Integrated Dose Escalation for Advanced, Localized Gynecologic Cancer
(The IDEAL –Gyn Trial)

Principal Investigator
Junzo P. Chino, M.D.
Assistant Professor
Department of Radiation Oncology
Duke University Medical Center
DUMC Box 3085
Durham, NC 27710

Sub-Investigator
Oana Craciunescu, Ph.D.

Biostatistician
Gloria Broadwater, Ph.D.

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Abbreviations:
3D – 3 Dimensional
5-FU – 5 fluoro-uracil
AE – Adverse events
ANC – Absolute Neutrophil Count
AP/PA – Anterior to Posterior, Posterior to Anterior
APC – Argon Plasma Coagulation
BED – Biologically Equivalent Dose
BID – twice daily
CBC – Complete Blood Count
CBCT – Cone Beam Computed Tomography
CDDP – Cisplatin
Chemo – Chemotherapy
CPC – Cancer Protocol Committee
CRT – Chemoradiotherapy
CT – Computed Tomography
CTCAE – Common Terminology Criteria for Adverse Events
CTEP – Cancer Therapy Evaluation Program
CTV – Clinical Target Volume
D10cc – Minimum dose to the 10 milliliters of any volume receiving the highest dose
D2cc – Minimum dose to the 2 milliliters of any volume receiving the highest dose
DCI – Duke Cancer Institute
DLT – Dose Limiting Toxicity
Dmax – Maximum dose to any voxel within a volume
DUHS – Duke University Health System
ECOG – Eastern Cooperative Oncology Group
EFRT – Extended Field Radiotherapy
EQD2 – Equivalent dose at 2 Gray per fraction
FIGO - International Federation of Gynecology and Obstetrics
G3 or G4 – Grade 3 or Grade 4 toxicity
GI – Gastrointestinal
GOG – Gynecologic Oncology Group
GTV – Gross Tumor Volume
GU – Genitourinary
Gy – Gray
GYN – Gynecologic
HDR – High Dose Rate
ICRU – International Commission on Radiation Units and Measurement
ID – Identification
IMRT – Intensity Modulated Radiation Therapy (including Volumetric Modulated Arc Therapy)
IRB – Institutional Review Board
LDR – Low Dose Rate
LRC – Loco-regional control
MRI or MR – Magnetic Resonance Imaging.
MTD – Maximum Tolerated Dose
MV – Megavoltage
NCI – National Cancer Institute

OS – Overall Survival
PA – Para-aortic
PET – Positron Emission Tomography
PI – Primary Investigator
PTV – Planning Target Volume
RTOG – Radiation Therapy Oncology Group
SOC – Safety Oversight Committee
TD5/5 – Toxic dose of 5% at 5 years
V18 – Partial volume receiving greater than or equal to 18 Gray
WAI – Whole abdominal irradiation
WPRT or WP – Whole Pelvic Radiotherapy

1.0 STUDY SYNOPSIS

This study involves administration of an integrated radiotherapy boost to cancerous unresected pelvic and para-aortic nodal disease from gynecologic cancers. Many studies have utilized a sequential boost to deliver a total dose of 55 – 60 Gy to the pelvic sidewall (covering the lower pelvic lymph nodes), including 8-10 Gy that is usually delivered with brachytherapy [3,9,32]. This study treatment plan will escalate the dose to pelvic and para-aortic nodal disease from 60 Gy in 2.4 Gy per fraction to 70Gy in 2.8 Gy per fraction in 3 dose cohorts, using an integrated boost technique utilizing the same number of fractions for all cohorts (25 fractions) while the elective volumes are held constant at 45Gy . The cervix and uterus will be preferentially boosted with brachytherapy if clinically indicated.

2.0 HYPOTHESIS

Using a simultaneous integrated boost, the dose to treat involved para-aortic and pelvic lymph nodes can be safely escalated from 60 Gy in 2.4 Gy per fraction to 70 Gy in 2.8 Gy per fraction for a constant 25 total fractions.

3.0 OBJECTIVES

3.1 Primary Objective

3.1.1 To determine the feasibility and maximum tolerated dose of integrated boost radiation therapy, administered with IMRT technique with concurrent chemotherapy (cisplatin).

3.2 Secondary Objectives

3.2.1 To determine local-regional control, disease free survival, and overall survival rates with integrated boost radiation therapy.
3.2.2 To prospectively gather acute and late toxicity data.

4.0 BACKGROUND AND SIGNIFICANCE

4.1 Introduction

Concurrent radiation therapy and chemotherapy is the standard of care for node positive gynecologic cancer. While there are several acceptable means to boost the disease in the low pelvis (i.e. brachytherapy, IMRT, or external beam), there is limited research into boosting gross disease in the pelvis or para-aortic region. This protocol is designed to determine the maximum tolerated dose of treating tumor bearing regions within the abdomen and pelvis, using an integrated boost technique and concurrent chemotherapy.

4.2 Role of dose escalation in node positive cervical cancer

The standard of care for FIGO stage IB-IV International Federation Gynecologic Oncology (FIGO) cervical cancer concurrent cisplatin and whole-pelvis radiation therapy, followed by brachytherapy [7,16,17,21,25,29]. The addition of chemotherapy improves overall and disease-free survival. There is, however, a lack of information regarding the optimal total dose for grossly involved para-aortic and pelvic nodes in gynecologic cancers. For patients with FIGO IIIB disease, additional radiation is often given to bring the total dose to the parametria to 55-65Gy, usually performed with simple anterior and posterior fields, however little has been done to examine the possibility of boosting grossly involved nodal basins [3,9,10,32].

Nodal involvement is a clear negative prognostic factor for cervical cancer. A review of three Gynecologic Oncology Group (GOG) trials revealed that pelvic and para-aortic (PA) lymph node metastasis portend an increased risk of relapse and death[30]. In these trials, the 5 year progression-free survival was 20% for positive PA lymph nodes, 36% for positive pelvic lymph nodes alone, and 50-60% for no involved lymph nodes. This then is a potential cohort of women who may benefit from treatment intensification.

