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Protocol Page

3D Image-guided Intracavitary Brachytherapy Treatment Planning for Cervical Cancer using a Novel Shielded Applicator
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Core Protocol Information

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Study Chair:	Ann Klopp
Additional Contact:	Donna M. White Toni Williams Victoria Cox
Department:	Radiation Oncology
Phone:	713-563-6930
Unit:	1202
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Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

Primary objective

- Determine whether 3D Image-guided treatment planning can improve the quality of intracavitary brachytherapy in cervical cancer.

Secondary objectives

1. Determine if MRI imaging is superior to CT imaging in delineating a high risk target volume.
2. Identify clinical and tumor characteristics of patients in whom CT or MRI can improve dosimetric tumor coverage and normal tissue sparing.
3. Evaluate the feasibility of MRI-based treatment planning utilizing the shielded MD Anderson adaptive applicator.
4. Compare resource utilization for MRI and CT based treatment planning as compared to standard film based planning techniques.

2.0 Background

Role of Intracavitary Brachytherapy in Treatment of Cervical Cancer

Intracavitary brachytherapy (ICBT) is a critical component of definitive radiation therapy for cervical cancer. ICBT is typically administered upon completion of five weeks of external beam radiation therapy (EBRT). Because of rapid dose fall-off, optimal implant placement allows for high dose delivery to the cervix and parametrial tissue while limiting dose to critical adjacent tissues, including the bladder, rectum and sigmoid colon. Patients with small tumors have high central control rates and relatively low complication rates with this approach. However, women with a larger volume of disease have higher rates of local recurrence.[1,2]

Standard Intracavitary Brachytherapy

At MD Anderson, our standard and extensively validated approach has been to optimize implant geometry by careful implant placement and selection of the optimal applicator based on patient anatomy and disease extent.[3] Orthogonal x-ray films are used intra-operatively to verify optimal placement of the applicator and proximity to the cervix.

Treatment planning is performed by optimizing dwell times for radiation sources which step through a series of dwell positions in the intrauterine tandem and vaginal applicator. Treatment decisions are informed by physical examination, evaluation of pre-treatment imaging and the type and position of the brachytherapy applicator used and for specific patients additional 3D imaging obtained at the time of implant. The goal is to create a dose distribution which delivers adequate dose to sterilize disease in the tumor bed and parametrial tissues while minimizing dose to bladder, rectum and sigmoid colon. The dose to bladder and rectum is limited to standard constraints (65-70

Gy to the rectum and 70-75 Gy to the bladder) which are represented by standard reference points on orthogonal images. For patients with particularly challenging anatomy or implants, additional imaging (in the form of CT or MRI) is often obtained following the implant to verify placement of the system.

