSA > 1.75 $m^2$
* There will be no dose-re-escalation after dose reduction

# 7.0 STUDY PARAMETERS

## 7.1 Observations and Tests **(06/13/2011) (05/12/2014)**

The following observations and tests are to be performed and recorded on the appropriate form(s):

| PARAMETER | Prior to entry | Weekly during Treatment | Every 3 months (1st 2 years) | Every 6 months (3-5 yrs) | Annually |
|---|---|---|---|---|---|
| Physical/Pelvic Examination | 1 | | X | X | |
| Toxicity Assessment | 4 | X | X | X | |
| Quality of Life Questionnaire | X* | 2 | 3 | | |
| Smoking Questionnaire | 1 | | | | |
| CBC/Diff/ platelets | 4 | 5,6 | | | |
| Creatinine, Alkaline phosphatase, SGOT, Bilirubin | 4 | 5,7 | | | |
| | | | | | |
| Follow-up CT or MRI or PET/PET-CT | | | | | 9** |
| Chest Imaging (x-ray or CT scan of the chest) | 1 | | | | 8 |

1. Within 28 days prior to initiating protocol therapy
2. Three weeks and seven weeks following the first day treatment
3. 9 months following the first day of treatment
4. Within 14 days prior to initiating protocol therapy
5. Must be drawn within 4 days of re-treatment
6. If ANC < 500/mcl or platelet < 50,000/mcl, twice weekly
7. Weekly in CRT group and monthly in RT group. If Creatinine > ULN or Bilirubin > 1.5 x normal, Alkaline phosphate and SGOT > 3 times normal, weekly
8. Every 6 months for the first 3 years, then annually thereafter
9. Every 6 months for the first 3 years, then annually thereafter, if chest imaging not already included in surveillance CT, MRI, or PET/PET-CT.

* QOL Questionnaire should be given prior to randomization

** A CT of the chest/abdomen/pelvis or PET/CT is required within 30 days of documentation of any initial site of recurrence. Other potential sites of recurrence will be reported as:

I) Pelvic
   a) Vaginal mucosa
   b) Paravaginal/parametrial
   c) Lateral pelvic sidewall/pelvic nodes
   d) Posterior pelvis/presacral

II) Extrapelvic
   a) Common iliac nodes
   b) Paraaortic nodes
   c) Other (specify, eg liver, lung, bone, peritoneum etc)

## 7.2 STAINED PATHOLOGY SLIDE REQUIREMENTS FOR CENTRAL REVIEW TO CONFIRM ELIGIBILITY

H&E stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. One or more representative H&E stained slide demonstrating the primary site, histologic cell type, grade, and most advanced stage of disease are required. **If the most advanced stage of disease is not documented by histology, the method of stage documentation needs to be stated (e.g. CT, MRI, etc.).**

**In addition, representative H&E stained slide (or slides) will be required to document depth of cervical stromal invasion (see note below) and capillary-lymphatic space involvement (if present).**
**(Note:** Women will be dichotomized as having (1) positive capillary-lymphovascular space involvement and one of the following: deep third penetration, middle third penetration and clinical tumor ≥ 2cm or superficial third penetration and clinical tumor ≥ 5 cm or (2) negative capillary-lymphovascular space involvement and middle or deep third penetration and clinical tumor ≥ 4 cm.

When submitting pathology material to the GOG Statistical and Data Center, individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date.

Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides, three copies of both the Pathology Form F (if required for the protocol) and the official pathology report in your own shipping containing using postal mail at your own expense directly to the **Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263**; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting pathology reports and Form F to the GOG Statistical and Data Center. Please see section 4.2 and 10.2 for additional requirements and instructions.

## 7.3 TRANSLATIONAL RESEARCH

### 7.31 Specimen Requirements **(05/12/2014)**

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions within the United States are required to submit the patient's translational research specimens as outlined below (unless otherwise specified).

| **Required Specimen (Specimen Code)** | **Time Point** | **Ship To** |
|---|---|---|
| FFPE Primary Tumor (FP01)*<br>• 1st choice: Block<br>• 2nd choice: 16 Unstained Slides (charged, 5µm) | Prior to all treatment | GOG Tissue Bank within 8 weeks of registration[1] |
| Whole Blood (WB01) 7-10Ml drawn into purple-top (EDTA) tube(s) | Prior to or after starting treatment | GOG Tissue Bank the day the specimen is collected |

*A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank

[1] GOG Tissue Bank/Protocol GOG-0263, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBank@nationwidechildrens.org

### 7.32 Laboratory Testing **(05/12/2014)**

FFPE tumor and DNA extracted from whole blood will be banked for future research.

### 7.33 Future Research **(05/12/2014)**

Details regarding the banking and use of translational research specimens for future research can be found in Appendix II.

## 7.4 Quality of Life Research

Please see sections 4.5 and 4.6 for information regarding the QOL assessments for this protocol and a description of the time points for these assessments. Specific information about the assessment time points and proper administration of the QOL questionnaires is out lined below.

Time Points for Quality of Life Data Collection

| | Prior to randomization | At 3 weeks*+ | 7 weeks* | 9 months* |
|---|---|---|---|---|
| One Scantron form with 52 Questions.<br>FACT-Cx (42),<br>Neurotoxicity questions (4),<br>Additional toxicity questions (5),<br>brief pain question (1). | X^ | X | X | X |

^ Within 28 days prior to initiating protocol therapy
* Following first day of treatment.
+ In women receiving cisplatin chemotherapy the QOL assessment 3 weeks following the first day of treatment should be done prior to starting a cisplatin cycle.

7.41 **If a patient progresses or is removed from the study treatment for any reason, continue to follow the schedule of QOL assessments when possible regardless of subsequent treatments**. Whenever possible, QOL questionnaires should be administered at the clinic visit before the patient is seen by the physician and before evaluations or test results are shared with her. In the event that the questionnaires are not administered at the clinic visit, the QOL data can be collected by telephone or mail as back-up methods, with telephone data collection being the preferred back-up method.

7.42 The Quality of Life Liaison (Nurse/Data Manager) at each institution has overall responsibility for the administration of the study questionnaire.

7.43 The Nurse/Data Manager should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record.

7.44 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on her own (e.g., difficulty in reading, elderly). It is important not to influence the response of the patient

7.45 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to cancer or

cancer treatment. Discourage family members from being present during questionnaire completion or from influencing the patient's response.

7.46 Review the questionnaire for completeness before the patient leaves the clinic/office.

7.47 If the patient has marked more than one answer per question, ask the patient which answer best reflects how she is feeling.

