PROTOCOL NUMBER STU 082013-064

A Phase II Study for Image Guided Hypofractionated Radiation Boost Therapy for Definitive Treatment of Locally Advanced Cervical Cancer

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Protocol Version	Date
1	10/03/2013
2	11/11/2013
3	02/10/2014
4	04/10/2014
5	06/24/2014
6	06/27/2014
7	03/25/2015
8	4/25/2017

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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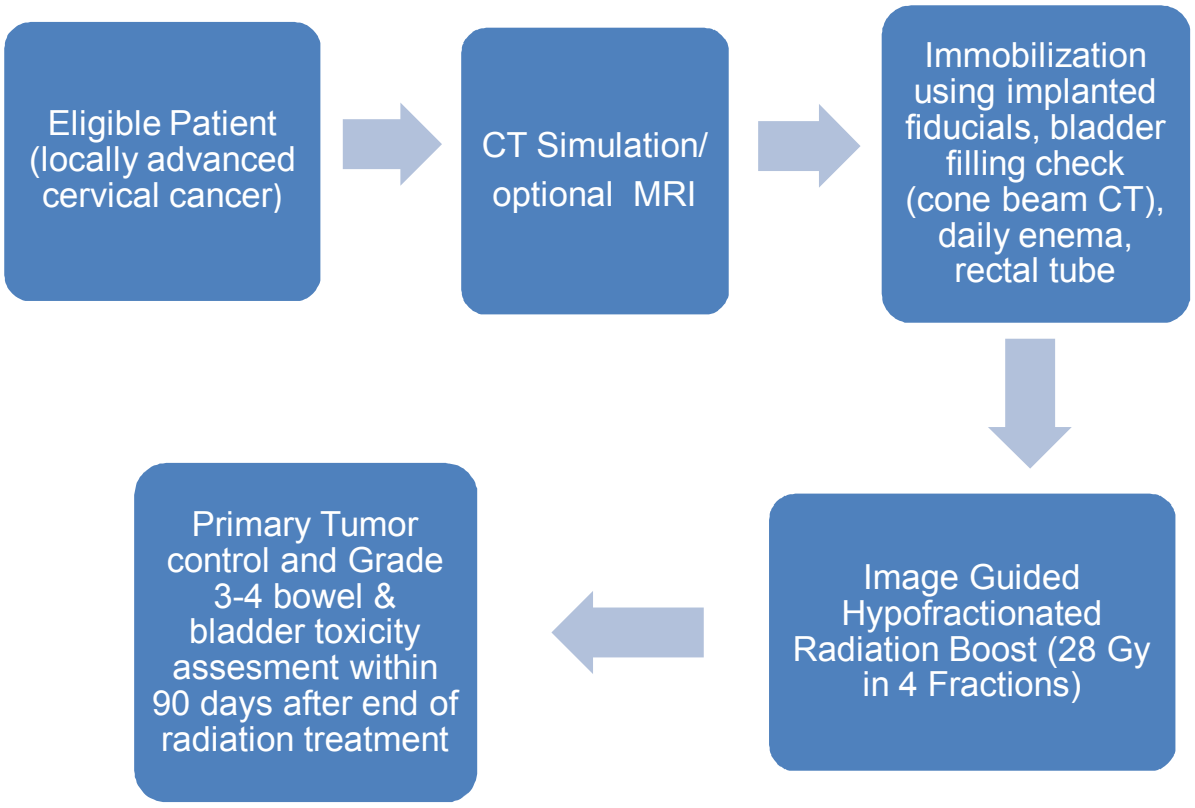
LIST OF ABBREVIATIONS

AE	Adverse Event
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Treatment Volume
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&P	History & Physical Exam
IMRT	Intensity Modulated Radiation Therapy
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	Per os/by mouth/orally
PR	Partial Response
PTV	Planning Treatment Volume
SAE	Serious Adverse Event
SD	Stable Disease
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase II Study of **Image Guided Hypofractionated Radiation** Boost Therapy for Definitive Treatment of Locally Advanced Cervical Cancer
Short Title	Image Guided Hypofractionated Radiation Treatment for Advanced Cervical Cancer
Protocol Number	STU 082013-064
Phase	Phase II
Methodology	Patients who are eligible for the study will be prospectively identified, treated using Image Guided Hypofractionated Radiation Treatment and followed for efficacy and toxicity.
Study Duration	Study accrual: 3 years Follow-up: 5 years
Study Center(s)	University of Texas – Southwestern Medical Center
Objectives	The purpose of this study is to determine whether Image Guided Hypofractionated Radiation Treatment is effective in women with locally advanced cervical cancer without increased risk of acute GI or GU toxicity.
Number of Subjects	21
Diagnosis and Main Inclusion Criteria	Inclusion Criteria • Biopsy proven squamous, adenosquamous, or adenocarcinoma of uterine cervix • Willing and capable of consent • FIGO Stage IB2 - IVB, cervical cancer
Study Product(s), Dose, Route, Regimen	Patients enrolled in this study must have received or planned to receive 45Gy of prior external beam radiation therapy. Following completion, patients will receive 28 Gy in 4 fractions using Image Guided Hypofractionated radiation therapy techniques.
Duration of administration	All radiation therapy should be preferably completed within 56 days.
Reference therapy	Image Guided Hypofractionated Radiation Treatment will be compared to standard of care which consists of standard chemoradiation followed by intracavitary high dose rate brachytherapy.

1. BACKGROUND AND RATIONALE

1.1 Disease Background

Locally Advanced Cervical Cancer (LACC)

There will be an estimated 12,300 new cases of cervical cancer diagnosed in the United States in 2013.with one third that number dying from the cancer [1]. While the incidence of cervical cancer in the United States has been gradually declining as a result of widespread screening, outcomes still remain poor for many with cervical cancer. In addition there has been a negligible survival improvement over the past decade .[2] Even with the increased screening in the U.S., 48% of patients still present at an advanced stage [2] Globally cervical cancer is widespread (no. 3 cancer in women) and lethal(with a mortality incidence ratio of 52%)[3]. Several prospective randomized trials compared concurrent chemotherapy and radiation to radiation alone for advanced cervical cancer and showed substantial improvement in local control and overall survival in the late nineties[4, 5]. As a result, the National Cancer Institute issued a treatment alert in 1999 establishing chemoradiation as the standard of care for advanced cervical cancer. Radiotherapy for cervical cancer currently consists of radiation in the form of external beam delivered over 5-6 weeks of daily therapy followed by or interdigitated with intracavitary or less frequently, interstitial brachytherapy. These procedures remain invasive and require use of supportive medications ranging from general anesthesia in the operating room to a combination of sedatives and narcotics for insertion of the brachytherapy devices. Furthermore, intracavitary brachytherapy delivers dose to a limited volume of tissue around the cervix and may be inadequate for delivering dose to tumors that extend to the pelvic sidewall. As a result, even with the use of chemoradiation, approximately 30% of patients with locally advanced disease will have a locoregional recurrence[5]These results of best local control for Stage III-IVA cervix cancer of 70% applies to carefully chosen patients in clinical trials. Patients with bulky advanced cervical cancers like the vast majority of patients we see at Parkland (PMH) and UTSW have an inferior local control which is hampered by poor performance status of these patients. In a recent review of patients from 2003-2011 at PMH, the actuarial overall survival for all II-IVa pts was only 34% at 5years [6]. A significant group of patients had locoregional failure or persistence, presumably due to bulky tumor volume exceeding the limitations of available radiation and chemotherapeutic modalities. Additionally, patients often present with multiple untreated co-morbidities which makes them often unable to undergo standard chemoradiation and brachytherapy often compromising the delivery of adequate radiation dose and hence the tumor local control. Furthermore, current treatments are often unpalatable for many patients because they are either too invasive, inconvenient or inadequate.