There is some data suggesting benefit to increasing the dose to involved nodes. A retrospective study of 200 patients at Washington University excellent lymph node control rates were reported with chemoradiation [10]. The mean dose to positive pelvic lymph nodes ranged from 67 to 74 Gy and the 2 year pelvic lymph node and cervix failure rates were 4% and 12% respectively. Two prospective studies, GOG 125 and RTOG 92-10, evaluated the use of a pelvic sidewall boost along with extended-field chemoradiation in patients with pathologically positive para-aortic lymph nodes (table 1) [9,32]. In RTOG 92-10, patients were treated with accelerated, hyperfractionated radiation and involved para-aortic lymph nodes were also boosted to total doses of 54-58Gy. Both studies showed that 30 to 40% of patients with pathologically proven positive para-aortic nodes were free of disease at 3 years. Overall, there was higher incidence of local-regional failures (30-50% at 3 years) compared to the Washington University or University of Pittsburgh series. The higher likelihood of failure, is probably related to the fact that patients had more advanced disease and were followed prospectively. Although in GOG 125 20% of patients had isolated pelvic failures but, central versus nodal recurrences were not scored separately, and so it is unknown if radiation doses were adequate to control nodal disease.

Thus, patients with residual or unresectable nodal disease have significantly worse outcomes in cervical cancer. Prospective studies using IMRT in the definitive treatment of cervical cancer are needed to correlate treatment volumes and radiation dose with pelvic and para-aortic disease control rates This study will accrue this subset of patients who have the most to gain from treatment intensification.

Table 1 Outcomes with concurrent EFRT and chemotherapy

Study	Study type *n*	Radiation	Chemo	Parametrial / PA nodal boost	LRC (yr f/u)	OS (yr f/u)	Acute GI	Late GI (yr f/u)
GOG 125 [32]	Phase II 95	Conventional WP + PA	Cisplatin 5-FU	Yes/No	(3) 70%	(3): 39%	G 3-4: 19%	G 3-4 (4) 14%
RTOG 92-10 [9]	Phase II 30	Conventional WP + PA RT BID	Cisplatin 5-FU	Yes/Yes	(3): 50%	(4): 29%	G 3-4: 50%	G 3-4 (3): 34%
Beriwal [3]	Retrospective 36	IMRT WP + PA	Cisplatin	Yes/Yes	(2): 80%	(2): 65%	G 3-4: 3%	G 3-4 (2): 10%

4.3 Rationale for Dose Intensification in Vulvar Cancer

The primary treatment for stage IB-IV vulvar cancer is surgery followed by adjuvant radiation with or without chemotherapy for risk factors including nodal involvement and close or positive margins [11]. For locally-advanced vulvar cancers with or without unresectable nodal disease, neoadjuvant chemoradiation to 46 Gy renders 70-80% of patients eligible for conservative pelvic surgery and has a 30-

50% pathologic complete response rate [2,4,19,20]. In these studies, many patients who achieve pathologic complete response have durable local control. Given these positive results, it may be possible to improve response rates and loco-regional control with radiation dose escalation. However, significant toxicity is associated with neoadjuvant CRT: acute grade 3-4 cutaneous toxicity in 50-60% of patients and surgical wound complications in 20-30% [19,20]. In two series representing 110 patients, 3 patients died from treatment complications including femoral artery necrosis, leukopenia and sepsis, and wound infection and sepsis [19,20]. It may be possible to reduce this complication rates using IMRT technique. At the University of Pittsburgh, 18 patients with locally-advanced vulvar cancer were treated with neoadjuvant IMRT to 46 Gy with concurrent chemotherapy [2]. Among these patients, 30% experienced surgical wound complications that healed 3-6 months postoperatively.

This protocol will include the subset of locally advanced vulvar cancer with gross residual or unresected disease within the pelvis, for those patients whom treatment intensification may hold some benefit.

4.4 Rational for Dose Intensification in Endometrial Cancer

Patients with stage IC to IVA endometrial cancer have a high risk of local and distant relapse; chemotherapy combined with radiation may be considered for these patients. One series of 43 high risk stage I-IV patients, including patients with lymph node involvement, treated with chemotherapy had a 40% pelvic relapse rate [23]. In the GOG 122 trial, women with stage III-IV endometrial cancer after hysterectomy were randomized to WAI versus chemotherapy with adriamycin and cisplatin. Patients treated with chemotherapy had improved 5-year progression-free and overall survival (42% and 53% versus 38% and 42%), though abdominal-pelvic relapse rates were 32%.

For patients with advanced endometrial cancer, combined chemotherapy and radiation has the potential to reduce local and distant relapses. A phase II trial, RTOG 9708, evaluated the safety and efficacy of concurrent CRT with cisplatin followed by cisplatin and paclitaxel for stage IC-IV endometrial cancer. Among 27 patients with stage III disease, 4-year local recurrence was 8%, distant metastasis 30%, and late grade 3-4 toxicity rate 20%. This study demonstrates favorable toxicity profile for postoperative CRT and improved local-regional control. In GOG 0184, patients with stage III-IV endometrial cancer were randomized to cisplatin and doxorubicin with or without paclitaxel after undergoing surgery and post-op RT to the pelvic +/- PA lymph nodes [12]. Three-year local-regional control rates in both groups were excellent at 90% though distant failure rates were 30%. In the subgroup with gross residual disease, the outcomes were significantly worse, with the control arm achieving a disease free survival of ~22%, while with more intensive chemotherapy this improved to ~45%. This suggests that treatment intensification is needed for these patients.

In conclusion, patients with locally advanced endometrial cancer have a significant risk of local recurrence, which is rarely salvaged with conventional treatment. In addition, those with gross residual disease have a poor prognosis, with some evidence of benefit from treatment intensification. These patients will be the subject of this protocol.

4.5 Rationale for Integrated Boost

In patients treated with radiation for cervical cancer, the duration of the entire treatment correlates with pelvic tumor control, disease-free survival and cause-specific survival [18,26]. The effect of total treatment time on outcome was illustrated in a retrospective study of 1224 patients with stage IB-III cervical cancer who underwent external beam and brachytherapy [26]. Pelvic tumor control was estimated

to decrease by 0.85% for each additional day of treatment time. Similar findings were noted in a patterns of care study, which confirmed inferior in-field pelvic control and overall survival as treatment time increased from 6 to 10 weeks [18]. These results are explained by the accelerated tumor repopulation in cervical cancer. Strategies to counter this effect include altered fractionation regimens that shorten overall treatment time. A theoretical advantage of integrated boost technique is that it shortens the overall treatment time by boosting gross parametrial and/or PA nodal disease concurrently as opposed to at the completion of primary whole pelvic radiation.

