THE IMPORTANCE OF IMMOBILIZATION AND LOCALIZATION OF GYNECOLOGICAL APPLICATORS IN HIGH DOSE RATE BRACHYTHERAPY TREATMENTS

by

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This thesis was prepared under the direction of the candidate’s thesis advisor, Silvia Pella, Ph.D., DABR, Department of Physics, and has been approved by the members of his supervisory committee. It was submitted to the faculty of the Charles E. Schmidt College of Science and was accepted in partial fulfillment of the requirements for the degree of Professional Science Master.

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Intracavitary high dose rate (HDR) brachytherapy is a form of radiation therapy generally in which a post-surgical tissue margin is treated. The dose gradient of HDR brachytherapy is very steep, and thus small displacements of the applicator, even as small as 1 mm, could potentially cause significant variations of dose which could result in undesired side effects such as overdose of a critical organ. In this retrospective dosimetric study, the variation of dose due to various small range motions of gynecological applicators is investigated. The results show that the implementation of additional immobilization and localization devices along with other safety measures needs to be further investigated.
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1. INTRODUCTION

1.1 Purpose

Cancer in the female gynecological tract can significantly distort the normal anatomy. The larger fraction sizes in high dose rate (HDR) brachytherapy may increase the risk of long term side effects; therefore the location of the normal tissues at treatment time is imperative\textsuperscript{1}. The rectovaginal tissue thickness also varies between patients. The small potential gain of 3D-plan vs a 2D library plan for these patients must be weighed against the uncertainty induced by patient movement between simulation, planning and treatment\textsuperscript{2}. Since HDR brachytherapy has a high dose gradient, the resulting dose distribution is very sensitive to motion and a small range motion of even 1mm for example could potentially cause undesirable effects such as overdose to the rectum which is a critical organ. The high dose gradient is illustrated in the context of a patient treatment plan created by the Oncentra treatment planning system (TPS) in Figure 1. The high dose gradient can also be illustrated in the context of an Ir-192 percent depth dose curve or point dose kernel. The purpose of this study is to investigate the need for the implementation and development of immobilization and localization devices and other improvements in safety measures in addition to those currently in use in current HDR treatment protocols involving gynecological applicators.
Figure 1. A figure obtained by editing a screenshot of the Oncentra TPS. The colored solid curves correspond to isodose lines. The blue curves represent the 1200 cGy dose per fraction isodose lines and the outermost teal curve represents the 480 cGy dose per fraction isodose line. The red line solid straight line segment represents a distance of 6.8 mm. The fact that the 480 cGy and 1200 cGy isodose lines both cross the redline allows us to roughly approximate the dose gradient $\Delta Dose/\Delta distance = 1059$ cGy / cm. This is just to illustrate the dose gradient, noting that one endpoint is within the tissue of the patient and the other within the applicator.
1.2 Gynecologic Cancers

It is estimated with statistics that about 80,000 women are diagnosed with gynecologic cancers in the United States every year\(^3\). Gynecologic cancers include cervical, endometrial, ovarian, vaginal, vulvar, and urethral cancers. Endometrial cancer is the most common gynecological cancer in the United States. It is the fourth most common malignancy in women after breast, lung, and colorectal cancer\(^4\). Cervical cancer is the leading cause of cancer mortality in women in developing countries and the third most common gynecological cancer in the United States\(^4\). Ovarian cancer is the fourth leading cause of cancer death in women and is also the leading cause of gynecologic cancer death\(^4\). Vaginal cancer is, constituting only one to two percent of all gynecologic malignancies\(^4\). Intracavitary HDR brachytherapy is a treatment option for cervical, endometrial, and vaginal cancers and it may be administered alone or in addition to other radiation and non-radiation treatments depending on the stage of the disease. Other modalities include External Beam Radiation Therapy (EBRT), Carbo/Taxol among other chemotherapy regimens and surgical procedures such as total abdominal hysterectomy bilateral salpingo oophorectomy (TAH/BSO).