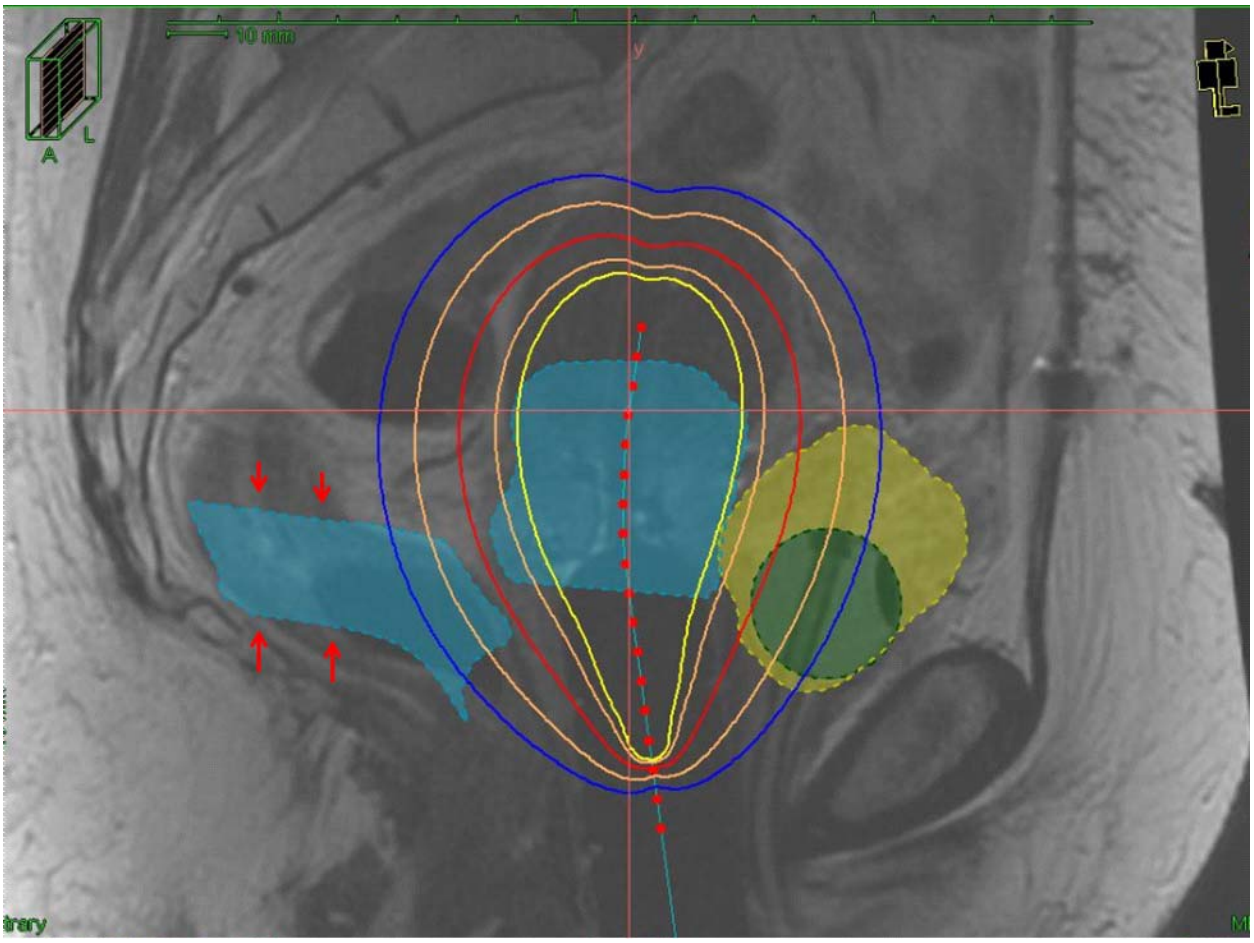
Image Guided Brachytherapy

The acquisition of 3D imaging at the time of brachytherapy allows for volumetric evaluation of dose to the target (the residual tumor and the whole cervix) as well as adjacent normal tissues. CT images taken with the intracavitary applicator in place are increasingly being used for brachytherapy treatment planning. Recently, a number of investigators have advocated the use of MRI-based treatment planning. Following acquisition, images can be exported to the radiation treatment planning system where dose to the target and normal tissues can be calculated (Figure 1). Dwell times for the iridium stepping source within the applicator can then be adjusted in order to modify the dose based on individual patient and tumor anatomy and response to prior treatment thus optimizing tumor coverage and minimizing dose to organs at risk.

CT- and MRI-based planning have advantages and disadvantages. CT imaging provides excellent visualization of normal pelvic tissues, but the tumor is generally difficult to distinguish from normal cervix as a result of their similar electron density. While still more expensive than 2D imaging, CT imaging is readily available to most radiation oncologists, and is the most common form of image-based treatment planning being used in the US today.[4]

T2 MRI images provide better visualization of tumor and paracervical soft tissue extension than CT.[5-7] This may be important, because areas of tumor extending into adjacent tissues may receive an inadequate dose with standard brachytherapy treatments.