4.6 Reported toxicity in cervical cancer trials

The standard of care for FIGO stage IB2-IV cervical cancer is concurrent cisplatin and whole-pelvis radiation therapy, followed by brachytherapy [7,16,17,21,25,29]. The addition of chemotherapy improves overall and disease-free survival. With this standard treatment, reported rates of severe (grade 3-4) acute GI toxicity range from 7-25%, GU toxicity from 1-3%, and hematologic toxicity from 5-37% (Table 2). Severe (grade 3-4) late GI toxicity ranges from 3-12% and late GU from 2-17%. The wide range in incidence of toxicity may relate to the use of different grading scales between studies, use of crude toxicity estimates, and variation in quality of patient follow-up. Additionally, treatment varied between trials, with some employing a parametrial radiation boost [17,29] or adjuvant hysterectomy [16], in addition to whole pelvis chemoradiation and brachytherapy.

Depending on the technique, treating the para-aortic nodes and the whole pelvis with concurrent cisplatin, increases rates of acute and late GI toxicity [3,9,32]. In two prospective trials, GOG 125 and RTOG 92-10, patients were treated with concurrent EFRT, 5-FU and cisplatin [9,32]. In both trials, patients received brachytherapy and a parametrial boost to a total dose of 55-65 Gy. In GOG 125, reported grade 3-4 acute (19%) and late GI toxicity rates (14%) were similar to trials treating the whole pelvis with chemoradiation [32] (Table 2). Meanwhile, acute and late GI toxicity rates were much higher in RTOG 92-10 (50% and 34%, respectively), which likely relates to the fact that fractions of radiation were delivered twice daily and para-aortic nodal disease was boosted to total doses of 54 – 58 Gy with 3D conformal technique [9]. At the University of Pittsburg women were treated with concurrent cisplatin and intensity-modulated EFRT, including an IMRT boost to involved lymph nodes to 55-60Gy and a conventional (3D) parametrial boost to 50-60Gy [3]. Two-year toxicity rates were acceptable at 3% and 10% for grade 3-4 acute and late GI toxicity, respectively. Although a follow-up time of two years is short when assessing late toxicity, IMRT holds promise as a technique to deliver EFRT and boost nodal disease with potentially acceptable toxicity.

Table 2- Incidence of Grade 3 or 4 Toxicity with Concurrent Radiation Therapy and Chemotherapy

Study	n	Concurrent chemotherapy	Acute Hemato.	Acute GU	Acute GI	Late GU (year f/u)	Late GI (year f/u)
Rose [29]	526	CDDP	20%	3%	7%	2% (9)	3% (9)
Eifel [7]	403	CDDP + 5-FU	37%	1%	16%	3% (5)	12% (5)
Keys [16]	369	CDDP	21%	2%	14%	NR	NR
Lanciano [17]	316	CDDP	33%	NR	25%	NR	NR
Pearcey [25]	259	CDDP	5%	2%	13%	17% (7)	7% (7)

NR-not reported

4.7 Predicting late toxicity

The TD5/5 for partial small bowel irradiation is thought to be 50Gy, though prospective data is lacking, and the dose volume interaction is poorly understood at very low volumes [8,15]. The risk of bowel

toxicity may be higher in patients treated for cervical cancer, where additional brachytherapy and external parametrial boosts are administered after patients complete up to 45 Gy to the whole pelvis. Various scales are used to rate late toxicity in cervical cancer patients, but we will approximate equivalent results to the RTOG scale [5] (Appendix B).

One review of 297 cervical cancer patients revealed that patients boosted to a parametrial dose of ≥54Gy or a cumulative rectal BED ≥100 had higher rates of late RTOG grade 3-4 enterocolitis (15-16% v 4%) and proctitis (11-12% v 4%), respectively [13] (Table 3). The highest rates of enterocolitis (26%) and proctitis (17%) seen in those patients with both parametrial dose ≥ 54Gy and cumulative rectal BED >100Gy. The cumulative rectal dose was calculated at the ICRU rectal point, located 0.5cm posterior to the vaginal wall and perpendicular to the ovoids. Patients received 34-49 Gy of whole pelvis radiation, followed by a parametrial boost to a median of 54Gy and high-dose rate brachytherapy of 24 Gy prescribed to point A given in 5 fractions. Only 5% of patients received chemotherapy in this series.

A series of 1456 patients treated for cervical cancer at Washington University revealed that patients treated to a cumulative rectal dose > 80 Gy or a parametrial dose > 60 Gy had higher rates of late RTOG grade 3-4 rectal toxicity (12% v 3%) and late RTOG grade 4 enterocolitis (4% v 1%), respectively [27] (Table 3). Patients were treated with 10-40 Gy of whole pelvis radiation, followed by 2 fractions of low dose rate brachytherapy and a parametrial boost to deliver a total of 70-90 Gy to point A and 50-70Gy to the parametrium. The cumulative rectal dose was calculated at the ICRU rectal point and was the summation of the whole pelvis dose plus the brachytherapy dose. In this series, only 2% of patients received chemotherapy. Late RTOG grade 3-4 bladder toxicity was higher if the cumulative bladder dose was > 80 Gy (10% v 5%) measured at the ICRU bladder point at the trigone. Similarly, 183 patients were treated for cervical cancer at the University of Chicago with whole pelvis radiation, followed by low dose rate brachytherapy to deliver 75-90 Gy to point A [28]. The cumulative rectal dose was the summation of the whole pelvis dose plus the brachytherapy dose. The rectal dose was the average received at 4 rectal points closest to the intracavitary source determined at simulation with a rectal tube or contrast. There was a higher 7 year rate of grade 1-4 proctitis in patients who received >80 Gy cumulative rectal dose (25% v 5%).