The implementation of Intracavitary brachytherapy (which is the most commonly applied form of Brachytherapy in the US)[7] in bulky tumors (esp. Stage IIIB tumors which extend to the pelvic side-wall), results in inadequate dosage to tumor especially at side-wall of pelvis . This occurs because of the rapid falloff of radiation dose from intracavitary brachytherapy sources which may explain the relatively high rate of local failure in bulky stage III cervical cancers.

More advanced methods of delivery are available, like Image Based high dose rate Brachytherapy with the Europeans being the innovators in this area. Under the aegis of the GEC-ESTRO group many new frameworks for HDR Cervix brachytherapy have been introduced with emphasis on volumetric assessment of dose to cervix CTV recommended to be based on MR imaging[8]. The most updated French Multicentric experience of over 600 patients with cervical cancer comparing 2D with 3D image based intracavitary brachytherapy

showed that in the advanced cervical cancer patients (mostly stage II; as IIIB were only 25% of group) local recurrence was still 25% . They did not break up recurrence by stage.[9]

For the bulkier tumors, in order to improve tumor control, interstitial brachytherapy is recommended by some. These are more invasive procedures and involve transperineal Interstitial needle placement into cervix tumor with General anesthesia , hospital inpatient stay, extensive support and involvement of considerable resources and provider-hours. Even with these invasive procedures, the best results provide 60-65% local control at 2-3 years for all stages [10, 11] . This is an important problem, since locally advanced cervical cancer continues to recur despite current treatments and more effective, less toxic and more convenient treatments are necessary.

The Vienna group has pioneered a combined Intracavitary- Interstitial technique which requires Intra-operative MRI suite which is impractical in the US setting and particularly in the county hospital setting which we work in.[12]

Their best results with IIIB disease are using 3D image based hybrid version of Intracavitary/interstitial brachytherapy using a customized ring applicator with needles achieved a local control of 86% for IIIB cancer .[13]This process is very resource intensive and requires interstial MR guided-Brachytherapy expertise which may not be available in most US centers.

We propose Precise Image Guided Hypofractionated Radiation treatment building on our experience with prostate cancer which has a similar anatomic profile to bulky cervical cancer albeit involves slightly larger volume of treatment. [14] Brachytherapy is very effective in delivering dose to fixed volume within close proximity cervix, while Image Guided Hypofractionated Radiation Treatment can be shaped to larger patient specific tumor volumes. We will use existing HDR brachytherapy regimens and modified Brachytherapy tumor targets to deliver precise doses of SABR in 4 fractions of 7Gy each delivered over 2-3 weeks.

It is predicted that the dose limiting toxicity from this treatment will likely relate to Grade 4 bladder/urethral dysfunction (e.g., ulceration, bleeding, pain, narrowing and frank stricture) and rectal damage (ulceration, bleeding, chronic inflammation, and pain or fistula) causing emergent and life-threatening situation requiring admission. Based upon the best results of Vienna combined Intracavitary-Interstitial Brachytherapy , we predict that with more complete radiation dose delivery to these tumors using Image Guided Hypofractionated Radiation Treatment, we will be able to increase the local control from 65 to 85%at 2 years. A safety-lead in will be used for the first 6 patients to see if we have any unexpected Grade 3,4 toxicity within first 90 days after commencement of Image Guided Hypofractionated Radiation boost .

1.2 Image Guided Hypofractionated Radiation Treatment

Stereotactic radiosurgery generally refers to a procedure designed to treat deep-seated brain tumors or abnormalities, and is commonly performed on a specialized machine, such as the Gamma Knife. This procedure involves immobilizing the patient (cranial halo), affixing a stable 3-D coordinate system (fiducial box and head frame), performing high resolution imaging (CT or MRI), registering the images to the coordinate system using a computer, virtually simulating delivery of very focal and conformal dose profiles of radiation with steep dose gradients toward normal tissue, and finally carrying out the treatment with millimeter accuracy. Typically very high doses of radiation (15-40 Gy) are given in a single treatment with this technique. Any adjacent normal tissues that receive this dose may be significantly damaged, thus the requirement for very conformal treatments with rapid dose fall-off. An alternate strategy has

been to divide total radiation dose into two or three fractions, still with fairly large dose per fraction (6-10 Gy), attempting to decrease adjacent normal tissue toxicity. These fractionated techniques are referred to as 'stereotactic radiotherapy,' and are carried out with hope that surrounding normal tissue will tolerate the treatment as a result of relatively more successful sublethal damage repair as compared to tumor.
Translation of the stereotactic radiosurgery and radiotherapy concepts to extracranial sites has not been straightforward.[15] With brain treatments, the skull serves as an excellent surface to rigidly couple the immobilization frame using stainless steel pins under local anesthesia. Such is not the case for extracranial sites. Inherent motion, such as the heart beating, lungs expanding and emptying, and bowels churning, results in movement of potential targets. In addition, the external surface anatomy does not have structures amenable to rigid fixation to a frame. In 1994, Lax, et al, from the Karolinska Hospital in Sweden reported on the development and testing of an extracranial frame that incorporated a fiducial stereotactic coordinate system along its side panels[16]. The system used vacuum pillows to make contact with three sides of the patient (maximizing surface area of contact) and correlation of external anatomical reference points on the sternum and calf for immobilization. To decrease respiratory excursion, an abdominal press was employed forcing the patient to perform relatively more chest wall rather than diaphragmatic breathing. A formal verification of reproducibility study was carried out, and target motion was reduced to within 0.5 cm in the axial plane and 1.0 cm in the caudal/cephalad plane. With this degree of accuracy (compared to 0.05 cm target position accuracy for the Gamma Knife), stereotactic radiosurgery could not be performed; however, they did set up a program treating patients with extracranial stereotactic radiotherapy.

Image Guided Hypofractionated Radiation Treatment is a new therapeutic paradigm for treating localized tumors outside of the central nervous system and involves delivering very high doses of focused radiation using unique beam arrangements and special immobilization equipment. As already demonstrated in lung and liver cancers, these treatments offer hope for improved local control of cancers that may translate into gains in survival especially for smaller early stage lesions. Image Guided Hypofractionated Radiation Treatment employs daily treatment doses dramatically higher than typical for conventionally fractionated radiation therapy (CFRT). In turn, it is incorrect to assume that Image Guided Hypofractionated Radiation Treatment radiobiology is similar to historical CFRT. Indeed, a unique biology of radiation response for very large dose per fraction treatments is being appreciated both in terms of tumor control as well as normal tissue consequences translating into unique clinical outcomes. For example, local control with CFRT in early stage lung cancer is consistently reported below 50% while several series using SABR show local control around 90% [17]

Image Guided Hypofractionated Radiation Treatment has been defined by the American College of Radiology (ACR) and American Society of Therapeutic Radiology and Oncology (ASTRO) to involve the use of very large dose per fraction [18]. Typically, only 1-5 fractions are used for Image Guided Hypofractionated RadiationTreatment depending on the tolerance of adjacent or intervening normal tissues. Linear structures (like the spinal cord) and tubular structures (like the bowels) are commonly called "serially functioning tissues" akin to series electrical circuits because their function is disrupted if there is a defect anywhere along their pathways.[19, 20] It has been shown that serial functioning tissues are less tolerant to Image Guided Hypofractionated Radiation Treatment than so-called "parallel functioning tissues" like the peripheral lung and liver. In response, typically more fractions are employed (e.g., five fractions rather than one) when serially functioning tissue cannot be avoided.