1.3 Current Radiation Treatment Modalities for Gynecological and Other Cancers

The most common radiation therapy modalities in clinical use today can be classified into two categories, namely external beam radiation therapy and brachytherapy.
1.3.1 External Beam Radiation Therapy

External beam radiation therapy (EBRT) is a treatment modality in which a beam of radiation is created outside of the patient, as opposed to having a radioactive source or radioactive material within the patient as is often the case with brachytherapy. The type of radiation can be electromagnetic, in which case we use photons, or particulate. The most common particles used in a clinical setting are electrons or protons. The energy and type of the radiation that is used depends upon the depth of the target along with what is clinically available among other things. Photon energies in the clinic are often within the range of 1 to 25 MV. EBRT in a clinical setting is often administered with a linear accelerator, such as that in Figure 2.

![Linear Accelerator](image)

**Figure 2.** True Beam linear accelerator at South Florida Radiation Oncology (SFRO) Boca East Clinic.
1.3.2 Brachytherapy

Brachytherapy is a treatment modality in which a radioactive material is placed within or very close to the target. There are various ways of classifying brachytherapy such as dose rate, treatment site or method of administration i.e. interstitial vs. intracavitary or superficial. There are various radioactive isotopes that have been or can be used clinically for HDR brachytherapy; however of these the one that is used at SFRO is Iridium-192. This thesis mainly concerns a specific implementation of brachytherapy called vaginal cuff brachytherapy (VCBT). More specific details involving VCBT shall be discussed within later sections as further necessary preliminary concepts are introduced.

1.4 Treatment Protocols, Prescriptions, and Fractionations

How to exactly administer a treatment for a patient suffering from a gynecological malignancy depends upon numerous variables involving the pathology of the disease, condition of the patient, and clinical judgment of the radiation oncologist among others. Examples of these variables include topographical and histological origin, stage, grade and geometric location of the disease with respect to organs at risk, and whether or not the patient is in a condition to be operated on surgically. Past treatments involving chemotherapy regiments and radiation also may have an effect on treatment decisions. However, there are various protocols, that is, combinations of radiation and non-radiation treatments that can be used to treat endometrial cancer and other gynecological malignancies. Decisions at this level are sometimes made in tumor conferences by a group of physicians.
Once radiation has been included as a treatment of choice, a radiation treatment protocol i.e. a choice of a modality or modalities is chosen. Ultimately the protocol on how to treat with radiation is determined by the radiation oncologist; for example HDR brachytherapy alone vs. whole pelvic EBRT + HDR brachytherapy.

Once the radiation treatment modalities have been chosen it is necessary to prescribe the dose to be delivered. Absorbed radiation dose is measured in grays (Gy). A prescription of radiation dose involves both geometric i.e. surfaces, depths or points, and radiobiological factors. These are discussed below in more detail.

A prescription also involves choosing a surface or point to prescribe dose to, since the dose distribution is non-uniform. For example, with EBRT dose is often prescribed to a volume and normalized to the isocenter. With gynecological applicators there are various ways to prescribe radiation dose. Often a prescription depth such as to the surface of a vaginal cylinder or 5mm away from the surface of the cylinder is picked along with a certain active length of the cylinder. It is even possible to prescribe dose to a point, as can be the case with the tandem and ovoid applicator as specified in the International Commission on Radiation Units & Measurements (ICRU) report 38.

A dose prescription also involves radiobiological factors such as overall duration of treatment, dose rate, and number of fractions. Clinical outcomes may differ drastically if any of these variables are modified. In order to compare various prescriptions and modalities with one another and also to evaluate additive effects, the notion of biologically effective dose (BED) or equivalent dose in 2 Gy fractions (EQD2) can be
used. These notions shall be discussed once more terminology is introduced and are discussed much further in depth in\textsuperscript{1,5}.

1.5 Introduction to Tissue Toxicities and Radiobiology

The main idea of a course of radiation therapy treatment is to give the prescribed dose to the tumor while sparing normal tissues as much as possible in order to achieve local control and improve survival rate while minimizing the undesired side effects associated with the treatment. Different types of organs and tissues including both healthy tissues and tumor react to radiation differently; some are more radiosensitive to side effects than others.

The unwanted side effects can in general be classified into two categories, namely acute effects and delayed effects. Unwanted side effects can also be classified by whether they are stochastic or threshold effects.