Table 3- Dose cutoff points predicting late grade 3-4 GI toxicity

Study	n	Risk of RTOG GI toxicity
Huang [13] Taiwan	297	Enterocolitis (5y) G3-4 Neither – 4% Parametrial dose≥54Gy – 15% Rectal BED >100Gy – 16% Both – 26% Proctitis (5y) G3-4 No RF – 4% Parametrial dose≥54Gy – 12% Rectal BED >100Gy – 11% Both – 17%
Perez [27] Washington Univ.	1456	Proctitis (11y) G3-4 Rectal dose≤80Gy – 3% Rectal dose>80Gy – 12% Enterocolitis G4 (11y) Parametrial dose≤50Gy – 1% Parametrial dose>60Gy – 4%

Roeske [28] Univ. Chicago	183	Proctitis G1-4 (7y) Rectal dose≤80Gy – 5% Rectal dose>80Gy – 25%

4.8 Decreasing Gastrointestinal Exposure with Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is currently being investigated as a technique to treat the tumor and areas at risk of recurrence, while sparing normal tissues, with the goal of reducing radiation side effects. A group of 40 patients with cervical or endometrial cancer were treated with IMRT to the primary tumor bed and pelvic lymph nodes and followed for two years [22,24]. These patients were predominantly stage I-II (80%) and treated in the post-operative setting (70%) with concurrent chemotherapy (60%), followed by brachytherapy (60%). When compared to a similar group of patients treated with conventional, 3D radiation, these patients had lower rates of moderate acute (60% v 91%, p=0.002) and chronic (3% v 17%, p=0.001) GI toxicity requiring medications. There are currently no long-term data available regarding pelvic control rates for these patients. The reproducibility, toxicity, and outcome of IMRT in post-operative cervical and endometrial cancer patients is further being investigated in a phase II trail, RTOG 0481.

We propose using IMRT to escalate the dose to gross parametrial and nodal disease, while minimizing dose and side effects to normal tissues. A dosimetric analysis validated this strategy in five cervical cancer patients with positive para-aortic lymph nodes, where it was possible to escalate dose to gross nodal disease while sparing normal tissues [1]. Compared to conventional 2 or 4-field plans treating the whole pelvis and para-aortic regions to 45 Gy, IMRT plans were able to escalate dose to 60 Gy (2.4 Gy per fraction) to gross nodal disease, while reducing dose to spinal cord and kidneys and maintaining a similar bowel dose.

A series of cervical cancer patients at the University of Pittsburg were treated with an approach that utilized both IMRT and 3D conformal radiation to deliver escalated doses of radiation to involved para-aortic and pelvic lymph nodes, respectively [3]. 36 patients were selected to undergo extended-field radiation with concurrent cisplatin for an estimated risk of para-aortic lymph node involvement of ≥ 15% based on FIGO staging, or for radiographically enlarged pelvic lymph nodes (50%). Patients received an integrated IMRT boost to involved lymph nodes to 55-60Gy, followed by a conventional parametrial boost to 50-60Gy. Toxicity was acceptable with this technique—1 patient experienced acute grade 3 GI toxicity and 10% of patients experienced late grade 3-4 GI toxicity at a median follow-up time of 1.5 years.

5.0 PATIENT RECRUITMENT

This will be a prospective study with all eligible patients offered enrollment prior to their radiation treatment. The subject population (with no minority restrictions) will include adult patients meeting the eligibility criteria. Inclusion of minorities is encouraged. We will not include patients under the age of 18 from this study. All patients must sign an IRB approved informed consent prior to enrollment. Eligibility of patients will be ascertained by reviewing necessary portions of their protected health information. Potential candidates for the protocol will be identified by the principle investigator and/or the treating radiation oncologist before treatment planning is complete (i.e. after a full consultation and discussion of options and before the first fraction of RT is delivered). After introducing the study and determining patient interest in participating, potential subjects will be given the consent to review by the protocol nursing team. Final eligibility will be determined by a physician not directly involved with the protocol as a primary or co-investigator upon review of the criteria and the relevant medical records.

6.0 PATIENT SELECTION

6.1 Conditions for Patient Eligibility

1. Biopsy confirmed . malignancy of the gynecologic tract.
2. Involved pelvic or para-aortic lymph nodes by imaging or pathology.
3. Treatment plan to include delivery of concurrent chemoradiotherapy .
4. Zubrod/ECOG performance status 0-2
5. ≥ 18 years of age.
6. Negative pregnancy test in women of child-bearing potential
7. ANC >1000, Hgb >8.0 g/dl, Platelets >80,000 within 30 days of study entry
8. Creatinine <1.5
9. Signed study-specific informed consent.

6.2 Conditions for Patient Ineligibility

1. Prior abdomino-pelvic irradiation.
2. Prior history of Scleroderma or Inflammatory bowel disease.
3. Contraindication to chemotherapy or radiation

7.0 PRETREATMENT EVALUATION

1. A complete history and physical to include performance status and medical comorbidities.
2. Laboratory studies will include a complete blood count (CBC) with differential within 30 days before study entry.
3. Baseline staging exams to include (performed within 4 weeks prior to registration):
    a. Clinical pelvic exam
    b. MRI, CT, or PET-CT of the Abdomen and Pelvis.
4. Pregnancy test for women of child-bearing potential within 48 hours of radiation planning

8.0 TREATMENT

8.1 Radiation Therapy

Radiation therapy is to be initiated concurrently with chemotherapy, at the discretion of the treating radiation, medical or gynecologic oncologist.

8.1.1 Equipment

All patients will be treated using primarily using intensity modulated techniques with a linear accelerator using photon energies of between 6 and 15 MV.

8.1.2 Treatment Planning

The patient will be immobilized, simulated and treated supine, with arms on the chest or positioned above the head. Intravenous and oral contrast may be administered at the treating physician's discretion unless there are medical contraindications, such as an allergy to iodinated contrast or decreased renal function. Plans will be CT based; however, fused PET and/or MRI may be used at the treating radiation oncologist's discretion. DCE-MRI may also be used for treatment planning.

8.1.3 Target Volumes

GTV:

The gross tumor volume (**GTV**) will include the primary tumor (**GTV primary**) as well as positive pelvic and para-aortic lymph nodes (**GTV node**). Note that there will be no **GTV primary** in patients who are being treated postoperatively. The GTVs may be contoured separately or as a single **GTV**.

CTV 45:

A clinical target volume (**CTV 45)** will be contoured on and CT scans and including the GTV primary, cervix, uterus, parametria. The mesorectum may be included in the CTV for patients with radiologic or clinical evidence of uterosacral involvement. A distal vaginal margin of 4cm on clinical or radiographic disease will be required. These **CTVs** may be contoured as a single volume. Either the CTV or a separate ITV must then include an additional margin for organ motion on the cervix and uterus, which will be 1-2cm in the anterior/posterior/superior directions, and 0.5 – 1 cm in the lateral and inferior directions.