7.48 It is essential that the questionnaires be completed according to the schedule described in Section 7.1 and in the above table.

7.49 If the patient refuses or cannot complete the questionnaire at any time point, she should be asked to do so at the next scheduled administration time.

# 8.0 EVALUATION CRITERIA

## 8.1 Outcome Measures

The major parameters of outcome are recurrence-free survival and overall survival.

8.11 Recurrence is defined as clinical, radiological or histological reoccurrence of disease since study entry.

8.111 Site of First Recurrence (e.g. para-aortic or supraclavicular lymph nodes, lung, liver, bone, etc.) will also be documented.

8.12 Recurrence Free Survival is defined as the date from protocol registration to date of first documented recurrence, death or date of last contact.

8.13 Overall Survival will be defined as observed length of life from entry into the study to death; or for living patients, the date of last contact regardless of whether or not this contact is on a subsequent protocol.

8.14 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the active version of CTCAE.

# 9.0 DURATION OF STUDY

9.1 Each patient should complete the study treatment unless disease recurrence occurs or toxicity prohibits further therapy.

9.2 Each patient should be followed quarterly for two years and every six months for three additional years, and thereafter annually or at the time of recurrence until death.

# 10.0 STUDY MONITORING AND REPORTING PROCEDURES

## 10.1 ADVERSE EVENT REPORTING FOR ALL REGIMENS (COMMERCIAL AGENTS AND RADIATION THERAPY ADMINISTRATION) **(05/12/2014)**

### 10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and 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 CTEP Active Version of CTCAE.

A copy of the CTCAE Manual is also available on the GOG member web site (http://www.gog.org under MANUALS).

### 10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational or commercial agents, and role of the pharmaceutical sponsor, an AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP Adverse Event Reporting System (CTEP-AERS). All CTEP-AERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through CTEP-AERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AE's to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AE's to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AE's should be reported by the investigator.

### 10.13 Phase 2 and 3 Trials Utilizing a Commercial Agent: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Commercial Agent on Phase 2 and 3 Trials

| | Grade 1 | Grade 2 | Grade 2 | Grade 3 | | Grade 3 | | Grades 4 & 5[2] | Grades 4 & 5[2] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Unexpected | | Expected | | | |
| | Unexpected and Expected | Unexpected | Expected | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | Unexpected | Expected |
| **Unrelated Unlikely** | Not Required | Not Required | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | 7 Calendar Days |
| **Possible Probable Definite** | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | 7 Calendar Days | 7 Calendar Days | Not Required | 24-Hrs; 3 Calendar Days | 7 Calendar Days |

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a commercial agent require reporting as follows:

CTEP-AERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although Actep-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

**Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent." March 2005**

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.**

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.

  "7 calendar days" – A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via CTEP-AERS if the event occurs following treatment with a commercial agent.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:

- All Grade 2, 3, and 4 myelosuppression (including neutropenia, anemia, and thrombocytopenia) that does not require hospitalization is exempt from expedited reporting.

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 CTEP-AERS Expedited Reports **(06/13/2011)**:

Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplatic syndrome, or 3) Treatment related secondary malignancy.

In the rare occurrence when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.15 Automated CDUS reporting

For studies using commercial agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AE's reported through CTEP-AERS will also be included with the quarterly CDUS data submissions.

## 10.2 GOG DATA MANAGEMENT FORMS

The following forms must be completed for all patients registered and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. Protocol forms and instructions can be submitted through or printed from the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. **Pathology material (Form F, pathology reports and slides) should be submitted together via mail. The GOG Uploader Application in SEDES is an alternate method for submitting the operative report, discharge summary, Form F and pathology reports to the GOG SDC. Additionally radiation materials (forms, copies, films, reports, etc) must be submitted together via postal mail.**

| **Form**[±] | **Due within** | | **Copies*** | **Comments** |
|---|---|---|---|---|
| | **Weeks** | **Event** | | |
| Form R (Registration Form) | 2 | Registration | 1 | Mandatory submission via SEDES |
| Form OSC (Primary Cervical Cancer On Study Form) | 2 | Registration | 1 | Mandatory submission via SEDES |
| Specimen Consent Application | 1 | Registration | NA **(05/12/2014)** | Mandatory submission via SEDES **(05/12/2014)** |
| Form DR (Pre-Treatment Summary Form) | 2 | Registration | 1 | Mandatory submission via SEDES |
| Hysterectomy and Pelvic Lymphadenectomy: | | | | |
| Form C (Surgical Reporting Form) | 4 | Registration | 1 | Mandatory submission via SEDES |
| Operative Report | 4 | Registration | 2 | Submit via postal mail or upload via SEDES. |
| Discharge Summary | 4 | Registration | 2 | |
| Primary disease: | | | | |
| Diagnostic Biopsy: | | | | |
| Form F (Pathology Form) | 6 | Registration | 2** | Submit together via postal mail to GOG SDC in Buffalo, New York or submit using the report upload to SEDES. |
| Pathology Report | 6 | Registration | 3** | |
| Stained Slides | 6 | Registration | ** | |
| Hysterectomy and Pelvic Lymphadenectomy: | | | | |
| Form F (Pathology Form) | 6 | Registration | 2** | |
| Pathology Report | 6 | Registration | 3** | |
| Stained Slides | 6 | Registration | ** | |
| Form SHQ (Smoking History Questionnaire) | 2 | Registration | 1 | Mandatory submission via SEDES |

| | | | | |
|---|---|---|---|---|
| Quality of Life Scantron Form:<br><br>Form – baseline assessment<br>Form – 3 week assessment<br>Form – 7 week assessment<br>Form – 9 month assessment | <br><br>2<br>5<br>9<br>41 | <br><br>Registration<br>Treatment Start<br>Treatment Start<br>Treatment Start | <br><br>1<br>1<br>1<br>1 | Submit Original Scantron Form via postal mail to GOG SDC in Buffalo, New York |
| Radiation Materials:<br>External beam:<br>▪ simulation films or digitally reconstructed radiograph<br>▪ portal films<br>▪ daily treatment records<br>▪ CT/MRI showing relevant target volume<br>▪ dosimetry calculations<br>▪ Isodose distribution curves<br>▪ Form G (Radiation Treatment Form)<br>▪ 3D Plan<br><br>IMRT Rapid Review (See Section 4.31) must submit all the required data for IMRT as stated below prior to treatment of patient.<br><br>IMRT:<br>IMRT Treatment Plan electronically submitted to ITC.<br>The IMRT Treatment Plan should include:<br>▪ CT/MRI showing relevant target volume<br>▪ dosimetry calculations<br>▪ Dose Volume Histograms (DVH) | 4 | Completion of RT | <br><br>1<br><br>1<br>2<br>1<br><br>2<br>2<br><br>1<br><br>2 | Form G must be submitted via SEDES. Paper copies should also be submitted with radiation materials via postal mail.<br><br>Submit electronically to the ITC (http://atc.wustl.edu)<br><br>Submit electronically to the ITC (http://atc.wustl.edu) |
| Form D2R (Cycle Dose Drug Form) | 2 | Completion of each cycle of therapy on Regimen II | 1 | Mandatory submission via SEDES |
| Form T (Common Toxicity Form) | 2 | Regimen I: three weeks after completion of RT<br><br>Regimen II: Start of each subsequent cycle and 3 weeks after last cycle | 1 | Mandatory submission via SEDES |