There are also specific scales by which unwanted side effects are evaluated. For example Radiation Therapy Oncology Group (RTOG), Late Effects of Normal Tissues-Subjective, Objective, Management criteria with Analytic laboratory and imaging procedures (LENT-SOMA), and Common Terminology Criteria for Adverse Events (CTCAE) v4.0 each have a scale on how to rank and classify rectal toxicities resulting from radiation treatments. In order to balance unwanted side effects with tumor control, treatments are fractionated.

In addition to fractionation, in order to balance unwanted side effects with tumor control, plans are evaluated both subjectively by using physician experience and quantitatively by using various dose constraints and plan metrics.
1.6 Dose Constraints and Plan Metrics

Just as there are various methods as how to prescribe dose, there are many dose metrics that can be used to quantitatively evaluate or report dose in a radiation treatment, such as dose-volume statistics, or specific reference points explicitly specified by very large groups such as the ICRU. Dose–volume statistics are explicit values of dose-volume parameters that can be extracted from the Dose Volume Histogram (DVH) of a given treatment plan. Figure 3 shows an example of a cumulative DVH. Examples of Dose-volume statistics include: maximum point dose, mean dose, and percentage volume receiving greater than or equal to an established tolerance dose for organs at risk.6
Figure 3. Cumulative DVHs are shown for an HDR brachytherapy plan. For any given value of dose, the value of volume on the graph represents the volume of the critical organ in question receiving at least that dose. For example by looking at the top graph we see that 10 cm$^3$ of the rectum receive 200 cGy or more. On the top graph absolute volume vs. absolute dose is depicted whereas on the bottom, the volume is normalized to the total volume of the critical organ and the dose is normalized to prescription dose.
However on the other hand according to Moore et al.⁷ “Despite many studies over the last 3 decades that have attempted to explicitly quantify the decision-making process for radiotherapy treatment plan evaluation, judgments of an individual’s plan of quality are still largely subjective and can show inter- and intra-practitioner variability even if the clinical treatment goals are the same.”

Dose constraints in the literature are often created by research groups administering clinical trials. Often, a clinical endpoint, for example RTOG grade ≥ 2 rectal toxicity is picked, and patients in a clinical trial are followed for a period of time. DVH statistics considered to predict the toxicities in question are then published into the literature. However, there can be a great variation in biological effects among various treatment modalities and techniques, fractionation schemes, methods of prescription of dose, etc, even if the total radiation doses administered are the same. Thus, one cannot simply compare the dose volume statistics in terms of total dose which is measured in Gy if the modality or fractionation scheme used in the clinical trial differs from the modality or fractionation scheme that the result of the trial is to be compared to. In order to make comparisons based on tumor control, early adverse effects, or late adverse effects that are more or less crude among treatment modalities and fractionation techniques, the concepts of BED and EQD2 are used. For brief explanatory purposes the equations involved shall be discussed below, but a more comprehensive discussion of these notions may be found in references ¹ and ⁵.
1.7 Biologically Effective Dose (BED) and Equivalent Dose in 2 Gy Fractions (EQD2)

For fractionated treatments, such as EBRT and HDR, with \( n \) fractions with dose per fraction \( d \) yielding a total dose of \( nd \), the biologically effective dose can be calculated as:

\[
BED = nd \left( 1 + \frac{d}{\alpha/\beta} \right)
\]  \hspace{1cm} (1)

where the parameter \( \alpha/\beta \) is called the alpha beta ratio, which arises from the well known linear quadratic model from radiobiology described in reference 5. The alpha beta ratio depends on the biological effect and tissue type being considered amongst treatments that are compared, such as tumor control, acute normal tissue toxicity effects, and late normal tissue toxicity effects. Typically, for most tissues, \( \alpha/\beta = 10 \) for acute normal tissue toxicities and \( \alpha/\beta = 3 \) for late normal tissue toxicity effects. If the fraction sizes are not all the same, the above formula may be used with \( n=1 \) for different fraction sizes and the individual fractions may be added to get the total BED, i.e. if we have a treatment with \( n \) fractions with the dose for the \( i \)-th fraction being \( d_i \) then the BED for the treatment is given by:

\[
BED = \sum_{i=1}^{n} d_i \left( 1 + \frac{d_i}{\alpha/\beta} \right)
\]  \hspace{1cm} (2)
The quantity EQD2 is a way of normalizing a BED with respect to a treatment that has been fractionated with a dose of 2 Gy per fraction, which at a time was a conventional method of fractionation. To accomplish this normalization, the BED is simply divided by \(1 + \frac{2}{a/\beta}\) to obtain:

\[
EQD2 = \frac{BED}{1 + \frac{2}{a/\beta}}
\]  