The **CTV45** will include the common, internal iliac, external iliac, obturator, and presacral lymph nodes. The inguinal nodes will be included for all tumors involving the distal vagina and vulva. The para-aortic nodes will be included for patients with involved pelvic lymph nodes. The CTV 45 will be contoured to include a 7 mm margin around the pelvic vessels with the following modifications [6,31]: To encompass lymph nodes around the common iliac vessels, contours will be extended to the psoas muscle and vertebral body posterolaterally. Obturator nodes will be covered by extending the external iliac contour posteriorly to join the internal iliac volume. The presacral lymph nodes will be covered by contouring a 1cm wide margin anterior to S1 to S3. The CTV 45 will stop inferiorly at the level of the femoral head and superiorly at the diaphragm (approximately T12-L1). All critical normal tissues will be excluded from the CTV expansions, as well as anatomic barriers to spread (i.e. fascial planes and bone). The nodal CTV will also be expanded to accommodate all pelvic and PA nodes seen on the planning image. (See the RTOG GYN atlas for examples: http://www.rtog.org/gynatlas/main.html.)

PTV 45:

A **PTV 45** will be created by expanding the union of all CTVs by 5-7mm in all directions to account for daily set-up uncertainty. All patients will have verification of treatment setup with on-board kV imaging and cone beam CT at the start of treatment and on a weekly basis, or more frequently if required.

The **PTV 45** will be planned with the goal of 95% coverage to 45Gy in 25 fractions (1.8Gy/fraction).

For patients with evidence of parametrial extension (**CTV/PTV 55**):

The **CTV 55** will be defined as the parametrium extending from the pelvic sidewall to 2cm from the center of the cervical canal, or center of the cervix if canal is not visible. Anteriorly this volume will be limited by peritoneum and bladder, posteriorly by the peritoneum and rectum. Superiorly and inferiorly it will be bounded by the extent of the cervix or **GTV**.

The **PTV 55** will be created by expanding the **CTV 55** by 5 mm, excluding critical normal tissue. **PTV 55** may be modified in the following manner to achieve appropriate sparing of bowel: The small bowel contour will be expanded by 3mm, and subtracted from the **PTV 55** volume.

The **PTV 55** will be planned to receive a goal of 95% coverage to 55 Gy in 25 fractions (2.2Gy/fraction).

The cervix and uterus will be preferentially boosted with brachytherapy. If this is not achievable, a sequential IMRT boost may be performed.

CTV/PTV boost:
The **CTV boost** will be created by expanding the GTV node by 3mm to account for microscopic extracapsular extension, excluding critical normal tissues.

The **PTV boost** will be created by expanding the CTV nodal boost by 5 mm, excluding critical normal tissue. **PTV boost** may be modified in the following manner to achieve appropriate sparing of bowel: The small bowel contour will be expanded by 3mm, and subtracted from the **PTV boost** volume. In dose cohorts 2 and 3, the same will be applied to the large bowel contour (including sigmoid and rectum). These may be further modified to meet the strict criteria for normal tissue as outlined below.

The **PTV boost** will be the target of dose escalation in this trial and will receive 60 through 70Gy in 25 fractions (2.4 Gy/fraction – 2.8 Gy/fraction)

8.1.4 Treatment Planning Technique

The following normal tissues will be contoured on every slice of the CT scan. The bladder will include the portion inferior to the planning target volume. The rectum will include the portion inferior to the planning target volume and superior to the level that it leaves the posterior pelvis in the rectosigmoid transition. The small and large bowel will include at least 2 cm above the planning target volume. The femoral heads should be contoured to include the greater trochanter.

All patients on the dose escalation study will be treated using IMRT, which requires inverse treatment planning. This involves setting dose constraints on the IMRT treatment planning software.
The following dose constraints must be met for all plans:

1. Small bowel D2cc ≤ 55 Gy
2. Large bowel (including the sigmoid) D2cc ≤ 65 Gy
3. Rectum D10cc ≤ 70Gy
4. Small bowel < 10% to receive ≥ 50 Gy
5. Bladder D10cc ≤ 70 Gy
6. Spinal cord Dmax (maximum point dose) < 45 Gy.
7. Individual Kidneys V18(volume receiving 18Gy or more) < 33%

If constrains cannot be met after IMRT optimization, the PTV volumes may be reduced to meet criteria. These modifications will be recorded as part of the protocol to determine the feasibility of this approach.

The following dose constraints serve as ideal goals, however, coverage of the PTVs will be prioritized above these values, and modifications of volumes will not be performed to meet them. Plans exceeding the following constraints will not be protocol violations.

8. Femoral head D2cc <50 Gy
9. Femoral head ≤ 15% to receive ≥ 30 Gy
10. Sigmoid < 20% to receive ≥ 55 Gy
11. Sigmoid < 50% to receive ≥ 50 Gy
12. Rectum < 20% to receive ≥ 60Gy
13. Rectum < 50% to receive ≥ 50 Gy
14. Bladder <30% to receive ≥ 60Gy

15. Bladder < 50% to receive ≥ 50 Gy

8.1.5 Radiation Dose Escalation Levels

This protocol will be using simultaneous, integrated boost using "dose painting" planning techniques. With this several volumes receive different daily doses. In general, the goal of this protocol is for the standard elective volumes to receive a fixed 1.8Gy per fraction, and for the boost volumes to receive higher doses per fraction to achieve the "boost" dose. All patients will receive a minimum of 45Gy in 25 fractions (i.e. 1.8 Gy per fraction) to the central disease (if intact uterus/cervix) and the elective nodal basins. The central disease will be boosted subsequent to this either by brachytherapy for further external beam as per the treating physicians preference, in accordance with the standard of care . Patients with parametrial or pelvic sidewall involvement will undergo an integrated boost to **PTV 55** as described above. In this setting, the IMRT plan will deliver 55 Gy in 25 fractions (2.2Gy per fraction) to **PTV 55**. This will be an integrated boost which occurs at the same time as the elective 45Gy (using dose painting treatment planning).

Patients will accrue to the following dose-escalation scenarios to treat **PTV boost** with an integrated boost (occurring at the same time as the above described plan, using dose painting treatment planning):

Dose level 1: 2.4 Gy X 25 fractions = 60 Gy
Dose level 2: 2.6 Gy X 25 fractions = 65 Gy
Dose level 3: 2.8 Gy x 25 fractions = 70 Gy

If the 2 dose limiting toxicities are dose level 1, therapy will be de-escalated to Dose level 0 defined below.

Dose level 0: 2.2 Gy X 25 fractions = 55 Gy

Patients will be set up daily using on-board imaging +/- cone-beam CT. Radiation will be given with 5 daily fractions per week, with exceptions made for dates in which the clinic is closed due to holiday or for linac maintenance.