1.3 Rationale

1.3.1 Previous experience with Image Guided Hypofractionated Radiation Treatment for Gynecological Tumors and Cervix cancer

There is limited experience in the literature utilizing Image Guided Hypofractionated Radiation Treatment for primary cervix cancer. Most of the series are for recurrent or persistent gynecological tumors in pelvis or retroperitoneum [21-25]. These have been successful as an alternative to brachytherapy with comparable toxicity. For primary cervix cancers , while intracavitary brachytherapy provides the best results , there are a group of patients unable to have standard brachytherapy for whom pilot studies of Image Guided Hypofractionated Radiation Treatment have been performed [21, 26][27, 28] . These have been able to demonstrate in small patient samples that Image Guided Hypofractionated Radiation Treatment for cervix cancer can be delivered safely in the clinic but systematic followup and local control data are unavailable in some of the recently published studies. There have also been dosimetric studies showing feasibility of Image Guided Hypofractionated Radiation Treatment for primary cervix cancer as a replacement for brachytherapy with equivalent dose parameters [29-31]. We will base our planning on our previous experience with Image Guided Hypofractionated Radiation Treatment for prostate cancer which has similar central pelvic location like cervix cancer [14, 32] In that patient cohort , we demonstrated that Linac based Image Guided Hypofractionated Radiation Treatment could be safely administered for men with prostate cancer in five fractions without acute dose limiting toxicity with complete PSA response in this Phase I study.

1.3.2 Current protocol

In the case of treating cervical cancer, the rectum and bowel is an adjacent serially functioning tissue while the bladder is a parallel functioning tissue directly anterior to the cervix. The cervix will be delineated with fiducial CT-visible markers in 4 quadrants and if required the lower end of any intravaginal component will also be marked.

The volume to be treated by Image Guided Hypofractionated Radiation Treatment will be similar to the volume recommended by the GEC_ESTRO group for Intracavitary/Interstitial brachytherapy and with identical fractionation to have a frame of reference for this unique approach to cervix cancer.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to improve primary tumor local control of eligible LACC using Image Guided Hypofractionated Radiation Treatment as the mechanism for delivering boost therapy to 85% at 2 years post treatment.

A phase I safety lead-in will be performed as described in section 8.

For the safety lead-in phase, acute grade ≥ 3 gastrointestinal (GI) toxicity (perforation, obstruction, bleeding, ulceration ,necrosis , proctitis and diarrhea requiring elective or urgent hospitalization) and grade ≥ 3 genitourinary (GU) toxicity (cystitis, hematuria and incontinence requiring elective or urgent hospitalization) within 90 days from the commencement of Image

Guided Hypofractionated Radiation Treatment boost will be assessed. Toxicity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.

2.2 Secondary Objectives

2.2.1 To determine the acute (< 90 days) and late (90-365 days) grade ≥ 3 GI and GU toxicity as assessed by CTCAEv4 from the commencement of Image Guided Hypofractionated Radiation Treatment boost.
2.2.2 To determine the patient reported quality of life (FACT-CX)

3. PATIENT ELIGIBILITY

All screening procedures must be performed prior to study enrollment.

3.1 Inclusion criteria

3.1.1 Biopsy proven Locally Advanced stage Cervical Cancer (LACC, FIGO IB2 – IVB)
3.1.2 Zubrod performance status 0-3
3.1.3 Women of child-bearing potential (See note) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
3.1.4 Patients should have **any of** the below to be eligible

- Are not candidates for intracavitary brachytherapy due to poor geometry or poor response to external beam RT
- Patients with co-morbid medical conditions, bleeding disorders , poor anesthetic risk precluding brachytherapy
- Patients who refuse brachytherapy or prefer external beam hypofractionated approach
- Patients requiring interstitial brachytherapy

Note: Patients may be discovered during standard therapy and enrolled prior to boost.

Note: A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.2 Exclusion criteria

3.2.1 Pregnancy
3.2.2 Concurrent untreated cancer excluding non-Melanoma skin cancer
3.2.3 Previous pelvic radiation for prior cancer
3.2.4 Patients with active Inflammatory Bowel disease or Collagen vascular disease –SLE, scleroderma
3.2.5 Age <18
3.2.6 Unable to consent for study
3.2.7 Severely immunocompromised patients (eg Transplant, on immunosuppressive drugs)

4. RADIATION THERAPY

4.1 Dose Specification

a. Initial Pelvic (+/- Para-aortic) fractionated external beam Radiation with 45 Gy to combined PTV with a boost to 55Gy for PET positive/CT enlarged nodes;
b. Image Guided Hypofractionated Radiation Treatment boost to Cervix High risk CTV/PTV 28GY/4 fx.

Patients will receive 4 fractions of 7 Gy each via stereotactic body radiation as boost therapy to a volume that encompasses the cervical tumor. A minimum of 40 hours should separate each treatment.

4.2 Details of Planning for external Beam Pelvic RT:

Daily external beam radiation (with concurrent weekly cisplatin) will be preferably given using intensity modulated radiation therapy (IMRT) to the primary tumor in the cervix and pelvic lymphatics. The para-aortic lymph nodes will also be treated only if there is 18F-FDG uptake on the staging PET/CT scan. The following targets will be outlined.

- Gross tumor volume-node (GTV node): This will be designated by the 18F-FDG avid lymph node as outlined on the PET/CT scan.
- Clinical target volume-nodal (CTV nodal): This volume will be contoured as recommended by Consensus Guidelines For Delineation of Clinical Target Volume for Intensity Modulated Pelvic Radiotherapy in the Definitive Treatment of Cervix Cancer [33]
- Clinical Target Volume Cervix and Parametria (CTV cervix): This volume will be contoured as recommended by Consensus Guidelines For Delineation of Clinical Target Volume for Intensity Modulated Pelvic Radiotherapy in the Definitive Treatment of Cervix Cancer [33]

For pelvic /Para-aortic radiation, dose should preferably be given as follows (All targets will be treated simultaneously, except as noted.):

- The planning target volume-nodal (PTV nodal) (CTV nodal with 7 -mm margin) will receive 45 Gy. Treatment will be delivered once daily, 5 fractions per week. The planning target volume cervix (PTV cervix) (CTV cervix with 7mm margin) inferiorly and superiorly lateral and posterior margin will be 7-10 mm based upon rectal distension.
- The planning target volume gross node (PTV Node Boost) (GTV node+5mm margin) laterally, posteriorly, inferiorly and superiorly; this volume will not extend into bowel will receive 55 Gy in 25 fractions. Treatment will be delivered once daily, 5 fractions per week.
- The prescription dose should encompass at least 95% of the PTV. No more than 10% of any PTV will receive > 110% of its prescribed dose. No more than 1% of any PTV will receive < 90 % of its prescribed dose. No more than 1% or 1 cc (whichever is smaller) of the tissue outside the PTV nodal will receive > 110% of the dose prescribed to the PTV.

4.3 Details of Planning for Image Guided Hypofractionated Radiation Boost:

The term “stereotactic” for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space guided by one or several fiducials of known 3-D coordinates. This differs from conventional radiation therapy in which therapy is directed toward skin marks or bony landmarks and assumed to correlate to the actual tumor target based on a historical simulation. Image Guided Hypofractionated Radiation Treatment is mostly about ablative range dose per fraction, accounting properly for errors including motion, careful construction of dosimetry that compacts high dose into the tumor and not normal tissues, and extra careful treatment conduct. This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward an isocenter or target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radio-opaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (e.g. acquiring tomographic views of the tumor simultaneously with the treatment). CT visible markers will be required for all patients treated on this protocol.

4.4 Premedications

Unless contraindicated, it is recommended that all patients receive corticosteroid premedication (e.g. Decadron 2-4 mg p.o. in a single dose, or equivalent) 15-60 minutes prior to each of the Image Guided Hypofractionated Radiation treatments for the intended purpose of modulating immediate acute inflammatory effects. Contraindications to corticosteroids will be respected. Analgesic premedication, such as Tylenol 650 mg 30 minutes prior to therapy and as needed every 6 hours; to avoid general discomfort during long treatment durations also is recommended when appropriate.