(3)

1.8 Vaginal Cuff Brachytherapy (VCBT)

The most common curative treatment performed on patients suffering cancer of the endometrium of the corpus of the uterus is a curative hysterectomy, but with this therapy alone there was an approximate 12% recurrence rate in a study done in 1971.\(^8,9\) The most likely site of recurrence is the “vaginal cuff”, which is a term used for the anastomosis where part of the vagina used to be attached to the uterus\(^8\). Thus the intent of and rationale behind vaginal cuff irradiation is prophylactic, meaning to prevent the recurrence of disease. As most of the patients whose treatment plans were analyzed within this retrospective dosimetric study had VCBT as a treatment, relevant features of this treatment shall be discussed within this section.

1.8.1 Protocols

According to Thomadsen\(^8\) “Depending upon the extent of myometrium invasion, radiotherapy may include external beam and brachytherapy (often considered for more than 50% invasion) or brachytherapy (less than 50%).” Sometimes, a chemotherapy regiment such as Carbo/Taxol is administered in addition to radiation therapy. The significance of chemotherapy being administered in addition is that it can also contribute
to tissue toxicities. Thomadsen\textsuperscript{8} also states that “Probably the most common approach to vaginal cuff irradiation uses sources in a plastic cylinder placed in the vagina.”

1.8.2 Prescriptions

HDR VCBT with the use of a cylinder is usually prescribed by specifying a depth of prescription and the active length of the cylinder. The depth of the prescription tends to be from the surface of the cylinder up to 5mm. The prescription depth for a specific patient can be a constant value such as 5mm, or it may be variable along the length of the cylinder depending upon the location of the bladder and rectum. The prescription length can be specified either in centimeters, or as a fraction of the length of the cavity being treated, for example “upper ½ of the vagina”.

1.8.3 Fractionations

According to Thomadesen\textsuperscript{8}, when brachytherapy to the vaginal cuff is administered alone without EBRT, an HDR brachytherapy regiment consisting of 3 fractions of 12.2 Gy has been used at the University of Wisconsin, and that the HDR brachytherapy component of the dose varies when brachytherapy is being administered in addition to EBRT. A dose prescription of 3 fractions of 6 Gy at vaginal surface as a vaginal cuff boost treatment within the context of endometrial cancer is mentioned in Hansen\textsuperscript{4}.

1.9 The Clinical Procedure and Equipment

The clinical procedure of how HDR brachytherapy is administered is described within this section. The administration can be thought of as consisting of initial patient consultation, CT/simulation, treatment planning, which is ultimately followed by
treatment delivery. Relevant details of these procedures shall be discussed within this section.

1.9.1 Patient Evaluation

In order for VCBT treatment to occur, a patient receives consultation from a radiation oncologist, who explains the pros and cons of the treatment along with answers to any questions that she may have. Once the patient agrees and consents to receive brachytherapy, a CT/simulation may be scheduled.

1.9.2 CT/Simulation

The term CT/simulation is the process of acquiring axial images of a patient in treatment position for the purpose of visualizing the volume of the patient surrounding the area which is to be treated as well as treatment planning and monitoring dose to critical organs. A picture of the CT scanner used at SFRO Boca East is shown in Figure 4.

![CT Scanner](image)

Figure 4. Two views of the CT scanner used in SFRO Boca East clinic.
The radiation therapist adjusts the patient to the proper position on the CT scanner. Once the patient is setup in the proper position, a radiation oncologist will insert the vaginal cylinder within the patient. Various vaginal cylinders used for gynecological brachytherapy are depicted in Figure 5. Special panties are used for the immobilization and localization of the vaginal cylinder applicator. Scout images of the patient are then taken immediately before the actual scan to insure that the appropriate region/volume of the patient will be scanned. The patient is then scanned in the supine position and the images are exported to the Oncentra TPS and treatment planning is ready to begin. For vaginal brachytherapy treatments with CT/MR vaginal cylinders in SFRO, 140 kV are used for acquiring the CT images and a slice thickness of 1.25 mm.