Figure 1. Sagittal T2 weighted MRI with dose distribution displayed. HR-CTV located centrally in aqua color, bladder in yellow, foley bulb in green, and rectum located posteriorly in aqua delineated with red arrows.



Within the last decade there has been a European lead movement towards MRI-based treatment planning in which the brachytherapy dose is prescribed to a 3D image-derived target volume with set constraints set for doses to critical organs at risk for radiation injury. The GEC-ESTRO working group developed recommendations for concepts and terms in 3D image-based treatment planning and has worked to define targets compatible with clinical experience from three prominent European institutions.[8,9] Early clinical results using the above described systematic approach have been viewed as promising with 3-year local control rates of 82% for patients with tumors >5 cm and 96% for 2-5 cm.[10] However, these local control rates are not obviously different from those reported for patients treated at MD Anderson using traditional techniques.[1,11]

Interestingly, the practice of obtaining 3D imaging with the applicator in place has been rapidly adapted across the United States with a 2010 American Brachytherapy Society (ABS) patterns of care study showing that the majority of physicians obtain CT or MRI after insertion of the intracavitary device.[4] Despite the fact that MRI is the primary imaging modality used in the studies supporting 3D image guided brachytherapy the ABS patterns of care study shows that 70% of respondents use CT imaging while only 2% use MRI.

It is important to clarify the magnitude of potential benefit from these new approaches because utilization of 3D image-based treatment planning is substantially more expensive than standard planning; one study reported increased costs of 10-15% to setup 3D image based gynecologic brachytherapy.[10] MRI in particular, despite its potential benefits, is expensive, logistically difficult and is not as widely available for radiation oncology treatment planning as CT imaging. It also requires the use of specially-designed MRI-compatible applicators. As a result, Viswanathan and colleagues suggested a standardized approach to CT-based contouring.[12] When the authors compared CT with MRI, they found that CT was adequate for analysis of the doses to organs at risk, but that CT-based standardized contours tended to overestimate tumor width, leading to significant differences in target coverage. While this study is the only published series comparing CT to MRI, it included only 10 patients with a single radiation oncologist responsible for the contouring. Additionally, the CT quality was poor (with 4 mm slice thickness) compared to current standards (typically 1-2 mm slice thickness). To date, there are no studies evaluating the role of modern CT scanning in an adequate number of patients to determine if there is a select group in which CT may be equivalent to MRI in delineating a target volume.

MRI-Compatible Adaptive Applicator

Because utilization of MRI for treatment planning requires special MRI-compatible applicators, the shields that are used to reduce dose to the bladder and rectum in standard applicators have been eliminated. The use of shields in standard applicators have been shown to reduce the dose to the bladder and rectum by as much as 25%, but create extensive image artifacts hindering image based brachytherapy planning.[13,14]

At MD Anderson, we have developed a novel applicator with moveable MRI-compatible shields, which allows for acquisition of high resolution CT images.15 Our group recently completed a prospective pilot study using this applicator and demonstrated the feasibility of its use in ICBT planning with superior image quality when the adaptive shields were shifted from the treatment position as compared to in the treatment position.16 The applicator that we are using is based off of Nucletron's FDA approved MRI compatibility applicators (see Appendix C).

3.0 Rationale

Standard approaches for ICBT in cervical cancer are backed by extensive clinical experience with high rates of local control and relatively low toxicity.[17] MRI- and CT-based treatment planning have potential to further improve outcomes for certain patients by allowing tailored treatment based on patient specific anatomy and tumor response.

The current standard at our institution takes into consideration initial clinical exam, pre-treatment imaging, pre-brachytherapy examination under anesthesia, applicator features, quality of the brachytherapy placement and doses to normal tissue reference

points collectively allowing for development of the optimal 2D brachytherapy treatment plan. As part of this protocol each patient will have a 2D treatment plan created in this way prior to the treating physician reviewing the MRI or CT obtained with the applicator in place.