| | | | | |
|---|---|---|---|---|
| Form SP-FP01-0263*** FFPE primary **(05/12/2014)** | 8 | Registration | NA **(05/12/2014)** | Mandatory submission via SEDES [f] **(05/12/2014)** |
| Form SP-WB01-0263 whole blood **(05/12/2014)** | 8 | Registration | NA **(05/12/2014)** | Mandatory submission via SEDES[f] **(05/12/2014)** |
| Form Q0 (Treatment Completion Form) | 2 | Completion of study Rx and change in Rx | 1 | Mandatory submission via SEDES |
| Form TLC (Follow-Up Period Adverse Event Reporting Form) | 2 | Each follow-up toxicity assessment following completion of study therapy | 1 | Mandatory submission via SEDES |
| Form Q (Follow-Up Form) | 2 | Disease progression; death; normal follow-up | 1 | Mandatory submission via SEDES quarterly for 2 years, semi-annually for 3 more years, and annually thereafter |

* The number of required copies including the original form which must be sent to the Statistical and Data Center.

** At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade, and **one** H&E stained slide showing the most advanced stage of disease will be required. **In addition, representative H&E stained slide (or slides) will be required to document depth of cervical stromal invasion and capillary-lymphatic space involvement.** See Sections 4.2 and 7.2 for additional details and instructions for submitting this material.

*** A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank.**(05/12/2014)**

*f* Form SP must be submitted regardless of whether the specimen is submitted for research. **(05/12/2014)**

± Use the SDC Electronic Data Entry System (SEDES), available on the GOG website, to view and print a copy of each form along with instructions, and to submit forms electronically. Please check SEDES periodically as forms that are not currently available for electronic data entry will be made available for electronic data entry over time.

This study will be monitored by the **Abbreviated** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted quarterly to CTEP by electronic means.

# 11.0 STATISTICAL CONSIDERATIONS (03/05/18)

## 11.1 Study Design and Registration

This study is designed as a randomized (allocation ratio is 1:1) Phase III clinical trial of adjuvant RT (control arm) versus weekly cisplatin concurrent to RT in post-operative intermediate risk Stage I-IIA cervical cancer patients. Intermediate risk patient characterization is based on three post-surgical prognostic factors namely, capillary lymphatic space (CLS) involvement, stromal invasion and tumor size.[5, 17, 40,41] **(14-MAR-2022).**

Prior to registration (and randomization) patient eligibility will be reviewed and verified using a study specific fast fact sheet (FFS). All patients on this study will be registered (and randomized) centrally at the GOG Statistical and Data Center (SDC).

Treatment assignments will be concealed from institutions and patients until the registration process is completed. Randomization will be balanced within five stratification factors; CLS involvement (positive or negative), stromal invasion (deep, middle, superficial), performance status (0/1, 2), RT modality (XRT, IMRT) and cooperative group (KGOG, GOG). A dynamic allocation (minimization) randomization algorithm with equal probabilities to the two treatment arms within strata will be used to facilitate optimal balance between arms.[42]

## 11.2 Study Objectives

The translational research (TR) objective is to collect specimens for future research. Valid patient outcome endpoints will be used to assess primary, secondary and Quality of Life (QOL) objectives. Recurrence free survival (RFS) is recognized as the primary study endpoint.

### 11.21 Primary objective

To determine if post-operative adjuvant CRT therapy improves RFS when compared to RT alone in post-operative intermediate risk stage I-IIA cervical cancer patients

### 11.22 Secondary objectives

#### 11.221 To determine if post-operative adjuvant CRT therapy improves overall survival (OS) when compared to RT alone in post-operative intermediate risk stage I-IIA cervical cancer patients

#### 11.222 To summarize and compare differences in frequency and severity of therapy attributed adverse events (according to the active version of CTCAE) between treatment arms

11.223 To provide assessment of patient risk- benefit (positive study only)

11.23 QOL Objective

To determine whether post-operative adjuvant CRT improve the health related QOL and produce favorable toxicity profiles compared to RT alone.

11.3 Data Elements and Endpoints

The following data elements and endpoints will be used to determine the relative therapeutic treatment effect of the two regimens:

11.31 Outcome variables: recurrence-free survival (RFS), overall survival (OS) and local control (LC). RFS will be the primary endpoint.

11.32 Baseline disease characteristics: FIGO stage (I or IIA), tumor grade, cell type (squamous, adenosquamous or adenocarcinoma), capillary lymphatic space tumor involvement (positive/negative), clinical tumor size and extent of stromal invasion (deep 1/3, middle 1/3 or superficial 1/3).

11.33 Site(s) of recurrence: local (pelvis regions, including vaginal) or distant (abdomen, lung, bone, brain and other).

11.34 Patient characteristics: age, performance status, race and ethnicity.

11.35 Frequency and severity of adverse events as assessed by the active version of CTCAE.

11.36 Treatment compliance: Number of cycles and amount of CRT administered, treatment span, incidence and duration of treatment delays, reason for delays, and reason why off study therapy.