Figure 5. Left: Miami Vaginal Applicator. Used for treatment of vaginal, cervical, uterine and rectal carcinomas. The applicator contains six lateral tubes, which are equally spaced around the surface of the cylinder along with a central tube. Image taken from nucletron catalogue. Middle: Varian Medical Systems, Inc. All rights reserved. The Capri Applicator has a soft foam core with 13 channels and is intended to treat cancer of the vagina, vaginal stump, and rectum. Right: Vaginal CT/MR Multi Channel Applicator used in the treatment of endometrial and other gynecologic cancers. Image taken from Nucletron catalogue.
Immediately after the scan, the patient is transported to the shielded brachytherapy treatment suite while minimally disturbing the patient geometry. While the patient specific treatment plan is being created with the recently scanned images, the patient is instructed to remain as still as possible until treatment delivery is ready to begin. This typically takes anywhere from 30 to 40 minutes depending upon the complexity of the treatment plan.

1.9.3 Treatment Planning

A customized patient specific treatment plan is made for each fraction of each treatment in the course of an HDR VCBT plan for each patient. The reason for doing this is to spare the organs at risk from overdoses of radiation while ensuring that the treatment target gets a sufficient amount of dose. For VCBT treatments, the organs at risk include the bladder and the rectum. Treatment planning also allows one to calculate and monitor the dose that the target and critical organs receive.

Treatment planning can be thought of as consisting of the following parts: contouring, catheter reconstruction, dose prescription and optimization which are ultimately followed by approval of the treatment plan.

Once the images from the CT/simulation have been exported from the CT scanner and imported into the Oncentra TPS treatment planning may begin. The organs at risk are graphically contoured by the medical physicist. Digitally reconstructed images are created, and using these, the catheters of the vaginal cylinder applicator through which the Ir-192 source is to travel, are graphically constructed. This is called catheter reconstruction. Once contouring and catheter reconstruction is complete the dose
prescription is implemented and the dose is calculated using the TG-43 dose calculation formalism. It is important to note that the TG-43 dose formalism models the human body as if it consisted of water equivalent material and does not take into account tissue heterogeneities. In order to create a highly desirable dose distribution, the dose can be optimized using the Inverse Planning Simulated Annealing (IPSA) algorithm which is implemented in the Oncentra TPS. This algorithm uses dose volume constraints to calculate the dwell positions and dwell times of the Ir-192 source within the catheters, which result in an optimal patient specific dose distribution. Figure 6 shows a dose distribution for a fraction of a patient plan.

Once the dose distribution has been optimized, a second-hand calculation is made of selected points to verify that the TPS has calculated the dose correctly. A second medical physicist then verifies the plan, after which the radiation oncologist verifies and sometimes slightly modifies the plan, which is then approved by the radiation oncologist. Once the plan has been approved it is exported using the TPS and imported into a computer that controls the remote afterloader used to administer the HDR treatment within the brachytherapy treatment room.
Figure 6. Edited screenshot taken from Oncentra TPS showing isodose curves of a dose distribution along with contoured organs at risk.

1.9.4 Treatment Delivery

Once the treatment plan is imported into the computer that controls the remote afterloader, the list of the dwell times and the dwell positions is printed from both the treatment planning computer and the computer that controls the remote afterloader to ensure that they are correct. A picture of the remote afterloader is shown in Figure 7.
Afterwards, the radiation therapist and/or medical physicist connect the catheters from the remote afterloader to those of the applicator within the patient. A “dry run” with an inactive source is performed on the patient to help ensure that the source will not get stuck within the catheters within the applicator of the patient during the treatment. Once the dry run is complete, the door to the shielded treatment room is closed and the actual treatment is remotely administered by the radiation therapist and physicist who are outside of the room. A typical treatment takes anywhere from 5 to 15 minutes. Following the treatment, the catheters connecting the afterloader to the applicator within the patient
are disconnected and the applicator is removed from within the patient, after which the patient can go home.

### 1.10 Sources of Error throughout a Brachytherapy Treatment

According to American Association of Physicists in Medicine (AAPM) report no. 13 page 5, sources of error in radiation therapy include tumor localization, lack of patient immobilization, human errors in calibration, calculation, daily patient setup and equipment-related problems. Some of these errors are random while others are non-random. AAPM report no 13 page 7, states that “an uncertainty propagation considering the cumulative effect on the uncertainty in the dose delivered to a specified volume within a patient is very difficult and considered by many to be scientifically unsound because we are dealing with the combined effect of systematic (non-random) and random uncertainties.”