Currently at our institution imaging, including CT and MRI, is taken into account on a case-by-case basis allowing for subtle adjustments to the treatment plan as necessary. This protocol will deliver treatment according to this standard practice while systematically evaluating the potential impact of image-based planning on the quality of treatment planning.

Patients enrolled on this protocol will have both a CT and MRI obtained after insertion of the intracavitary applicator. Once the optimal 2D plan has been created, these images will be reviewed by the treating physician before treatment to rule out any possible rare major deviations in applicator placement such as uterine perforation as well as to inform the treating physician of size and location of any residual disease and proximity of organs at risk. This will be done so that subtle adjustments to standard loadings can be made. For example, if bowel is identified to be in close proximity to the implant the adjacent dwell positions may be loaded to a lesser degree in order to better spare that bowel. Patients will be treated with this 2D plan informed by the 3D images consistent with our current standard of care for patients who have additional imaging at the time of implant.

Obtaining the CT and MRI will also allow us to create additional 3D image based treatment plans which will be used only for comparison purposes (not for actual treatment). We will compare the 3D image based treatment plans to the standard 2D treatment plan to determine if we are able to dosimetrically improve target coverage, while respecting adjacent tissue tolerances, with either form of 3D image guidance. We will also keep track of the number of person-hours required for planning using each imaging modality by documenting the time spent generating contours on both CT and MRI and the amount of time spent generating each individual plan. We will also keep track of the amount of time that each additional imaging modality takes to acquire. Through the billing department, we will also capture the fees associated with the additional MRI and CT scan as well as the charge of the MRI compatible applicators for each patient and compare this to the fees for a routine implant in which a comparable standard applicator is used and MRI and CT at the time of implant are not obtained. In combination, this will allow us to determine which imaging modalities are most efficient and practical and which add the most to the treatment planning process. Additionally, we will determine if there are specific patient and tumor characteristics most and least likely to gain from image guided brachytherapy.

4.0 Patient Eligibility

Inclusion Criteria

- Women with stage $\geq$ IB2 cervical cancer treated with definitive chemoradiation or radiation therapy who require intracavitary brachytherapy.

Exclusion criteria

- Patient or tumor anatomy that requires use of a non-MRI-compatible applicator.
- Patients who require interstitial brachytherapy.
- Patients whose treating physician feels that they require additional 3D imaging at the time of implant based on physical exam or initial findings
- Patients with implantable cardioverter-defibrillator, pacemaker or other implanted device, which precludes MRI acquisition.

5.0 Treatment Plan

Patient Evaluation and External Beam Therapy

Patients may not be enrolled on protocol until after external beam therapy has been started so pretreatment workup will be according to standard practice which typically includes CBC, BUN/Cr, chest imaging, CT abdomen/pelvis, MRI of the pelvis, and physical examination. Patients who are candidates for this protocol will have physical exam findings documented at the time of diagnosis and on the day of the implant. Pertinent information including whether tumor is exophytic or bulky/endocervical, tumor diameter, parametrial involvement, pelvic sidewall, rectal, or vaginal involvement will be documented on a protocol specific form (Form A, Appendix D). Patients will then be treated with external beam radiation therapy with or without chemotherapy as determined by the treating radiation oncologist and gynecologic oncologist. External beam irradiation may consist of conventional treatment or Intensity Modulated Radiation Therapy (IMRT).

Intracavitary Applicator Placement

On the day of the implant, an examination under anesthesia will take place per our standard approach. The tumor characteristics will be documented on Form A (Appendix D). The appropriate MRI-compatible applicator will be inserted using ultrasound guidance to verify tandem placement in the uterus. Tandem and ovoids, tandem and cylinders, or tandem and ring will be chosen to accommodate the patient's tumor and vaginal anatomy. Gel impregnated gauze packing will be placed in the vagina for stabilization of the applicator and displacement of rectum and bladder.