4.5 Supportive Medicines

One tablespoon of Milk of Magnesia may be taken the night before simulation/treatment (*Note: Inform patient that this will cause diarrhea*). Fleet’s enema should be taken 2 hrs before simulation/ and every treatment. An antibiotic (Bactrim or similar) may be prescribed to alleviate UTI if necessary. This should be taken at standard doses as needed.

4.6 Technical Factors

4.6.1 Physical Factors

Only photon (x-ray) beams produced by linear accelerators with photon energies 6-21 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed.

4.6.2 Dose Verification and QA

IMRT QA will be performed per guidelines for Image Guided Hypofractionated Radiation Treatment at UTSW per institutional guidelines.

4.7 Localization, Simulation, and Immobilization

4.7.1 Patient Positioning for Image Guided Hypofractionated Radiation Boost

Patients will be positioned supine in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the stereotactic coordinate system. Patients will be treated in the immobilization device with a full bladder (10 oz half hour before / or catheter if required) and we will use a barium soaked tampon to stabilize vagina if required. A rectal balloon may be used if indicated to stabilize cervix.

4.7.2 Inhibition of Effects of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (i.e., breathing, etc.) on target positioning and reproducibility. In some cases, the intrafractional tumor motion is small and no special maneuvers are required to achieve motion limits. Internal organ inhibition maneuvers must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined with any significant probability (i.e. < 5%). Assessment of this motion will be left to the institution and may include identifying the position of radio-opaque seeds implanted into the cervical tumor prior to each treatment. This type of interfractional motion analysis with correction is only required by protocol just prior to each separate treatment. Intrafraction assessment during the course of each treatment (dynamic and adaptive maneuvers) is allowed and encouraged especially if treatment times are long.

4.7.3 Localization and treatment maneuvers

A more direct method of localization of the cervical tumor fiducial markers than conventional treatment (i.e., one that uses skin) must be used in this protocol. Acceptable methods would include placing a radio-opaque seed or marker that can be visualized and triangulated using dual imaging. Radio-opaque fiducials will be placed prior to boost-4 in total in cervix and additional at lower end of vaginal involvement if indicated. Cone beam CT will be performed prior to each treatment in the treatment position to identify the target directly. Image quality should be good enough to identify the fiducial markers.

Verification CT scans and portal films may be taken at the discretion of the treating physician, but are not required for protocol participation.

4.8 Treatment Planning/Target Volumes

4.8.1 Image Acquisition

Computed Tomography (CT) will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting. Treatment planning images should be performed in

the treatment position using all aids/maneuvers described above. Axial acquisitions will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape. Image fusion with PET/CT will be utilized to help delineate the target and normal tissues. Prior to Image Guided Hypofractionated Radiation Treatment planning – if available a T2W MRI will also be obtained (OPTIONAL)

4.8.2 Dosimetry and Treatment volumes

Treatment volumes (CTVCxHR) will be modeled after those published in GEC-ESTRO brachytherapy guidelines (High risk Cervix CTV)[34]. In addition 2 cm of the full thickness of uterine canal length from the external os or proximal end of tumor (whichever is superior) will be included in the CTVCXHR and targeted to prescription dose with Image Guided Hypofractionated Radiation Treatment .However the extension of tumor beyond cervix which will be covered by dose may result in a larger and more irregular base to the “pear”. Depending upon the extent of uterine canal extension of the tumor; we will cover the length of the uterine canal with the 2 cm longitudinal margin or greater if necessary (depending upon tumor extent) from the center of the uterine canal An additional 0.3-0.5 cm in the axial plane and 0.5cm in the longitudinal plane (cranio-caudal) will be added to the CTV to constitute the planning treatment volume (PTV) depending on the institution’s accuracy and treating physician’s preference.

Three-dimensional coplanar or non-coplanar Intensity Modulated Radiotherapy (IMRT) beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, 7-15 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam’s eye view (i.e. no additional “margin” for dose build up at the edges of the blocks or MLC jaws beyond the PTV). As such, prescription lines covering the PTV will typically be the 70-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue and dose heterogeneity is expected. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor) and translated to the treatment record.

The treatment dose plan will be made up of multiple beams. The prescription dose in 4 fractions will be delivered to the margin of the PTV and fulfill the requirements below.

For purposes of dose planning and calculation of monitor units for actual treatment, all tissues within the body should be modeled in the planning system as to their electron density. Proper heterogeneity correction algorithms should be approved by the PI. Regarding planning constraints; we will follow RTOG recommendations –in that attempts will be made to successfully satisfy all criteria without deviation. In some circumstances deviations maybe acceptable depending upon the organ involved. Suggested priority for planning is to first respect all spinal cord and cauda equina constraints; then dose compactness constraints (prescription dose coverage and high dose spillage) and finally meet critical structure constraints as given in table.

Successful treatment planning will require accomplishment of all of the following criteria:

1) Prescription Isodose Surface Coverage
   The prescription isodose surface will be chosen such that at least 90% of the target volume (PTV) is conformally covered by the prescription isodose surface and at least 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose.
2) High Dose Spillage
   a) Location
      Any dose greater than 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside of the PTV. Therefore, the cumulative volume of all tissue outside of the PTV receiving a dose greater than 105% of prescription dose should be no more than 15% of the PTV volume. *However, if possible, attempts should be made to avoid higher than the prescription isodose to the rectal or bladder walls.* Ideally, these hot spots will be manipulated to occur within the HRCTVcervix. IMRT and other techniques will be encouraged to accomplish this goal.
   b) Volume
      Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1) through 2) to the volume of the PTV is ideally less than 1.3.
3) Respect all critical organ dose-volume limits listed in Section below.
4) Critical organ "hot spot" avoidance. It is recommended that efforts be made by the use of compensation or intensity modulation to avoid excessive dose to the bladder or rectal wall. These will be identified as an avoidance structure such that dose beyond the prescription dose ideally does not fall on these structures.

4.8.3 Critical Structures

4.8.3.1 Critical Organ Dose-Volume Limits

The following table lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation (See Section 4.11). The dose is listed as total over the entire course of therapy (daily radiation+ Image Guided Hypofractionated Radiation boost).

These limits were formulated with the approval of the study committee using known tolerance data, radiobiological conversion models, norms used in current practice at academic centers. Prudent treatment planning principles will be used to avoid unnecessary radiation exposure to critical normal structures irrespective of these limits.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instruction for the contouring of these organs will follow below.

Organ	Volume	Dose (Gy) from Whole pelvis	Dose (Gy) from boost (4 fractions)	Total Dose (Gy)
Spinal Cord	Maximum point dose	45 Gy	0 Gy	45 Gy
Small intestine	Maximum point dose	45Gy	20Gy	65Gy
Femoral heads	max	45 Gy	12 Gy	57 Gy
Skin	Maximum point dose	45 Gy	28 Gy	73 Gy
Rectum superior to PTVcervix/Sigmoid	≤2cc	45 Gy	19.6 Gy	max 45 Gy from pelvis and 19.6 Gy from the boost)
Bladder	Maximum point dose	45 Gy	28 Gy	73Gy
	≤2cc	45 Gy	25.2 Gy	70.2 Gy
	≤15cc	45 Gy	12.2 Gy	57.2Gy
Peri-PTVcervixrectal wall	≤3cc	45 Gy	28 Gy	73Gy
	≤33% of wall circumference on mid-PTV axial projection	45 Gy	23.2 Gy	68.2Gy

4.9 Contouring of Normal Tissue Structures

4.9.1 Spinal Cord

The spinal cord will be contoured as one structure based on the bony limits of the spinal canal. The spinal cord should be contoured anywhere it is visualized in the treatment plan (typically superior to L2).