The dose will be escalated in a 3X3 fashion, as defined below in **section 9.1.7** [14].

8.1.6 Dose Limiting Toxicities (DLTs)

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be used to score and grade treatment-related toxicity.

Two distinct toxicities are to be considered in this protocol: acute and late. These types of toxicity are distinct in terms of time of onset, character, management, and expected course, thus they will be considered separately for the purposes of determining the MTD.

Since integrated radiation dose escalation is unlikely to substantially affect the hematopoietic system, only non-hematologic, grade 3-4, acute toxicity will be considered the primary dose-limiting toxicity (acute DLT).

Acute DLT will be defined based on the side effects inherent from radiation therapy for gynecologic cancers, including effects on bowel, bladder, and skin. Dose limiting toxicity will include any of the following during treatment or within 6 weeks of completion:

1. Acute Grade 3-4 enteritis or proctitis requiring:
    a. Tube feedings
    b. Total parenteral nutrition
    c. Hospitalization secondary to inadequate oral caloric or fluid intake
    d. Prolonged treatment breaks secondary to enteritis (> 1 week)

e. Life-threatening consequences such as bowel perforation, obstruction, or bleeding requiring transfusion.

2. Acute Grade 3-4 bladder toxicity
   a. Bladder ulceration or necrosis
   b. Grade 3-4 cystitis including hematuria requiring transfusion
   c. Urinary obstruction not due to clot passage

3. Grade 4 dermatologic toxicity (skin necrosis or ulceration of full thickness of dermis)

Late DLTs will be defined at grade 3-4 GI or GU toxicity with onset after 6 weeks of treatment. The CTCAE v 4.0 will be used for determination of late toxicity grade, with one exception: the use of plasma coagulation or similar procedure for rectal bleeding will not be considered a late DLT, even though it is considered a grade 4 toxicity by the CTCAE. If however, there are other consequences of radiation proctitis which meeting grade 3-5 criteria, this will be considered a late DLT.

8.1.7 Dose Escalation Schema

Dose escalation will operate in the following fashion based on acute DLTs:

1. 3 patients will be accrued to dose level X (starting at level 1)
2. If there are any acute DLTs noted in these initial three participants, and additional three will be accrued (for a total of six).
3. If there is a second acute DLT, accrual will be halted for that cohort, and the dose will be deescalated to level X-1.
4. If 0/3 or 1/6 participants have an acute DLT, after a minimum follow up of 6 weeks, accrual to cohort X+1 may begin.
5. The candidate cohort for MTD will accrue a total of 6 patients. Thus if the dose deescalates, the dose cohort X-1 must have 6 participants before declaration of MTD. Similarly if the protocol proceeds to level 3, then it will accrue 6 participants even if no patient has an acute DLT.

The following schema will be used for late DLTs in conjunction with the above acute rules:

1. Patients will be monitored for late toxicity at every follow-up for 3 years.

2. If a late DLT observed in cohort Y, accrual in that and any higher cohort will be held until there is a minimum of 3 month follow up for all patients.

3. If a second late DLT is observed in cohort Y, then the dose will be de-escalated to Y-1 as per the above schema.

4. If there are no additional late DLTs in cohort Y, then a total of 6 patients must accrue to cohort Y, with a minimum of 3 months follow-up with no further late DLTs before the dose may be escalated to, or for accrual to resume in cohort Y+1.

Of note, acute and late DLTs will be counted separately. Thus if a patient has both an acute DLT and a late DLT, they will be counted as 1 DLT for both schema. If a patient has an acute DLT but not a late DLT, they will only be counted in the acute schema. The only exception will be a patient has an acute

DLT which does not resolve to less than grade 2 by 3 months: these will be counted as both acute and late toxicity for determination of MTD.

8.1.8 Treatment Interruptions during RT

The majority of RT-induced side effects requiring treatment breaks will be gastrointestinal in nature and include nausea/vomiting, weight loss, and dehydration. Dietary adjustments, anti-emetic therapy will be pursued. Treatment breaks due to enteritis/proctitis will be given at the discretion of the radiation oncologist. Other reasons for a treatment break will be:

1. Neutropenia with ANC < 500
2. Thrombocytopenia with platelets < 10,000
3. Non-hematologic grade 3-4 toxicity if felt by treating radiation oncologist that a break is necessary (i.e. significant skin reaction).

8.2 Brachytherapy

Brachytherapy is allowed for all patients with an intact uterus. Both LDR and HDR implants are allowed. Both interstitial and intracavitary treatment are also allowed. These will be done as per the standard of care. As a general guideline, the goal of treatment will be to obtained a cumulative dose to the central target, either defined by MR guidance, or by point system (i.e. point A), to 75-95Gy at the equivalent dose at 2 Gy/fraction (EQD2).

Intravaginal boosts will be allowed for patients are being treated postoperatively and have evidence of gross or microscopic disease, or for those with cervical involvement from endometrial cancer. The preferred (but not required method) is via HDR, with 3-5 fractions of 4-6Gy per fraction depending on the clinical scenario.

8.3 External Beam Boosting of Primary

In cases where the boosting primary tumor is not achievable with brachytherapy, integrated or sequential IMRT boosting of the disease may be performed to total doses of 55-80Gy depending on the treating physicians discretion, and the standard of care. Irradiation of the primary lesion may be treated at the accelerated dose per fraction of the current dose level, or may be performed at standard dose per fractionation (1.8 – 2.0Gy per fraction). When the total dose of the intended boost exceeds that of the current dose level, the remaining dose must be delivered in a sequential fashion at standard dose per fraction.

8.4 Chemotherapy

Chemotherapy is allowed and preferred on protocol, and is to be administered at the discretion of the treating Gynecologic or Medical Oncologist as per their standard practice.

9.0 EVALUATIONS DURING AND AFTER TREATMENT

9.1 Overall Schema

Patients will undergo CT scans prior to treatment as part of the standard staging procedure for gynecologic cancers. Some patients may also undergo PET and/or MRI scans at the discretion of the attending radiation and gynecologic oncologists. Patients will be assessed on a weekly basis, or more frequently as indicated, during the course of therapy by the attending radiation oncologist. During this visit, an interim history and directed physical examination will be performed and treatment-related

toxicity will be prospectively recorded using CTCAE version 4.0. A CBC will be obtained weekly during treatment. Other laboratory work will be obtained as deemed necessary. Cone Beam CT (CBCT) scans will be obtained weekly for the first 2 weeks and then at the discretion of the attending radiation oncologist. Patients will then be evaluated by either gynecologic oncology or radiation oncology every 3 months for follow-up. Assessment for late toxicity at 3-4 months after treatment, and will continue at 6 month interval for 2 years following treatment.