Per our standard treatment protocol, orthogonal plain films will be obtained in the operating room to assess appropriate applicator placement. Optimized loadings will then be recommended according to standard rules. Following the reversal of anesthesia, patients will be taken to recovery. After recovery from anesthesia, patients will be transported to diagnostic imaging for MRI acquisition and to the department of radiation oncology for CT imaging.

MRI Acquisition

Currently, baseline MRIs are obtained on the majority of patients at diagnosis and this will be performed according to standard practice.

On the day of the intracavitary implant, after placement of the MRI compatible applicator, MRI acquisition will be performed on 1.5 T or 3 T scanner. Images will be obtained utilizing an 8 channel cardiac coil. MRI compatibility of the applicator will be documented prior to placement of the patient in the scanner. High resolution T2 FRFSE images will be obtained in the coronal plane (3mm contiguous slices/FOV 18-22 cm/TR>3000/TE>100msecs). The coronal plane will be used to generate oblique sagittal and oblique axial images of the cervix and applicator – parallel and perpendicular to the applicator device within the cervix, respectively. Axial T2 weighted T2 FRFSE images of the entire pelvis will be obtained at the end of the exam. Additionally a T2 Axial Cube image with isotropic 1mm voxels will also be obtained. On the day of the implant, MRI images will be evaluated for adequate applicator position within the uterus and cervix to rule out any possible rare major deviations in applicator placement such as uterine perforation.

CT Acquisition

The same procedure used in previously approved protocol 2008-0455 will be used for CT acquisition. In brief, CT images will be acquired using the GE Lightspeed CT simulators available in the MDACC Radiation Oncology clinic. Images will be acquired with 120 keV, 200mA with 2 mm slice thickness. Patients with shielded applicators will have the shields shifted during image acquisition, according to previous protocol specifications. After acquisition of the CT, the medical physicist will insure that both rectal and bladder shields are locked into the radiation treatment position and check the overall applicator integrity. A CT scout image will also be acquired to verify that the shields have been moved to the appropriate place. A medical physicist will be present during the CT acquisition for patients with adaptive applicator which requires shield shifting to insure correct procedure is followed. It is expected that patients will spend 15-30 minutes in the Radiation Oncology department for the CT procedure.

Contouring and Treatment Planning

As is standard, our dosimetrists will develop a 2D plan according to the loadings recommended by the physician based on the physical examination, initial diagnostic imaging ,and orthogonal films. As is routine the treating physician will then evaluate the 2D plan looking at doses to specific points (rectal and bladder) delineated on the 2D imaging and make adjustments as they see fit. Following acquisition of both MRI and CT and finalizing of the 2D treatment plan, images will be reviewed by the treating physician before treatment to rule out any possible rare major deviations in applicator placement such as uterine perforation. The 3D imaging will also be used to inform the physician prescribing the dose of the location and size of any residual disease and

location of critical organs such that they may make subtle adjustments to the 2D treatment plan. Based on this a new plan, 2D plan informed by 3D imaging, will be created, and the patient will be treated with this plan.

Dosimetric Contouring Study

As part of the lab based portion of this protocol, the MRI and CT images will be uploaded into our brachytherapy treatment planning software, Oncentra. After reviewing the patient's initial diagnostic imaging and physical examination at the time of diagnosis and the time of implant the radiation oncologist involved in the procedure and one additional radiation oncologist will contour a HR-CTV based on the GEC-ESTRO guidelines (Appendix E) on the CT followed by the MRI. One of the primary investigators will also contour a HR-CTV as well as critical structures (rectum, bladder, sigmoid colon) on both the MRI and CT scan. The 2D plan will then be registered on the MRI and CT within the treatment planning software. Based on the primary investigators approved contours several additional plans will be created for purpose of comparison (See Table 1).