4.9.2 Cauda Equina

The caudal equina will be contoured as one structure based on the bony limits of the spinal canal. The cauda equina should be contoured starting superiorly at the bottom of the spinal cord (typically around L2 and terminal at the inferior extent of the thecal sac (typically at S3).

4.9.3 Sacral Plexus

The left and right sacral plexus will be contoured collectively as one structure. The location of the sacral plexus will be approximated by contouring the space defined medially by the sacral foramina from S1-S3 including contouring within the sacral foramina, posteriorly along the limits of the true pelvis, laterally to 2-3 cm lateral to the sacral foramina, and anteriorly about 3-5 mm from the posterior limits of the contour.

4.9.4 Peri-cervical PTV Rectal wall

This structure is adjacent to the cervical cancer PTV (PTVcervix). Stool in the rectum is NOT included as part of the structure. Instead, the rectal wall of this structure is contoured starting inferiorly just above the anal sphincter and extending superiorly to 1 cm above the superior extent of the PTVcervix target.

4.9.5 Rectum Superior to PTVcervix

Starting inferiorly at the superior extent of the Peri-PTVcervix Rectal Wall described above, the entire wall and lumen of the rectum should be contoured up to the level of the sacral promontory.

4.9.6 Small Intestine

The small intestines should be contoured as a conglomerate of all bowel loops within each CT cut starting at the first appearance of small intestine in the pelvis and extending superiorly up to the level of the sacral promontory within each cut.

4.9.7 Bladder: contoured 2 ways

a) Lumen
b) Circumference: The bladder should be contoured in its entirety absent its contents. As such, only the wall of the bladder is included in the dose volume analysis. The bladder wall may be approximated by contouring the outer outline of the entire bladder and subtracting this volume from the same volume minus 0.5 cm in all directions (to define the inner surface of the bladder).

4.9.8 Femoral heads

The femoral heads will be contoured bilaterally as one structure.

4.9.9 Skin

The skin will constitute the external contour minus 5 mm and needs to be contoured especially in region of lower pelvis.

4.9.10 Uterus

The uterus will constitute the portion of the uterus that is not included within the PTVcervix.

4.10 Documentation Requirements

In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

4.11 Compliance Criteria

4.11.1 Dosimetry Compliance

Section 4 describes appropriate conduct for treatment planning dosimetry. Criteria for both major and minor deviations are provided in the table in Section 4.1. In addition to the criteria in section 4.1, the table in Section 4.1.6 lists dose volume limits for specific organs and structures. Exceeding these limits by more than 2.5% constitutes a minor protocol violation. Exceeding these limits by more than 5% constitutes a major protocol violation.

4.11.2 Treatment Delivery Compliance

Prior to dose delivery; CBCT will be compared to planning CT from the same beam's eye view. Any perceived error should be corrected prior to dose delivery, however if deviations are not corrected then we will apply the following rule:
Deviations of less than 0.5 cm will be considered compliant.
Deviations from 0.5-0.75 cm will be considered minor protocol deviations.
Deviations greater than those listed as minor will be considered major protocol deviations.

4.12 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.
In the absence of treatment delays due to adverse events, treatment may continue for **until completion of all fractions** or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.12.1 Gastro-intestinal

Monitored treatment related toxicity associated with gastrointestinal function will include colitis, dehydration, diarrhea, enteritis, fistula, nausea, vomiting, obstruction, proctitis, fecal incontinence, stricture/stenosis, hemorrhage, and ulcer. The consequences of gastro-intestinal toxicity should all be graded according to the CTCAEv4.

4.12.2 Genitourinary

Monitored treatment related toxicity associated with renal and genito-urinary function will include cystitis, fistula (except in patients with IVA disease at presentation), urinary incontinence, urinary obstruction, stricture/stenosis, hemorrhage, and urinary retention. The consequences of renal/genitourinary/sexual and reproductive toxicity should all be graded according to the CTCAEv4.

4.12.3 Neurology

Monitored treatment related toxicity associated with neurology function will include myelitis, motor and sensory neuropathy, plexopathy, and pain. The consequences of neurology toxicity should all be graded according to the CTCAEv4.

4.12.4 Constitutional Symptoms

Monitored treatment related toxicity associated with constitutional function will include fatigue, fever, and weight loss. The consequences of constitutional toxicity should all be graded according to the CTCAEv4.

4.12.5 Skin

Monitored treatment related toxicity associated with skin function will include fibrosis, rash (desquamation), ulceration, and telangiectasia. The consequences of skin toxicity should all be graded according to the CTCAEv4.

4.12.6 Other Toxicities

Other treatment related toxicity attributed to the therapy will be captured, recorded and the consequences of should all be graded according to the CTCAEv4.

4.13 RT Quality Assurance Review

Dr. Kevin Albuquerque will perform an RT Quality Assurance Review within 3 weeks after complete data for cases enrolled has been received.

5. DRUG THERAPY

5.1 Concomitant Medications/Treatments:

Patients will be allowed to receive chemotherapy at the discretion of the treating Gynecologic Oncologist except on day of delivery of *Image Guided Hypofractionated Radiation Treatment* fraction.

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6. STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

The screening procedures include:

6.1.1 Informed Consent
6.1.2 Medical history: Complete medical and surgical history, history of infections
6.1.3 Demographics: *Age, gender, race, ethnicity*
6.1.4 Review subject eligibility criteria
6.1.5 Review previous and concomitant medications
6.1.6 Physical exam including vital signs, height and weight
6.1.7 Zubrod performance status
6.1.8 Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

6.2 Procedures at the End of Boost Therapy

- Toxicity (include DLT) evaluations
- FACT-CX QOL (optional)

6.3 Follow-up Procedures

Patients will be followed for 5 years after completion of treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be seen at clinic at 1 month, 3 months, 6 months, 12 month, 18 month, 24 month , then annual for 3 more years post-therapy for evaluation of disease progression as well as radiation toxicities.

- For the purposes of this protocol completion of therapy will be considered the day on which the fourth and final fraction of Image Guided Hypofractionated Radiation Treatment is delivered
- Any visit between one month and four month after the completion of therapy will be considered the three months visit
- Any visit between five months and eight months after completion of therapy will be considered the sixth month follow up
- Any visit between ten months and fourteen months after the completion of therapy will be considered the one year follow up
- Follow ups beyond one year can be scheduled ± 2 month for each time point.

6.3.1 Procedure

- At each follow up patients will receive a complete physical exam and receive assessment for toxicity
- Patient should receive axial imaging at least once within fourteen months after completion of therapy
- FACT-CX QOL (optional) at 3, 12 and 24 Months post-treatment follow-up visits.

6.4 Time and Events Table

Schema	Prior to Boost Therapy	End of Boost Therapy	Follow-up
Informed Consent	**X**		
History and PE	**X**		**X**
Performance Status	**X**		**X**
Toxicity (include DLT) Evaluations		**x**	**X**
Tumor assessment	**X**[2]		**X**[1]
CT, MRI or PET/CT	**X**[2,3]		**X**[1]
FACT-CX QOL (optional)	**X**	**X**	**X** M3, then years 1 & 2

[1]Patient should receive axial imaging at least once within fourteen months after completion of therapy but preferably at 3 months after completion.
[2]Measurable lesions are not mandatory for patients to be enrolled to this study.
[3]The same technique should be used for both prior and after radiation treatments for tumor assessment.