11.37 Health related QOL metrics: FACT-Cx TOI for cervix cancer patients, FACT-GOG/Ntx4 subscale (four items) for neuropathy symptoms, BPI single item for pain, and five additional toxicity questions

11.38 Smoking history: prevalence of active smoking and extent of nicotine dependence.

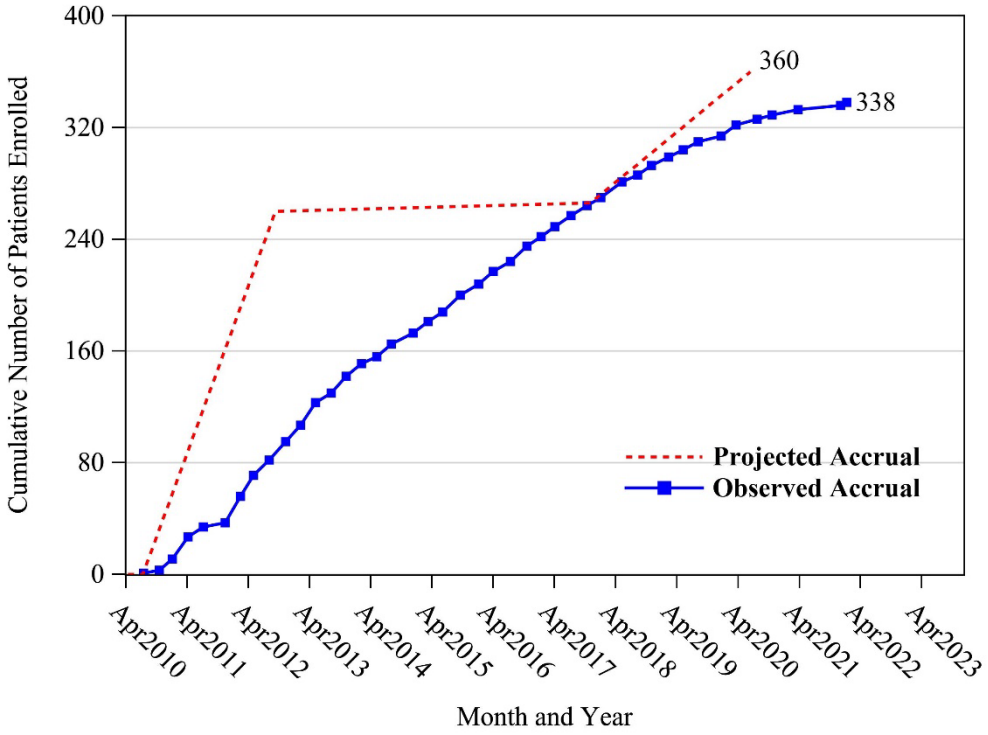
11.4 Accrual

The anticipated annual accrual (based on GOG-0092 and the Korean Gynecologic Oncology Group (KGOG) experience is 120 patients (24 and 96 from GOG and KGOG treatment centers respectively). Power analysis and sample size calculations (see Section11.5), suggests this study will require at least 480 eligible and evaluable cases.

Update (11/2017): As of November 2017, the observed annual accrual is approximately 36 patients, smaller than the anticipated annual accrual of 120 patients. Accounting for this slower accrual, the study will now require at least 342 eligible and evaluable cases without any changes to the study operating characteristics.

**Update (03/2022):** As of January 2022, GOG-0263 accrued 338 patients, with an overall average accrual rate of 2.4 patients per month. Accrual has declined considerably since 2019 (see Figure 1) averaging 1.7 patients per month from 1/1/2019 to 2/29/2020, and 0.76 patients per month from 3/1/2020 to 1/7/2022. On this basis, accrual is being permanently suspended. **(14-MAR-2022)**

**Figure 1**
**Cumulative Accrual for GOG 0263 - Data as of 1/7/2022**




11.5 Hypothesis, Planning Parameters and Sample Size

The "design" hypothesis is based on the primary objective to determine if post-operative adjuvant CRT can significantly improve 3 year RFS in intermediate risk stage I-IIA cervical cancer patients when compared with adjuvant RT alone (1-sided alternative hypothesis). The log-rank test will be the primary significance test.[43]

Previous studies including GOG-0092 suggests a significant proportion of patients on this study will be cured.[17] Thus, to model the expected performance of

the control arm we assume the Gompertz ~ $(\gamma, \theta)$ survival probability distribution with initial hazard $\gamma$ and hazard dissipation $\theta$.[44-47]

Equations 1, 2, and 3 lists survival, hazard, and cure rate functions respectively under the Gompertz ~ $(\gamma, \theta)$ survival probability distribution assumption.

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

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

$$\pi = \exp\left(\frac{\gamma}{\theta}\right) \quad (3)$$

Naturally we derived parameter estimates $\hat{\gamma}_{\text{MLE}}$ and $\hat{\theta}_{\text{MLE}}$ using the outcome data of GOG-0092 RT arm, since this historic information came from patients whose disease and treatment profiles best mimics the control arm.[17] 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 12, 36, and 60 months are listed in Table 11.1.

| Historic Data (GOG-0092 RT arm) | | | Control Arm | | | |
|---|---|---|---|---|---|---|
| $\hat{\gamma}_{\text{MLE}}$ | $\hat{\theta}_{\text{MLE}}$ | $\hat{\pi}_{MLE}$ | Time (months) | 12 | 36 | 60 |
| 0.0068 | -0.0315 | 0.8058 | ECPR | 0.0657 | 0.1362 | 0.1674 |

Table 11.1

Figure 11.1 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-0092 RT arm (dash curve) respectively.

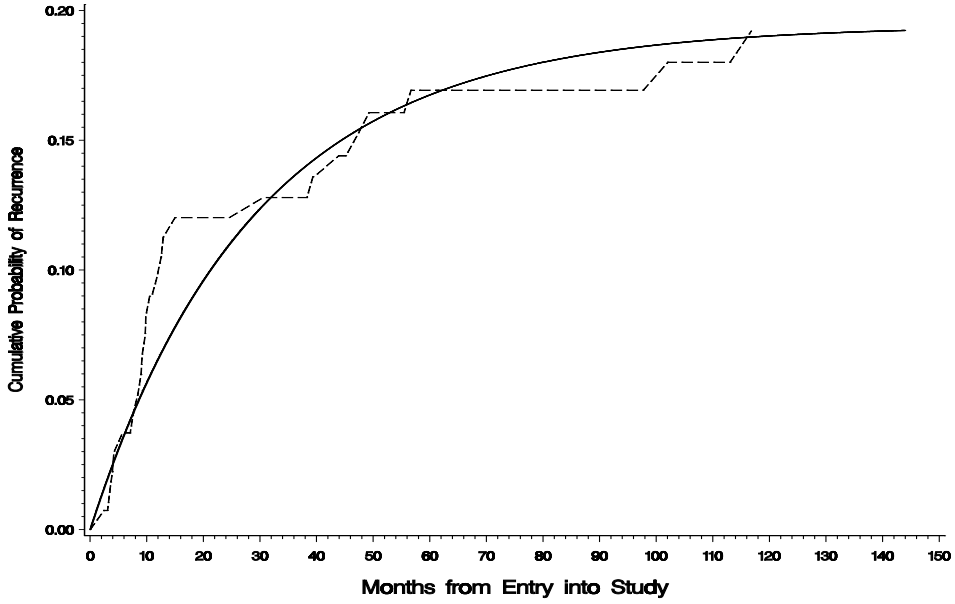



Figure 11.1

11.51 Minimum Detectable Difference

A change in RFS of 6.3% (i.e. from 87% to 93.3%) is considered a clinically important treatment advantage to detect. This difference translates into a relative hazard ratio of 0.4980 for increasing the RFS. This difference will require a total 36 recurrences in the control arm to afford statistical power (probability of a true-positive study) of at least 0.80 when keeping the probability of type I error (one tail test) at significance level, $\alpha$ =0.05.[47] The expected total number of recurrences conditioned on the alternate hypothesis is 54.[47 – 49]