	Pre Treatment	***Week 1***	***Week 2***	***Week 3***	***Week 4***	***Week 5***	***Follow-up[1]***
CBC	X	X	X	X	X	X	
Toxicity assessment		X	X	X	X	X	X
CBCT[3]		X	X	X[2]	X[2]	X[2]	
PET-CT (optional) MRI (optional) for planning	X						

1. Follow-up post radiotherapy for radiation oncology at 4-6 weeks, and every 6 months for 2 years with interval gynecology oncology follow-up (+/- 3 month)
2. Optional
3. Cone beam CT

9.2 Criteria for Going Off Protocol

9.2.1. Development of local, regional, or distant progression during treatment.
9.2.2. Intolerable side effects from therapy despite in spite of measures to ameliorate them.
9.2.3. Noncompliance with protocol requirements.
9.2.4. Patient refusal or withdrawal of consent.
9.2.5. Discretion of PI or treating physician.

9.3 Reporting Adverse Events

For all possible treatment related adverse events/toxicities reported or observed, the information should be recorded in the patient's medical record and on the study's Toxicity Evaluation Form or in the study's toxicity database. This should include a description of the event, its severity grade, the relationship to the study treatment and the onset date.

CRITERIA FOR REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

	Grade 3 or 4	**Grade 4**	**Grade 4 & 5 Unexpected**
	With Hospitalization	**Without Hospitalization Expected**	

Unrelated, Unlikely	Not required	Not required	10 Calendar Days
Possible, Probable or Definite	**Unexpected** 10 Calendar Days	Not required	5 Calendar Days

Any late death (> 30 days after end of radiation) attributed to the protocol treatment should be reported within 5 calendar days of discovery

Treatment-related toxicity and adverse events should be documented in a routine manner at each study visit. Timely reporting of serious adverse events should be followed per DUHS IRB requirements. Because of the medical importance of serious and/or unexpected adverse events, the PI and study staff should review any expedited report prior to submission to the DUHS IRB.

Definitions for Adverse Event Reporting
Study therapy - Study therapy is the required treatment or procedure as defined by the protocol.
Expected events - Expected events are those that have been previously identified as resulting from treatment of gynecologic cancer with radiation therapy and chemotherapy. For purposes of this study, an adverse event is considered unexpected when either the type of event or the severity of the event is not listed in the protocol informed consent.

For purposes of this study, reporting requirements are determined by the assessment of the following adverse event characteristics: the type or nature of the event; the severity (grade); the relationship to the study therapy and whether the event is expected or unexpected.

For purposes of this study, grade 1 lab abnormalities will not be considered significant and thus, will not be captures as AEs. Only lab abnormalities greater than grade 1 and related to the treatment under study will be captured.

The recommended assessment steps include:
- Weekly appraisal of the patient during treatment.
- Identification of adverse events using the NCI CTCAE Version 4.0 terminology. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov).
- Grading the severity of the adverse event using the NCI CTCAE Version 4.0.
- Determination as to whether the adverse event is related to the study therapy using the following categories: Unrelated, Possible, Probable, and Definite.
- Determine whether the adverse event is expected or unexpected.

10.0 RISKS/BENEFIT ASSESSMENT

Patients with locally-advanced gynecologic cancers are at high risk of relapse and death. Long-term (3-4 years) survival is ~30-40% in patients with good performance status. Local failure after concurrent chemotherapy and radiation therapy occurs in ~40-50% of patients. Thus, increasing the intensity of RT is rational and may improve clinical outcomes for these patients.

The expected acute side effects of RT to the pelvis include fatigue, skin erythema, enteritis, proctitis, and cystitis. The incidence of acute grade 3-4 enteritis / proctitis with conventional therapy is 20-35% of

patients, while that of hematologic toxicity is 20-40% and cystitis is 5%. It is possible that the risk of severe enteritis / proctitis (requiring treatment breaks, intravenous fluids, hospitalization, etc.) will be greater with increased radiation boost dose. We will attempt to avoid this by utilizing IMRT, which can better spare normal tissues from the high dose component of treatment. In addition, it is possible that the use of IMRT (which can potentially increase the volume of normal tissues getting a low dose of RT) will increase the risk of acute side effects. The patients will be monitored weekly during RT and regularly after treatment to evaluate these toxicities and determine the maximum tolerated dose.

11.0 STATISTICAL CONSIDERATIONS

The maximum sample size of this study is 24 (6 patients at each of the 4 dose cohorts). The accrual rate is estimated to be about 4 patients per year. The dose-limiting toxicities are defined in Section 9.1.6 The dose cohorts and the dose escalation rules are defined in Section 9.1.5 and 9.1.7 respectively. These sections show that there are separate and independent dose escalation rules for early DLT's (toxicities that occur in the first 4 weeks of treatment) and late DLT's (toxicities that occur after 4 weeks). Likewise, there are separate definitions of dose-limiting toxicity for early and late toxicities. Thus, the trial could de-escalate due to either early or late toxicities. Because of the independence of the two sets of rules, a dose cohort of 6 patients in which one patient has an early DLT and one patient has a late DLT would not result in de-escalation of the dose. If a patient has both an early and a late DLT, the dose escalation rules would treat these DLT's as if they happened to two different patients.

Toxicities will be tabulated within each dose cohort by type, grade, and whether they were early or late. All toxicities will also be evaluated for their relationship to treatment and whether they were expected or unexpected. Time to local-regional recurrence (TTLR), time to distant recurrence (TTDR), disease-free survival (DFS), and overall survival (OS) will be estimate in all patients using the Kaplan-Meier method. TTLR will be defined as the time from first radiation treatment to local or regional (nodes) recurrence, whichever comes first, ignoring distant failures and censoring deaths. TTDR will be defined as the time from first radiation treatment to distant recurrence, ignoring local and regional failures and censoring deaths. DFS will be defined as the time from first radiation treatment to any recurrence (local, regional, or distant) or death, whichever comes first. OS will be defined as the time from first radiation treatment to death due to any cause.

12.0 REFERENCES

[1] Ahmed RS, et al. Imrt dose escalation for positive para-aortic lymph nodes in patients with locally advanced cervical cancer while reducing dose to bone marrow and other organs at risk. *Int J Radiat Oncol Biol Phys* 2004;60:505-512.