6.5 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

6.5.1 Patient voluntarily withdraws from treatment.
6.5.2 Patient withdraws consent)
6.5.3 Patient is unable to comply with protocol requirements
6.5.4 Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator).
6.5.5 Patient experiences toxicity that makes continuation in the protocol unsafe.
6.5.6 Treating physician judges continuation on the study would not be in the patient's best interest.
6.5.7 Patient becomes pregnant during active treatment (pregnancy to be reported along same timelines as a serious adverse event).
6.5.8 Lost to follow-up. *Example language: If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.*

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

7.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with radiation.
Evaluable for objective response: Only those patients who have clinically evaluable or measurable disease (by imaging) present at baseline, have received at least one fraction of Image Guided Hypofractionated Radiation Treatment, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Image Guided Hypofractionated Radiation Treatment will also be considered evaluable.)

7.1.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease: Will be evaluated clinically. The response will be recorded based on the clinical digital exam.

Target lesion: For purposes of this study the cervical tumor is the target lesion, longest diameter (LD) will be measured from T2W MR studyif available or contrast CT scan. The baseline LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the radiation treatment.

The same method of assessment and the same technique should be used to characterize the identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT or MRI: These techniques should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Study Patients should receive some form of cross sectional imaging before initiation of therapy as well as at least once within fourteen months after completion of therapy.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

7.1.4.2 Evaluation of Non-Target Lesions (para-aortic/ pelvic nodes)

Complete Response (CR): Disappearance of all non-target lesions.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

7.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

7.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

This will be further differentiated as Local tumor (cervix-which is primary endpoint) , Regional(pelvic nodal) and distant (Paraortic and visceral organ)metastatses.

7.2 Safety/tolerability

Analyses will be performed for all patients having received all three fractions of *Image Guided Hypofractionated Radiation Treatment*. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html).

8. STATISTICAL CONSIDERATIONS

8.1 Primary Endpoint

8.1.1 Study Design/Study Endpoints

The study is a prospective single-arm phase II trial of Image Guided Hypofractionated Radiation Treatment in the definitive treatment of locally advanced cervical cancer. The study will determine whether Image Guided Hypofractionated Radiation Treatment boost is efficacious in women with locally advanced cervical cancer without increased risk of acute GI or GU toxicity. Study endpoints include local control rate, and toxicity assessed by CTCAEv4,

For the safety lead-in not more than 1 of 6 patients should have more than Grade 2 toxicity over 90 days after commencement of Image Guided Hypofractionated Radiation Treatment boost

8.2 Secondary Endpoints

The secondary objectives are to:

- Determine the late grade ≥3 GI and GU toxicity as assessed by CTCAE v4 at 91-365 days from the start of protocol treatment. *This will be summarized using a proportion and a 95% confidence interval.*
- Measure Cervix cancer specific patient reported QOL at 6 time points using FACT-CX validated measurement tools with our VTOC system

8.3 Sample Size

8.3.1 Overview

Six patients will be used for a safety lead-in stage in this phase II clinical trial. In Standard Phase1 3+3 clinical trials, there is 0 or 1 DLT out of 6 patients at the MTD, which will be used for a subsequent phase II clinical trials. [36] Prior studies have shown the rate of ≥grade 3 GI toxicity to be 7-14% and 2-5% for ≥grade 3 GU toxicity. The treatment will not be considered to be feasible if the rate of acute GI/GU toxicity is >30%.In this phase II clinical trial, six patients will be used in a safety lead-in stage. If there is 0 or 1 DLT out of 6 patients at the safety lead-in stage, we will proceed to a phase II clinical trial. Otherwise, we will stop the trial, and will not proceed to a phase II trial with a given dose.

The primary goal of this study is to assess the 2 year pelvic local control (excluding nodes) from cervix cancer .Historical data shows that the 2 yr-pelvic local control rate is approximately 65%. [4, 5, 9] We expect that this will be increased to 85% with the treatment of cervix Image Guided Hypofractionated Radiation Treatment boost based on best results with Intracavitary/interstitial data [13]. We assume that the loco regional recurrence-free survival follows an exponential distribution. Accrual to the study is assumed to be uniformly distributed over time with no loss to follow-up. Twenty-one patients will achieve 80% power in detecting the difference between the null hypothesis of 2-year recurrence-free survival rate of 65% and the alternative hypothesis of 2-year recurrence-free survival rate of 85% at a two-sided 0.1 significance level assuming a 2-year accrual period and 2-year follow-up period. It is expected that 21 patients will be recruited in 2 years with an expected accrual rate of 10-11 patients per year.

8.3.2 Sample Size Derivation

Sample size was determined by estimating the number of potential patients likely to be (approximately 50% of referred patients meeting the eligibility criteria) to the UTSW Department of Radiation Oncology over a three year period. We estimate that approximately 50-60 patients meeting entry criteria will present to our facility over the accrual period of 3 years. Of these patients, slightly more than 50%, or 25-30 patients, will consent to be evaluated for the protocol. Of these patients, approximately 80% will meet the Image Guided Hypofractionated Radiation Treatment constraints for total of 20-24 patients enrolled over 3 years. Twenty one patients are required for a 80% power of detecting the improved pelvic local control for 2 year follow-up. The sample size was estimated using the SWOG one-sample survival calculator: http://www.swogstat.org/stat/public/one_survival.htm

8.4 Patient Accrual and Study

8.4.1 Duration

It is expected that it will take approximately three years to meet the accrual goal. The analysis for acute toxicity will be carried out after each patient has had at least 90 days of follow-up from the end of the radiation therapy. Study-related data will be stored for 5 years after

termination of the study when accrual is no longer taking place and all patients have discontinued follow-up procedures.

8.5 Analysis Plan

8.5.1 Interim Reports

Interim reports will be prepared annually until the results of the study are published or the study is terminated. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, compliance rate of treatment per protocol, the pelvic control rate based upon imaging and exam and the frequencies and severity of toxicity

The time to local failure will be estimated using the Kaplan-Meier method and the corresponding 95% confidence interval will be estimated using Greenwood's formula.. The rate of acute and late toxicity will be determined by proportions of patients reporting grade 3-5 toxicity relative to number of patients treated on the protocol, and the corresponding 95% confidence interval will be estimated using an exact binomial method. Additionally, time to toxicity will be estimated using the Kaplan-Meier method. One-sample log-rank test will be used to test if the 2-year local recurrence free survival rate is significantly different from the historical control rate of 65%.
Patient-reported functional status will be assessed with the lung cancer subscales of the Functional Assessment of Cancer Therapy-Cervix (FACT-CX). Changes in QOL will be analyzed using all available data at 6 predetermined timepoints with generalized estimating equations (GEE) to investigate if there is significant change in QOL over time.

8.5.2 The Analysis of Severe Late GU/GI Toxicity

This analysis will be carried out when each patient has had at least 90 days (i.e., 3 months) of follow-up after the end of the acute period. The time to the occurrence of severe late GU/GI toxicity is defined as the time interval from start of protocol treatment to the date of onset of grade 3-5 GU/GI toxicity. A Kaplan-Meier curve will be used to estimate the time to late toxicity. The time analysis for recording severe late GU/GI toxicity for this protocol will be limited to 180 days from after completion of protocol therapy, although every effort will be made to document any late toxicity during subsequent follow-up. If no such toxicity is observed before the time of the analysis, the patient will be censored at the time of the analysis.

8.6 Gender and Diversity

Projected Ethnic Diversity

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	10	NA	10
Not Hispanic or Latino	11	NA	11
Ethnic Category: Total of all	21	**NA**	**21**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	NA	0
Asian	1	NA	1
Black or African American	6	NA	6
Native Hawaiian or other Pacific	0	NA	0
White	14	NA	14
Racial Category: Total of all	21	NA	**21**

NA = Not Applicable

9. STUDY MANAGEMENT

9.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the University of Texas – Southwestern medical center IRB. All investigators will follow the University conflict of interest policy.

9.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the research office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if institution holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.4 Registration Procedures

All patients must be registered with the Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Research Office Study Coordinator.