11.52 Sample Size

Power analysis and sample size calculations using the Gompertz model suggest that enrolling at least 480 eligible and evaluable patients will result in the required number of recurrences.

Assuming uniform accrual and 10% lost to follow-up, the targeted accrual is 534 patients over 54 months. The study will be considered sufficiently mature for final analysis of the primary endpoint (RFS) when there are at least 36 events (recurrences) in the control arm. Conditioned on the anticipated rate of recurrence on the control arm, the post accrual follow-up period will be at least 18 months.[47, 48]. The timing for OS assessment will coincide with the primary analysis of RFS (see Section 11.3).

Update (11/2017): Based on the observed accrual rate through November 2017, power analysis and sample size calculations using the Gompertz model suggest that enrolling at least 342 eligible and evaluable patients will result in the required number of recurrences without any changes to the study operating characteristics. Assuming uniform accrual with 5%

ineligible proportion estimated from this study, the targeted accrual is 360 patients expected to be met in 2020. The study will be considered sufficiently mature for final analysis
of the primary endpoint (RFS) when there are at least 54 RFS events observed among all patients. Conditioned on the anticipated rate of recurrence on the control arm, the post accrual follow-up period will be at least 24 months.[47, 48]

**Update (03/2022):** Due to very slow accrual since 2019, enrollment is being permanently suspended. As of March 11, 2022, 340 patients enrolled onto GOG-0263, of whom 311 were eligible. The study will be considered sufficiently mature for final analysis of the primary endpoint (RFS) when at least 54 RFS events are observed among all patients. Given the anticipated rate of recurrence on the control arm, the post accrual follow-up period will be about 40 months. **(14-MAR-2022)**

11.6 Analyses and Evaluation of Study Endpoints

By definition the intent to treat (ITT) analysis set consists of all randomized patients.[49-51] However, it is possible, after randomization, for a given case to be excluded (upon centralized GOG reviews) for a variety of reasons including, incorrect baseline risk assessment, inadequate pathology, wrong stage, and improper surgery. On GOG-0092, approximately 7% of randomized cases were excluding upon either gynecologic or pathologic central reviews.

Despite being randomized (and possibly treated), excluded cases will not be included in the analysis of RFS or OS. Thus, for evaluation of primary endpoints we define the modified intent to treat (MITT) analysis set to include all **eligible and evaluable** patients as randomized.

Regarding the assessment of AE objectives, in additional to utilizing the MITT set; analyses will also be conducted on all randomized patients **as treated**.

11.61 Evaluation of RFS and OS

Product-limit estimates according to the method of Kaplan and Meier and the one sided log-rank test ($\alpha$ =0.05) will be used to compare survival endpoints (RFS and OS) between treatment arms.[43, 53, 54]

Gompertz hazard regression will be employed to evaluate relative risk (hazard ratio) and cure rates, adjusting for known prognostics factors. It is plausible to used the infamous Cox proportional hazard regression, the advantage of the Gompertz approach is its provision of estimates of the cure rate.[47, 55]

11.62 Evaluation of Site(s) of Recurrence

The site(s) of first disease recurrence will be classified as: pelvic-only, extra-pelvic-only or pelvic-and-extra-pelvic and tabulated by treatment

group. The test of the hypothesis that the probability of local failure is independent of randomized treatment will be assessed with Exact Logistic Regression adjusted know prognostic factors.[56]

11.63 Toxicity analysis

Adverse events will be graded according to the active version of CTCAE (Grades 0 - 5), but combining Grades 0, 1 and 2 data. In addition to displaying frequency of AE for each grade category, significance of observed differences between treatment arms within each AE category (e.g. GU, GI HM will be analyzed using Fishers' exact test.[57]

11.64 Health related QOL:

Health related QOL will be assessed using a one page form, made up of 52 questions: the FACT-Cx (42), Neuro-toxicity questions (4), additional toxicity questions (5), and pain question (1).

The pain question is scored using an 11 point integer scale (from 0 = no pain to 10 = the worst pain). All other questions are scored using a 5 point scale (0 = not at all; 1 = a little bit, 2 = somewhat; 3 = quite a bit; 4 = very much).

11.641 QOL assessment time points:

Each patient will complete the QOL questionnaire at the following time points regardless of the amount of study therapy received
T0: baseline, just prior to entry/randomization
T1: 3 weeks from planned (or actual) treatment start date
T2: 7 weeks from planned (or actual) treatment start date
T4: 36 weeks from planned (or actual) treatment start date

11.642 Construct and scoring:

The Treatment Outcome Index of the Functional Assessment of Cancer Therapy for cervix cancer (FACT-Cx TOI) is a subset of the FACT-Cx defined to assess general changes in QOL of cervix cancer patients. It consists of three subscales: Physical well-being (7 items), Functional well-being (7 items) and Cervix Cancer subscale (15 items).

The FACT/GOG Ntx4 subscale (i.e. the four neuro-toxicity questions) shown to be most related to cisplatin based chemotherapy will be used in this study. Regarding worst pain experiences, one question (the pain question) from the Brief Pain Inventory (BPI) will be asked. Within an individual assessment, one or more items may not be answered. A subscale score will be computed as long as more than 50% of subscale items have been answered. A subscale score $S_i$ with $N_i$ items will be calculated as:

$$S_i = N_i \times \frac{\sum_{j=1} \left( \delta_{ij} \times s_{ij} \right)}{\sum_{j=1} \delta_{ij}}$$

11.643 Where $\delta_{ij}$ is equal to 1 when the $j^{th}$ item has a valid response, otherwise it is equal to 0 and $s_{ij}$ is the response score of the $j^{th}$ item. The total FACT-Cx TOI score is the sum of the subscale scores if at least 80% of the FACT-Cx TOI items provide valid answers. The FACT-Cx TOI, and the FACT-GOG/Ntx4, total scores ranged 0 – 116, and 0 – 16 respectively.