[2] Beriwal S, et al. Preoperative intensity-modulated radiotherapy and chemotherapy for locally advanced vulvar carcinoma. *Gynecol Oncol* 2008;109:291-295.

[3] Beriwal S, et al. Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2007;68:166-171.

[4] Beriwal S, et al. Intensity-modulated radiotherapy for the treatment of vulvar carcinoma: A comparative dosimetric study with early clinical outcome. *Int J Radiat Oncol Biol Phys* 2006;64:1395-1400.

[5] Cox JD, Stetz J Pajak TF. Toxicity criteria of the radiation therapy oncology group (rtog) and the european organization for research and treatment of cancer (eortc). *Int J Radiat Oncol Biol Phys* 1995;31:1341-1346.

[6] Dinniwell R, et al. Pelvic lymph node topography for radiotherapy treatment planning from ferumoxtran-10 contrast-enhanced magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2009;74:844-851.
[7] Eifel PJ, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of radiation therapy oncology group trial (rtog) 90-01. *J Clin Oncol* 2004;22:872-880.
[8] Emami B, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21:109-122.
[9] Grigsby PW, et al. Long-term follow-up of rtog 92-10: Cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2001;51:982-987.
[10] Grigsby PW, et al. Lymph node control in cervical cancer. *Int J Radiat Oncol Biol Phys* 2004;59:706-712.
[11] Homesley HD, et al. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. *Obstet Gynecol* 1986;68:733-740.
[12] Homesley HD, et al. A randomized phase iii trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A gynecologic oncology group study. *Gynecol Oncol* 2009;112:543-552.
[13] Huang EY, et al. Dosimetric factors predicting severe radiation-induced bowel complications in patients with cervical cancer: Combined effect of external parametrial dose and cumulative rectal dose. *Gynecol Oncol* 2004;95:101-108.
[14] Ivy SP, et al. Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: A report from the clinical trial design task force of the national cancer institute investigational drug steering committee. *Clin Cancer Res*;16:1726-1736.
[15] Kavanagh BD, et al. Radiation dose-volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys*;76:S101-107.
[16] Keys HM, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage ib cervical carcinoma. *N Engl J Med* 1999;340:1154-1161.
[17] Lanciano R, et al. Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: A gynecologic oncology group study. *J Clin Oncol* 2005;23:8289-8295.
[18] Lanciano RM, et al. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: A patterns-of-care study. *Int J Radiat Oncol Biol Phys* 1993;25:391-397.
[19] Montana GS, et al. Preoperative chemo-radiation for carcinoma of the vulva with n2/n3 nodes: A gynecologic oncology group study. *Int J Radiat Oncol Biol Phys* 2000;48:1007-1013.
[20] Moore DH, et al. Preoperative chemoradiation for advanced vulvar cancer: A phase ii study of the gynecologic oncology group. *Int J Radiat Oncol Biol Phys* 1998;42:79-85.
[21] Morris M, et al. Phase ii study of cisplatin and vinorelbine in squamous cell carcinoma of the cervix: A gynecologic oncology group study. *J Clin Oncol* 2004;22:3340-3344.
[22] Mundt AJ, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;52:1330-1337.
[23] Mundt AJ, et al. Significant pelvic recurrence in high-risk pathologic stage i--iv endometrial carcinoma patients after adjuvant chemotherapy alone: Implications for adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;50:1145-1153.
[24] Mundt AJ, Mell LK Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:1354-1360.
[25] Pearcey R, et al. Phase iii trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *J Clin Oncol* 2002;20:966-972.

[26] Perez CA, et al. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;32:1275-1288.
[27] Perez CA, et al. Radiation therapy morbidity in carcinoma of the uterine cervix: Dosimetric and clinical correlation. *Int J Radiat Oncol Biol Phys* 1999;44:855-866.
[28] Roeske JC, et al. Late rectal sequelae following definitive radiation therapy for carcinoma of the uterine cervix: A dosimetric analysis. *Int J Radiat Oncol Biol Phys* 1997;37:351-358.
[29] Rose PG, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: A gynecologic oncology group study. *J Clin Oncol* 2007;25:2804-2810.
[30] Stehman FB, et al. Carcinoma of the cervix treated with radiation therapy. I. A multi-variate analysis of prognostic variables in the gynecologic oncology group. *Cancer* 1991;67:2776-2785.
[31] Taylor A, et al. Mapping pelvic lymph nodes: Guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63:1604-1612.
[32] Varia MA, et al. Cervical carcinoma metastatic to para-aortic nodes: Extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: A gynecologic oncology group study. *Int J Radiat Oncol Biol Phys* 1998;42:1015-1023.

APPENDIX A: Performance Status

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: RTOG Toxicity Scoring Criteria [5]

	Grade 1	Grade 2	Grade 3	Grade 4
Acute small bowel	≤5% wt loss, no medication intervention	≤15% wt loss, nausea or abdominal pain requiring medications	>15% wt loss requiring NG tube or parenteral support, severe abdominal pain despite medication, hematemesis or melena, abdominal distension	Ileus, obstruction, perforation, GI bleeding requiring transfusion, abdominal pain requiring surgery
Acute large bowel	Increased frequency or change in bowel habits not requiring medication	Diarrhea requiring medications, rectal discharge not requiring pads, rectal pain requiring analgesics	Diarrhea requiring parental support, rectal discharge needing pads, abdominal distension	Obstruction, fistula, perforation, GI bleeding requiring transfusion, abdominal pain requiring surgery
Acute bladder	Urinary frequency doubled, dysuria/urgency not requiring medication	Urinary frequency less than hourly, dysuria requiring local anesthetic	Urinary frequency hourly or more, dysuria/bladder spasm requiring frequent narcotic, passage of blood with or without clots	Ulceration, necrosis, hematuria requiring transfusion, obstruction not due to clot passage
Late large/small bowel	Mild diarrhea or cramping, BM ≤ 5/day, slight discharge or bleeding	Moderate diarrhea or colic, BM > 5/day, excessive mucous or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis, perforation, or fistula
Late bladder	Microscopic hematuria	Moderate frequency, intermittent macroscopic hematuria,	Severe frequency or dysuria, frequent macroscopic hematuria, bladder capacity <150 cc	necrosis, bladder capacity <100cc, severe hemorrhagic cystitis