10. DATA & SAFETY MONITORING

10.1 Data Management and Monitoring/Auditing

10.1.1 External Data and Safety Monitoring Board

The UTSW Simmons Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is the external review of trial-related documentation, which may include detailed assessment of subject records, regulatory and pharmacy review or may be more focused depending on the nature and reason for the audit. External reflects an independent reviewer within the CRO who is external to the DOT. DSMC audits are performed by the Quality Assurance and Education Coordinator (QAC) with the overall purpose of reviewing the conduct of a clinical trial to ensure quality results. The audit schedule prioritizes investigator-initiated institutional therapeutic trials and frequency is determined by the risk of the trial.

The SCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The Quality Assurance and Education Coordinator (QAC) works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the patient population to be studied; adequacy of the data management system; and procedures to ensure the safety of study subjects based on the associated risks of the study.

10.1.2 Internal Data and Safety Monitoring Committee

The Radiation Oncology Clinical Research Office (CRO) reports serious adverse events (SAEs) to Radiation Oncology Safety Assurance Committee (ROSAC) monthly. These SAEs are also reported to the University of Texas Southwestern Medical Center (UTSW) IRB per IRB guidelines and SCC DSMC.

All clinical trials are reviewed on monthly basis for enrollment. These trials are assessed for safety on a continual basis throughout the life of the trial. For investigator-initiated trials, all SAEs are monitored – both local and at affiliated institutions.

A data safety monitoring committee including radiation oncologists not participating in this trial will be formed to review toxicity endpoints and efficacy data. In the phase I component, the data safety monitoring committee will review and verify all reported DLTs. In particular, this committee will scrutinize the grading of adverse events and the attribution to therapy previously assigned by the investigators. This panel will have access to basic patient information so as to have the ability to critically review toxicity events. This study will use this committee to perform ongoing safety assessment at regular defined intervals defined in the statistics section of this protocol. Unexpected toxicities occurring between defined interim analyses points will be reported to the treating center's IRB and also to the University of Texas Southwestern Institutional Review Board.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

10.2 Adverse Events: Definitions and Reporting

Adverse Events will be reported as indicated by the appropriate following table (see below).

10.2.1 Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

10.2.2 Severity

Adverse events will be graded by a numerical score according to the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

10.2.3 Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets any of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study. Refer to the UTSW IRB website at http://www.utsouthwestern.net/intranet/research/research-administration/irb/study- management/adverse-events.html to determine when a serious adverse event requires reporting to the IRB.

10.2.4 Unanticipated Problems:

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets each of the following criteria:

- Unexpected (in terms of nature, severity or frequency) AND
- Definitely, probably, or possibly related to participation in the research AND
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

10.2.5 Follow-up

All adverse events will be followed up according to good medical practices.

10.2.6 Reporting

Local unanticipated problems require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB and to the SCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE

documentation that is available are also submitted to the DSMC Chair who determines if further action is required.

All local serious adverse events which occur on research subjects on protocols for which the SCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events within upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Participating sites of multi-institutional clinical trials coordinated by the UTSW Radiation Oncology:

Written reports to:

UTSW Radiation Oncology Study Coordinator or Clinical Research Manager within 1 working day to
Study Coordinator: Ying Dong at ying.dong@utsouthwestern.edu or
Clinical Research Manager: Jean Wu at jean.wu@utsouthwestern.edu
Fax: 214-645-8913

UTSW Radiation Oncology Study Coordinator or Clinical Research Manager will report to
UTSW SCC Data Safety Monitoring Committee Coordinator

UTSW SCC Data Safety Monitoring Committee Coordinator
Email: SCCDSMC@utsouthwestern.edu
Fax: 214-648-7018 or deliver to NB 2.418

UTSW Institutional Review Board (IRB)
Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. SAEs
   Local serious adverse events (SAEs) for studies where SCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

2. Unanticipated Problems
   - Local unanticipated problems require reporting to the UTSW IRB within 2 working days of PI awareness of the event.
   - Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227 351.pdf

10.3 Early Stopping for Toxicity/Stopping Rules

Stopping for toxicity will be as described in the statistical section and will be based on unacceptable toxicity, defined as grade 3 - 5 toxicity related to the following organ systems: gastrointestinal, genito-urinary, neurological, or any other grade 4 or 5 toxicity attributed to the therapy occurring in 30% or more of treated patients. If a single patient has more than one unacceptable toxicity, they will only be counted as one unacceptable toxicity for this analysis.

If more than three of the first nine or more than five of the first fifteen patients have ≥grade 3 GI/GU toxicity at 90 days *from the start of therapy, then the treatment will be considered unfeasible and the study will be closed.*

If the number of unacceptable toxicities observed demonstrate via the monitoring rules above that the treatment-related unacceptable toxicity rate is 30% or more, consideration will be initiated for stopping the study. In this case, the study PIs, and statistician will review the toxicity data along with the Data Safety Monitoring Committee and make appropriate recommendations about continuing the study. Additionally, the treatment-related unacceptable toxicity rate will continued to be monitored during the follow-up period. If the unacceptable toxicity rate exceeds 30% at any time during the follow-up period, the study chair, study PIs, and statistician will review the toxicity data along with the Data Safety Monitoring Committee and make appropriate recommendations about reporting the information.

10.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.5 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

10.6 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.

- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

10.7 Protocol Deviations:

Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

10.8 Protocol Violations:

Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

10.9 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.10 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.11 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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Patient Initials: _____

Case # _ _

Date: _ _/_ _/___ _

APPENDIX I: FACT-Cx (Version 4) English Version

FACT-Cx (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain...	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill…..	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
GS1	I feel close to my friends……	0	1	2	3	4
GS2	I get emotional support from my family..	0	1	2	3	4
GS3	I get support from my friends……..	0	1	2	3	4
GS4	My family has accepted my illness……..	0	1	2	3	4
GS5	I am satisfied with family communication about my illness……..	0	1	2	3	4

Patient Initials: _____

Case # _ _

Date: _ _/_ _/___ _

FACT-Cx (Versio

Please circle or m one number per li to indicate your response as it app to the past 7 days

GS6	I feel close to my partner (or the person who is my main support)……	0	1	2		
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4

GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now…….	0	1	2	3	4

Patient Initials: _____

Case # _ _

Date: _ _/_ _/___ _

FACT-Cx (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>ADDITIONAL CONCERNS</u>	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Cx1	I am bothered by discharge or bleeding from my vagina	0	1	2	3	4
Cx2	I am bothered by odor coming from my vagina	0	1	2	3	4
Cx3	I am afraid to have sex	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
Cx4	My vagina feels too narrow or short	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
Cx5	I am afraid the treatment may harm my body	0	1	2	3	4

BL4	I am interested in sex	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
BL1	I have trouble controlling my urine	0	1	2	3	4
BL3	It burns when I urinate	0	1	2	3	4
Cx7	I have discomfort when I urinate	0	1	2	3	4
HN1	I am able to eat the foods that I like	0	1	2	3	4

APPENDIX II: FACT-Cx (Version 4) Spanish Version

Patient Initials: _____

Case # _ _

Date: _ _/_ _/___ _

FACT-Cx (4ª Versión)

A continuación encontrará una lista de afirmaciones que otras personas con su misma enfermedad consideran importantes.

Marque un solo número por línea para indicar la respuesta que corresponde a los últimos 7 días.