11.644 QOL hypotheses and analyses:
The principal QOL research question is, are there differences in general QOL as determined with the FACT-Cx TOI, or in neuropathy symptoms as assessed by the FACT-GOG/Ntx subscale scores or in pain as assessed with the single item BPI question scores, between treatment arms:

$H_0$: $\mathbf{QS}_{\text{ARM 1}} = \mathbf{QS}_{\text{ARM 2}}$

Where $\mathbf{QS}_{(.)}$ is a vector of expected FACT-Cx TOI, FACT-GOG/Ntx4 and scores evaluated at specific time points for the patients on the indicated arms.

Regression models will be used to evaluate the hypothesis on the FACT-Cx TOI, and the FACT-GOG/Ntx4 subscale, adjusting for baseline FACT-Cx TOI scores and age.

QOL analyses using the pain question and the five additional toxicity questions will be considered exploratory, and 95% confidence interval will be reported for observed differences between treatment arms.

11.645 Power Analysis for QOL:
Since the primary QOL hypothesis ($H_0$) includes two primary QOL endpoints; the overall type 1 error rate can become large if the significant level for each endpoint of the hypothesis is set at 5%. To control the overall type I error rate at 5%; the significance level is set at 0.025 (0.05/2) using the Bonferroni method.
The accrual objective of this study is 342 eligible patients (171 per arm).

Based previous and current GOG studies QOL compliance is estimated to be at least 75% for all assessment points. Therefore the number of patients that will complete the QOL assessments at

each time point is estimated to be at least 128 eligible patients per arm. Assuming that QOL compliance is ≥75%, this study will be able to detect a difference of 0.5 standard deviation (SD) in QOL scores as measured by the FACT-Cx TOI and the FACT-GOG\Ntx4 subscale with at least 95% power at $\alpha = 0.025$ ( two-sided ).

11.7 Study Monitoring, Data Quality Control and Semi-annual Reports **(05/12/2014)**
The GOG SDC is responsible for the secure, efficient and accessible storage of the data. To assure the best possible data quality, the study statistician in collaboration with the data manager/coordinator (DM) will execute regular data checks. Inconsistencies and errors will be queried and sites will notify the DM upon resolution. In turn the DM will repeat data checks to make certain that query was indeed resolved. Every effort will be made to resolve outstanding queries promptly. Unresolved queries will be documented and briefly cited in the study scientific table.

CRFs will be reviewed by the study chair (co-chair) in May and November of each year of active accrual. Addition reviews may be scheduled in conjunction of interim futility and efficacy analyses. The purpose of these reviews is to access protocol compliance and possibly make recommendations.

After data checks, study chair (co-chair) reviews and data updates, a locked dataset void of protected patient information will be saved using standardized GOG SDC dataset achieving convention.

Reports, with treatment assignment blinded, will be generated periodically from the most recent locked information by the study statistician for inclusion into the GOG's Semi-annual Statistical Report (GOG SR). The SR is distributed to GOG members at the GOG Semi-annual Business Meeting and it is made available to group members via the GOG Website. The purpose is to access study progress regarding accrual (and patient accession), distribution of baseline traits, treatment compliance, patient safety (adverse events) and to facilitate the formulation of possible amendments as needed.

In addition to these reports, all serious (SAE) and unexpected adverse events regardless of attribution will be communicated promptly to the study chair, and any regulatory agencies mandated in the protocol. Furthermore, toxicity information will be reviewed by the GOG Safety Review Committee (SRC) at each semi-annual meeting during the period for which patients are on study**.**

The goal of the SRC is to review the AE data, including all new SAE reports (from ongoing GOG studies) submitted between consecutive GOG business meetings held in January and July each year.

In addition to the SRC, the study will also be supervised by the GOG Data Safety and Monitoring Board (DSMB). This group is charged with monitoring ongoing trials for early and convincing evidence of clinically important benefit or early evidence of harm. The DSMB may recommend that the trial continue as planned, be amended or be terminated (cease accrual) early. In general, the SRC reports to the DSMB.

## 11.8 Interim Analyses

### 11.81 Interim Safety Analysis **(05/12/2014)**

Each GOG SR for this study will include a safety analysis made up of a detail listing of the maximum grade for any AE attributed to therapy by blinded treatment. Significance of AE imbalance between treatment arms will be accessed informally or formally (e.g., Fisher exact test) according to the available information. Treatment assignment will be revealed to either one of respective data monitoring committees (SRC or DSMB) upon request.

### 11.82 Interim Analysis for Efficacy

Two interim analyses of RFS will be conducted just before the GOG semi-annual business meeting that reports for the first time at least 12 and 24 recurrences are observed in the control arm (i.e., approximately 33% and 67% of information needed for final analysis). Consideration will be given to stopping the trial at if dramatic differences in RFS are observed between the two treatment arms. The interim log-rank test of RFS will be adjusted for known prognostic factors.

Update (11/2017): The 1st planned interim analysis was performed at the 33% of the information time (i.e., 18 RFS events observed in both arms out of the 54 RFS events required in both arms). The 2nd planned interim analysis will be conducted at 67% of the information time (i.e., 36 RFS events observed in both arms out of the 54 RFS events required in both arms). This switch from the number of RFS events observed only in the control arm to the number of RFS events observed in both arms will not change the study operating characteristics, the pre-specified interim analyses' information time, and the pre-specified stopping rule for efficacy and futility.

The interim stopping rule assumes that three sequential tests are made using the O'Brien-Fleming spending functions to determine the test boundaries.[58, 59] If the null hypothesis can be rejected terminating accrual will be considered. The critical z-scores at interim analysis are z = 3.2003, z = 2.1409 and z = 1.6948 corresponding to 33%, 67% and 100% (final analysis) of the information time respectively. The tail probabilities associated with these z-scores are 0.0007, 0.0161 and 0.0451 respectively. This stopping rule will maintain the overall type I error for this one-sided

log-rank test at 0.05. **(14-MAR-2022)**

11.83 Interim Futility Analysis

If there is any degree of excess risk of recurrence in the experimental arm compared to the control arm then accrual will be terminated with a conclusion that the experimental arm did not exhibit a RFS advantage.[60] In this event, the null hypothesis will be accepted. The acceptance region during interim analysis at 33% of the information time will be $z < 0$ and at final analysis, $z < 1.6948$. This stopping rule increases the probability of type II error by 2.3%.