The contours devised by all three physicians on MRI and CT will also be compared to determine the interobserver variability for each specific imaging modality. Contours will be imported into Computerized Environment for Radiation Research (CERR), an open-source MATLAB (TheMathWorks, natick, MA) - based radiation therapy planning analysis tool. The "apparant agreement" method will be used to calculate the apparant volume overlap such that a volume - agreement cumulative histogram can be generated.

Dosimetric Treatment Planning Study

The first plan will be a CT based plan and will be optimized to improve the HR-CTV D90 (dose received by 90% of the target volume) to as close to 85 Gy as possible without exceeding the known tolerance dose to rectum and bladder (D2cc of rectum $\leq$ 70 Gy and D2cc of bladder $\leq$ 90 Gy).18 The second plan will be optimized the same as the first but with the HR-CTV, rectum, and bladder delineated on MRI instead of CT.

Table 1

Plan	**Description**
1) 2D Plan	This will be based on the standard loadings recommended by the physician after performing physical exam at time of implant and review of orthogonal films delineating applicator placement. The initial diagnostic imaging will be reviewed and help to inform this plan and adjustments will be made based on point doses.
2) 2D Plan informed by 3D images at time	This will be based on the standard loadings

of implant.	recommended by the physician after performing physical exam at time of implant and review of orthogonal films delineating applicator placement. The initial diagnostic imaging as well as the MRI and CT scan at the time of implant will be reviewed and help to inform this plan. The patient will be treated with this plan according to standard practice.
3) ICBT CT based optimized plan	This plan will start with the above described 2D plan and will be optimized to target the CT based HR-CTV (also informed by initial diagnostic imaging) with the same objectives as the GEC-ESTRO MRI guidelines.
4) GEC-ESTRO MRI based optimized plan	This plan will start with the above described 2D plan and will be optimized according to GEC-ESTRO guidelines taking into account the patient's initial diagnostic imaging as well as MRI scan with the applicator in place.

Each of the three treatment plans will be registered on the MRI, and the MRI contours will be used as the gold standard such that each treatment plan will be evaluated for its coverage of the HR-CTV and ability to meet constraints for the adjacent organs at risk. For each of the three treatment plans, we will evaluate the D90, D100, V100, V150, V200, for the HR-CTV and IR-CTV as well as the D0.1, 1, 2 cc for bladder, sigmoid, and rectum (see Table 2). Conformality index (CI=V100%/VCTV) and dose homogeneity index (DHI= (V100%-V150%)/V100%) will be calculated for HR-CTV.

Table 2 Using the contours created on MRI (HR-CTV, IR-CTV, Rectum, Bladder, Sigmoid) the following parameters will be evaluated for each of the three treatment plans.

HR-CTV*	IR-CTV	Rectum	Bladder	Sigmoid
D90**	D90	D 0.1cc	D 0.1cc	D 0.1cc
D100	D100	D 1 cc	D 1 cc	D 1 cc
V100	V100	D 2 cc	D 2 cc	D 2 cc
V150	V150			
V200	V200			

6.0 Statistical Considerations and Analysis

Primary Endpoint

The goal of this study is to determine if 3D image guided treatment planning allows for improved tumor coverage while respecting normal tissue constraints as compared to standard 2D treatment planning. To address this, the D90 (or the dose to 90% of the HR-CTV volume) and maximally irradiated 2 cc of the bladder (D2 cc bladder) and rectum (D2 cc rectum) will be compared (these parameters have been reported in the past to correlate with toxicity).

To better understand the dose distribution the other parameters listed in Table 2 will also be documented and compared for each of the three plans described above.