	ESTADO FÍSICO GENERAL DE SALUD	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchí-simo**
GP1	Me falta energía 0	0	1	2	3	4
GP2	Tengo náuseas 0	0	1	2	3	4

GP3	Debido a mi estado físico, tengo dificultad para atender a las necesidades de mi familia.	0	1	2	3	4
GP4	Tengo dolor	0	1	2	3	4
GP5	Me molestan los efectos secundarios del tratamiento	0	1	2	3	4
GP6	Me siento enfermo(a)	0	1	2	3	4
GP7	Tengo que pasar tiempo acostado(a)	0	1	2	3	4

	AMBIENTE FAMILIAR Y SOCIAL	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchí-simo**
GS1	Me siento cercano(a) a mis amistades	0	1	2	3	4
GS2	Recibo apoyo emocional por parte de mi familia	0	1	2	3	4
GS3	Recibo apoyo por parte de mis amistades	0	1	2	3	4
GS4	Mi familia ha aceptado mi enfermedad	0	1	2	3	4
GS5	Estoy satisfecho(a) con la manera en que se comunica mi familia acerca de mi enfermedad	0	1	2	3	4
GS6	Me siento cercano(a) a mi pareja (o a la persona que es mi principal fuente de apoyo)	0	1	2	3	4
Q1	*Sin importar su nivel actual de actividad sexual, conteste a la siguiente pregunta. Si prefiere no contestarla, marque esta casilla* ☐ *y continúe con la siguiente sección.*					
GS7	Estoy satisfecho(a) con mi vida sexual	0	1	2	3	4

Patient Initials: _____

Case # _ _

Date: / /

FACT-Cx (4ª Versión)

Marque un solo número por línea para indicar la respuesta que corresponde a los últimos 7 días.

	ESTADO EMOCIONAL	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchí-simo**
GE1	Me siento triste	0	1	2	3	4
GE2	Estoy satisfecho(a) de cómo me estoy enfrentando a mi enfermedad	0	1	2	3	4
GE3	Estoy perdiendo las esperanzas en la lucha contra mi enfermedad	0	1	2	3	4
GE4	Me siento nervioso(a)	0	1	2	3	4
GE5	Me preocupa morir	0	1	2	3	4
GE6	Me preocupa que mi enfermedad empeore	0	1	2	3	4

	CAPACIDAD DE FUNCIONAMIENTO PERSONAL	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchí-simo**
GF1	Puedo trabajar (incluya el trabajo en el hogar)	0	1	2	3	4
GF2	Mi trabajo me satisface (incluya el trabajo en el hogar)……	0	1	2	3	4
GF3	Puedo disfrutar de la vida	0	1	2	3	4
GF4	He aceptado mi enfermedad	0	1	2	3	4
GF5	Duermo bien	0	1	2	3	4
GF6	Disfruto con mis pasatiempos de siempre	0	1	2	3	4

GF7	Estoy satisfecho(a) con mi calidad de vida actual	0	1	2	3	4

Patient Initials: _____

Case # _ _

Date: / /

FACT-Cx (4ª Versión)

Marque un solo número por línea para indicar la respuesta que corresponde a los últimos 7 días.

		Nada	Un poco	Algo	Mucho	Muchí-simo
	OTRAS PREOCUPACIONES					
Cx1	Me molesta el flujo o sangrado por la vagina.....	0	1	2	3	4
Cx2	Tengo un olor vaginal que me molesta	0	1	2	3	4
Cx3	Tengo miedo de tener relaciones sexuales	0	1	2	3	4
B4	Me siento físicamente atractiva	0	1	2	3	4
Cx4	Siento la vagina muy estrecha o pequeña	0	1	2	3	4
BMT7	Estoy preocupada por mi capacidad de tener hijos	0	1	2	3	4
Cx5	Tengo miedo de que el tratamiento pueda hacerle daño a mi cuerpo	0	1	2	3	4
BL4	Me interesa el sexo……..	0	1	2	3	4

C7	Me gusta mi apariencia personal	0	1	2	3	4
Cx6	Me molesta el estreñimiento	0	1	2	3	4
C6	Tengo buen apetito	0	1	2	3	4
BL1	Tengo dificultad para controlar la orina	0	1	2	3	4
BL3	Siento ardor/escozor al orinar	0	1	2	3	4
Cx7	Siento molestias al orinar	0	1	2	3	4
HN1	Puedo comer lo que me gusta	0	1	2	3	4

Patient Initials: _____

Case # _ _

Date: _ _/_ _/___ _

APPENDIX III: FACT-Cx Scoring Guidelines

FACT-Cx Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-Cx).
5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____

Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____**=SWB subscale score**

EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____**=EWB subscale score**

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____**=FWB subscale score**

Patient Initials: _____

Case # _ _

Date: _ _/_ _/___ _

FACT-Cx Scoring Guidelines (Version 4) – Page 2

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
CERVIX	Cx1	4	-	_____	= _____
CANCER	Cx2	4	-	_____	= _____
SUBSCALE	Cx3	4	-	_____	= _____
(CxCS)	B4	0	+	_____	= _____
	Cx4	4	-	_____	= _____
Score range: 0-60	BMT7	4	-	_____	= _____
	Cx5	4	-	_____	= _____
	BL4	0	+	_____	= _____
	C7	0	+	_____	= _____
	Cx6	4	-	_____	= _____
	C6	0	+	_____	= _____
	BL1	4	-	_____	= _____
	BL3	4	-	_____	= _____
	Cx7	4	-	_____	= _____
	HN1	0	+	_____	= _____

Sum individual item scores:_____
Multiply by 15 : _____
Divide by number of items answered: _____**=CxC Subscale score**

To derive a FACT-Cx Trial Outcome Index (TOI):

Score range: 0- _____ + _____ + _____ =_____**=FACT-Cx TOI**

(**PWB** score) (**FWB** score) (**CxCS** score)

To Derive a FACT-G total score:

Score range: 0- _____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-Cx total score:

Score range: _____ + _____ + _____ + _____ + _____ =_____=**FACT-Cx Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**CxCS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

APPENDIX IV

ELIGIBILITY CHECKLIST

Case # _____ Name _____

_____(Y) 1. Squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix histologically confirmed by biopsy?

2. What is the FIGO Stage?

_____	IB2	_____	IIIA
_____	IIA2	_____	IIIB
_____	IIB	_____	IVA
_____	III	_____	IVB

_____(Y) 3. Is the patient 18 years of age or older?

_____(Y) 4. Is the Zubrod performance status 0-3?

_____(Y) 5. If patient is a woman of child-bearing potential, did she agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study treatment.

_____(Y) 6. Patient should have at least one of the following to be eligible: (Check all that apply)

_____ Is not a candidate for intracavitary brachytherapy due to poor geometry or poor response to external beam RT

_____ Has co-morbid medical conditions, bleeding disorders, poor anesthetic risk precluding brachytherapy

_____ Requires interstitial brachytherapy

_____ Refuses brachytherapy or prefer external beam hypofractionated approach

Note: Patients may be identified during standard therapy and enrolled prior to boost.

_____ (N) 7. Is the patient pregnant?

_____ (N) 8. Does the patient have concurrent untreated cancer excluding non-melanoma skin cancer?

_____ (N) 9. Has the patient had previous pelvic radiation?

_____ (N) 10. Does the patient have active inflammatory bowel disease or collagen vascular disease – SLE, scleroderma?

_____ (N) 11. Is the patient unable to sign consent for the study?

_____ (N) 12. Is the patient severely immunocompromised (e.g. transplant, taking immunosuppressive drugs, etc.)?

Completed by _____ Date _____

APPENDIX V Performance Scale

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).
5	Death (Karnofsky 0).

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX VI

FIGO STAGING FOR CERVICAL CANCER

Stage	
I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
IA	Invasive carcinoma, which can be diagnosed only by microscopy with deepest invasion ≤5 mm and largest extension ≥7 mm.
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm.
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 preclinical cancers greater than stage IA.[b]
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 >4.0 cm in greatest dimension.
IIB	With obvious parametrial invasion.
III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney.[c]
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 nonfunctioning kidney.
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.