11.84 Suspending Follow-up for the Final Analysis (03/2022) **(14-MAR-2022)**

The RFS endpoint is expected to mature about 40 months after the recommended early closure (Table 11.1).

To ensure timely and efficient dissemination of the study results, follow-up for the primary RFS analysis may be suspended 24 months after the last patient is enrolled on the study. If the primary endpoint has not matured by this time, the DMC may recommend closing the study for analysis. This decision will be informed by the number of events observed to date, the number of patients still at risk, the estimated RFS hazard, and other factors as appropriate.

Table 11.1 shows the projected time for final analysis using historical GOG-0092 RT arm as control arm by software EAST with accrual and drop-out information from GOG-0263. With 24 months of follow-up on 340 patients, we expected a total of 48 RFS events, which will provide 77% power to detect a hazard ratio of 0.498 without any compromise to the pre-specified study type I error and interim analysis decision rules.

**Table 11.1** Projected time for final analysis using historical GOG-0092 RT arm as control arm by software EAST with accrual and drop-out information from GOG-0263

| Number of RFS Events | Power† | Months from Accrual Suspension |
|---|---|---|
| 42 | 0.718 | 0 |
| 44 | 0.735 | 0 |
| 45 | 0.743 | 9 |
| 46 | 0.750 | 12 |
| 48 | 0.767 | 20 |
| 50 | 0.782 | 27 |
| 52 | 0.796 | 35 |
| 53 | 0.803 | 40 |

†: power without adjustment of interim futility analyses is the same as the original study design **(14-MAR-2022)**

11.9 Planned Minority Inclusion

The following are the race and ethnicity distribution anticipated for this trial based on GOG-0092:

| Accrual Targets | | | | | |
|---|---|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | | | |
| | **Females** | | **Males** | | **Total** |
| Hispanic or Latino | 55 | + | 0 | = | 55 |
| Not Hispanic or Latino | 479 | + | 0 | = | 479 |
| **Ethnic Category: Total of all subjects** | 534 (A1) | + | 0 (B1) | = | 534 (C1) |
| **Racial Category** | | | | | |
| American Indian or Alaskan Native | 2 | + | 0 | = | 2 |
| Asian | 52 | + | 0 | = | 52 |
| Black or African American | 128 | + | 0 | = | 128 |
| Native Hawaiian or other Pacific Islander | 3 | + | 0 | = | 3 |
| White | 349 | + | 0 | = | 349 |
| **Racial Category: Total of all subjects** | 534 (A2) | + | 0 (B2) | = | 534 (C2) |
| | (A1 = A2) | | (B1 = B2) | | (C1 = C2) |

Update (11/2017): The following are the race and ethnicity distribution anticipated for this trial based on GOG-0092 for a sample size of 360.

| Accrual Targets | | | | | |
|---|---|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | | | |
| | **Females** | | **Males** | | **Total** |
| Hispanic or Latino | 37 | + | 0 | = | 37 |

| | | | | | |
|---|---|---|---|---|---|
| Not Hispanic or Latino | 323 | + | 0 | = | 323 |
| **Ethnic Category: Total of all subjects** | 360 (A1) | + | 0 (B1) | = | 360 (C1) |
| **Racial Category** | | | | | |
| American Indian or Alaskan Native | 1 | + | 0 | = | 1 |
| Asian | 36 | + | 0 | = | 36 |
| Black or African American | 86 | + | 0 | = | 86 |
| Native Hawaiian or other Pacific Islander | 2 | + | 0 | = | 2 |
| White | 235 | + | 0 | = | 360 |
| **Racial Category: Total of all subjects** | 360 (A2) | + | 0 (B2) | = | 360 (C2) |
| | (A1 = A2) | | (B1 = B2) | | (C1 = C2) |

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APPENDIX I

CARCINOMA OF THE CERVIX UTERI
FIGO CLASSIFICATION
2009

| | |
|---|---|
| Stage I | The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded) |
| IA | Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5mm and largest extension ≥ 7 mm |
| IA1 | Measured stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0mm |
| IA2 | Measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not > 7.0 mm |
| IB | Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA* |
| IB1 | Clinically visible lesion ≤ 4.0 cm in greatest dimension |
| IB2 | Clinically visible lesion > 4.0 cm in greatest dimension |
| Stage II | Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina |
| IIA | Without parametrial invasion |
| IIA1 | Clinically visible lesion ≤ 4.0 cm in greatest dimension |
| IIA2 | Clinically visible lesion > 4 cm in greatest dimension |
| IIB | With obvious parametrial invasion |
| Stage III | The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney** |
| IIIA | Tumor involves lower third of the vagina, with no extension to the pelvic wall |
| IIIB | Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney |
| Stage IV | The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV |
| IVA | Spread of the growth to adjacent organs |
| IVB | Spread to distant organs |

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

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

APPENDIX II (05/12/2014)

# Translational Research Specimen Procedures

## I. Summary of Specimen Requirements

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions within the United States are required to submit the patient's translational research specimens as outlined below (unless otherwise specified)..

| Required Specimen (Specimen Code) | Time Point | Ship To |
|---|---|---|
| FFPE Primary Tumor (FP01)*<br>1st choice: block<br>2nd choice: 16 unstained slides (charged, 5µm) | Prior to all treatment | GOG Tissue Bank within 8 weeks of registration[1] |
| Whole Blood (WB01)<br>7-10mL drawn into purple top (EDTA) tube(s) | Prior to or after starting study treatment | GOG Tissue Bank the day the specimen is collected[1] |

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank

1 GOG Tissue Bank / Protocol GOG-0263, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBank@nationwidechildrens.org

## II. Obtaining a GOG Bank ID for Translational Research Specimens

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational research specimens and accompanying paperwork must be labeled with this coded and patient number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website (under Tools on the Web Menu page).

Obtain the patient's study ID (GOG#) for all GOG protocols with translational research specimen requirements before requesting a GOG Bank ID from the Tissue Bank Portal. **Be sure to indicate if the patient has a previous GOG# when registering.** This will ensure the patient is only assigned one Bank ID. The GOG ID-Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID.

Please contact GOG User Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@gogstats.org; Phone: 716-845-7767).

## III. Requesting Translational Research Specimen Kits

Kits are not provided for this protocol. A pre-paid FedEx air bill is provided for the submission of whole blood.