Sample Size

Preliminary data were collected on 4 patients who received MRI with the brachytherapy applicator in place. After the patient was treated a GEC-ESTRO MRI based manually optimized plan was created and compared to the 2D plan. Data for HR-CTV D90 and maximally irradiated 2 cc of bladder and rectum were collected. The paired differences in the 3 parameters of interest were:

- HR-CTV D90 - mean difference of 459.91 cGy with a standard deviation of 303.69 cGy. The mean HR-CTV 90 for the standard film method was 1368.73 cGy.
- D2 cc bladder – mean difference of 407.11 cGy with a standard deviation of 250.81 cGy. The mean D2 cc bladder for the standard film method was 1474.44 cGy.
- D2 cc rectum – mean difference of 159.83 cGy with a standard deviation of 194.44 cGy. The mean D2 cc rectum for the standard film method was 962.50 cGy.

We would like to demonstrate an improvement (i.e., increase) in HR-CTV D90 of at least 20% (i.e., at least 273.75 cGy) with MRI based planning over standard 2D planning. With a sample size of 30 patients we will have 96% power with a 2-sided significance level of 0.0056 to detect an improvement of at least 20% in the HR-CTV D90 with the MRI guided procedure using a t-test.

With a sample size of 30 patients we will have 90% power to detect an increase in D2 cc bladder of 0.80 standard deviations, or 200 cGy (i.e., 14.4%) with a 2-sided significance level of 0.0056 using a t-test.

With a sample size of 30 patients we will have 90% power to detect an increase in D2 cc rectum of 0.80 standard deviations, or 155 cGy (i.e., 16.1%) with a 2-sided significance level of 0.0056 using a t-test.

We use the Bonferroni correction to the significance level since we are testing 3 methods × 3 dosimetry parameters = 9 hypotheses (e.g., 0.05/9 = 0.0056). These sample size calculations were performed using nQuery Advisor ® 7.0 (Copyright ©

1995-2007, Statistical Solutions, Saugus, MA).

We anticipate that 25% of patients will not be evaluable due to inability to accommodate an MRI compatible applicator. In addition, we anticipate that 30% of patients will receive tandem and cylinders or non-adaptive tandem and ovoids. The applicator type used significantly alters the dose distribution which is expected to impact the relative dosimetric benefit of MRI. As a result, the primary analysis will be limited to patients with the adaptive, shielded ovoid, which is the most commonly used applicator in non-protocol patients. We would therefore like to accrue a total of 57 patients in order to achieve our goal of 30 evaluable patients treated with the adaptive tandem and ovoid system.

Analysis

We will use summary statistics to describe the clinical and demographic characteristics of patients. We will similarly summarize the dosimetry parameters listed in Table 1 for each of the three planning methods noted above.

We will compare the HR-CTV D90, D2 cc bladder, and D2 cc rectum for the MRI based treatment plan (method #4) and CT based treatment plan (method #3) to the standard 2D plan (method #1) and the 2D plan informed by 3D imaging (method #2). We will use analysis of variance methods with Dunnett's procedure to compare the outcomes from each of planning methods with the outcomes from planning method #1. We will similarly compare the other dosimetry parameters between the various planning methods.

We will also keep track of the number of person-hours required for planning using each imaging modality by documenting the time spent generating contours on both CT and MRI and the amount of time spent generating each individual plan. Through the billing department, we will also capture the fees associated with the additional MRI and CT scan as well as the charge of the MRI compatible applicators for each patient and compare this to the fees for a routine implant in which a comparable standard applicator is used and MRI and CT at the time of implant are not obtained.

Secondary Endpoint

As mentioned above, we will also track of the number of person-hours required for planning using each imaging modality by documenting the time spent generating contours on both CT and MRI and the amount of time spent generating each individual treatment plan. We will also keep track of the amount of time each additional imaging modality take to acquire. Through the billing department, we will capture the fees associated with the additional MRI and CT scan as well as the charge of the MRI compatible applicators for each patient and compare this to the fees for a routine implant in which a comparable standard applicator is used and MRI and CT at the time of implant are not obtained. For the purpose of comparison each of these data points will be compared to each other and to 2D orthogonal plans using.

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