## IV. Labeling Translational Research Specimens

A waterproof permanent marker or printed label should be used to label each translational research specimen with:

GOG Bank ID (# # # # - # # - G # # #)
GOG protocol number (GOG- # # # #)

specimen code (see section I)
collection date (mm/dd/yyyy)
surgical pathology accession number (tissue specimens only)
block number (tissue specimens only)

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

## V. Submitting Formalin-Fixed, Paraffin-Embedded Tissue

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (primary). Primary tumor should be collected prior to all treatment. Only one block may be submitted per tissue type.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 16 unstained slides (charged, 5 μm) should be submitted. All tissue sections should be cut sequentially from the same block.

**Note: Stained slides to confirm patient eligibility by central pathology review are required for this protocol, but are NOT sent to the GOG Tissue Bank (see protocol for details).** If these slides will be cut from the same block that will be submitted for translational research, your pathology department should cut these slides prior to submitting the block for translational research.

The type of specimen (block or slides) should be specified on Form SP.

All FFPE tissue should be submitted with the corresponding pathology report.

## VI. Submitting Whole Blood

1. Label the lavender/purple top (EDTA) collection tube(s) as described above. Multiple tubes may be used to collect the required amount.

2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.

3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.

4. Whole blood specimens should be refrigerated (4°C) until the specimens can be shipped. Ship whole blood to the GOG Tissue Bank the day the specimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) until the specimen can be shipped.

## VII. Submitting Form SP

Form SP must be submitted via SEDES for each required specimen regardless of whether the specimen is submitted for research.

A copy of the SEDES-completed Form SP must accompany each specimen shipped to the GOG Tissue Bank (or alternate laboratory). Handwritten forms will not be accepted.

Note: A copy does not need to be sent if the specimen is not collected.

Retain a printout of the completed form for your records.

Please contact GOG User Support if you need assistance (Email: support@gogstats.org; Phone: 716-845-7767).

## VIII. Shipping Translational Research Specimens

**A SEDES-completed copy of Form SP must be included for each translational research specimen.**

FFPE Tissue

FFPE tissue and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

GOG Tissue Bank / Protocol GOG-0263
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: GOGBank@nationwidechildrens.org

**Do not ship FFPE tissue for Saturday delivery.**

### B. Whole Blood

Whole blood specimens should be shipped to the GOG Tissue Bank (address above).

Whole blood specimens can be shipped to the GOG Tissue Bank **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Use your own shipping container to ship specimens via **FedEx priority overnight**.

When shipping whole blood specimens, **your institution must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the

GOG Tissue Bank at GOGBank@nationwidechildrens.org or by phoning 866-GOG-BANC (866-464-2262).

To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag. You may include up to four different blood specimens in one biohazard envelope.*

If you do not have these materials available at your institution, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

**Shipping Whole Blood Using Your Own Shipping Container**

1. Place the whole blood specimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.

2. Wrap the biohazard envelope in bubble wrap or another padded material.

3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.

4. Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).

5. Insert a copy of Form SP for each specimen.

6. Attach an Exempt Human Specimen sticker to the outside of the shipping container.

7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.

8. Make arrangements for FedEx pick-up through your usual institutional procedure or by calling 800-238-5355.

## IX. Distributing Translational Research Specimens

The GOG Statistical and Data Center and Tissue Bank (or alternate laboratory) will coordinate the distribution of specimens to approved investigators.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of translational research and for keeping accurate records.

Investigators will ensure the results are linked to the appropriate specimen-specific identifiers and are responsible for transferring relevant laboratory data to the Statistical and Data Center.

At the discretion of the Chair of the Committee on Experimental Medicine and the Director of the GOG Tissue Bank, investigators may be required to ship any specimens (or by-products) remaining after the completion of the translational research to the GOG Tissue Bank.

## X. Banking Translational Research Specimens for Future Research

Specimens will remain in the GOG Tissue Bank and made available for approved research projects if the patient has provided permission for the use of her specimens for future health research. The patient's choices will be recorded on the signed informed consent document and electronically via the online Specimen Consent Application. At the time of specimen selection for project distribution, the most recent consent information will be used.

**GOG institutions can amend a patient's choices regarding the future use of her specimens at any time if the patient changes her mind.**

If the patient revokes permission to use her specimens, the GOG Tissue Bank will destroy or return any remaining specimens. The patient's specimens will not be used for any <u>further</u> research; however, any specimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens distributed prior to revoking consent.

Note: If return of specimens is requested, shipping will be at the institution's expense.

APPENDIX III (05/12/2014)

## RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY

**Purpose**

1) Surgical cure of carcinoma of the cervix, upper vagina or endometrium.

**Indications**

1) Invasive cervical carcinoma clinically confined to the cervix or upper vagina.
2) Invasive vaginal carcinoma clinically confined to the upper vagina.
3) Endometrial carcinoma extending to the cervix.

**Contraindications**

1) More advanced stages of disease (surgical or clinical).
2) Poor surgical risk patient.
3) Inadequate facilities and/or personnel.

**Content of Procedure**

A) Pelvic Lymphadenectomy

1) Bilateral removal of all nodal tissue and skeletonization of all vessels from the mid portion of the common iliac artery to the circumflex iliac vein; laterally, from the mid portion of the psoas muscle to ureter medially including the hypogastric artery and vein and from the obturator fossa anterior to the obturator nerve

2) Palpably positive nodes should be sampled for histology
A pathologically positive pelvic or para-aortic node indicates that no further sampling from that area need be performed, unless debulking of these nodes is desired.
Unresectable nodes should be marked with clips

B) Radical Hysterectomy

1) Removal of the uterus and contiguous parametrial tissue to its most lateral extent along with para-vaginal tissue and upper 3 of the vagina along with the proximal utero-sacral ligaments. The uterine artery should be transected at its origin lateral to the ureter. The ureter must be unroofed from its entry into the broad ligament to its intramural portion in the bladder and dissected laterally from its attachment to the cardinal ligament

.

2) May be performed by minimally invasive techniques (laparoscopy, robotic)

## ADVERSE EFFECTS THAT MAY BE ASSOCIATED WITH AN UNEVENTFUL PROCEDURE

| SYSTEM | GRADE (up to and including) |
|---|---|
| Hematopoietic | 2 |
| Genitourinary | 1 |
| Gastrointestinal | 1 |
| Hepatic | 1 |
| Pulmonary | 1 |
| Cardiovascular | 1 |
| Peripheral Neurologic | 1 |
| Central Neurologic | 0 |
| Cutaneous | 2 |
| Lymphatics | 1 |
| Fever | 2 |
| Allergic | 0 |

APPENDIX IV (05/12/2014)(05/12/2020)

**General Chemotherapy Guidelines**:

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due)

- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.

- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).

- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for <10% weight changes. **(05/12/2014)**