Despite the above, report No. 13 suggests that an overall error be obtained by quadratic summation, in which sums of squares of both random and nonrandom uncertainties are added. Details of this procedure along with an example are provided within the report in the context of setting reasonable specifications for individual machine parameters which conform to acceptable overall uncertainties.

It is thus important to keep in mind that there are other uncertainties than those created by lack of immobilization and localization that are the focus of this thesis, and considering their combined effect is a difficult task. However, many equipment and calculation errors can be minimized through a program of periodic checks, which is where quality assurance comes in.
1.11 Description of Quality Assurance

According to AAPM report no 13, “quality assurance in radiation therapy includes those procedures that ensure a consistent and safe fulfillment of the dose prescription to the target volume, with minimal dose to normal tissues and minimal exposure to personnel.” Quality assurance usually sets guidelines, bounds and expectations for errors and uncertainties.

AAPM TG-40 report page 599 states that a brachytherapy treatment plan is more difficult to implement than an external beam plan and that high dose gradients make the specification of dose either at a point or throughout a volume less precise than in EBRT. It also states that it is generally accepted that dose should be delivered within 5% limits for EBRT treatments, but for intracavitary HDR brachytherapy treatments an uncertainty level of ±15% in the delivery of prescribed dose is a more realistic level.

TG-56 page 1564 states that: in most clinical applications of afterloaders, a positional accuracy of ±2 mm relative to the applicator system is reasonable, and that the NRC positional accuracy criterion of ±1 mm is not realizable in a clinically meaningful sense for many applicator source combinations. TG-56 page 1564 also states that a temporal accuracy criterion of ±2% seems easily achievable by commercially available remote afterloaders. TG-56 page 1565 states that source calibration accuracy of ±3% relative to existing air KERMA strength standards seems reasonable and that computer assisted dose calculations should have a numerical accuracy of at least ±2%.

Detailed aspects of QA involving multiple aspects of brachytherapy treatment procedures are described in detail in AAPM TG reports including AAPM report 13 by

AAPM report No 21 by task group 32, describes specification of brachytherapy source strength. AAPM report 41 by TG-41 describes in detail the acceptance tests and quality assurance involving remote after loading technology. TG-43 along with its 2004 update and supplement to the 2004 update discuss the brachytherapy dosimetry formalism.
2. MATERIALS AND METHODS

2.1 Equipment for Treatment

In this retrospective study 55 patient plans created by personnel at SFRO which involved gynecological brachytherapy treatments were analyzed using the Oncentra TPS. The contours of the critical organs were not modified retrospectively.

2.2 Patient Data: Pathology, Treatments, and Dose Prescriptions

The 55 plans that were dosimetrically analyzed post treatment involved treatments for 27 different patients. There are more plans than patients because for some patients multiple plans were analyzed.

When a patient is referred for treatment, a radiation oncologist performs an initial consultation and a note documenting relevant patient information is made, called a Radiation Oncology Initial Consultation Note. For each patient, the Radiation Oncology Initial Consultation Note was read and the following information was recorded: whether or not the patient had hysterectomy documented, whether or not the administration of pre-radiation therapy chemotherapy was documented, and diagnoses of the disease was listed for each patient including available information on surgical staging, histopathologic grading, body site of origin and histopathological classification. For two of the patients, initial radiation oncology consultation notes were not found in the database. For those patients another document called Radiation Therapy End of Treatment Consultation Note
was used to determine that hysterectomy had been performed and that chemo had been administered prior to HDR.

The patient population is very diverse in terms of gynecological malignancies. Many of the patients were diagnosed with an endometrial carcinoma of the uterus. The stages of disease as well as the histopathologic grades and subtypes vary greatly among the population of patients with this malignancy. Cervical cancers were also present amongst the patients. One patient had a cancer of the vaginal wall. Vaginal cuff recurrences of endometrial cancer were also among the malignancies within this patient population.

Eight of the twenty seven patients were documented having been administered chemotherapy before radiation therapy. The chemotherapy in four of these cases was documented to be paclitaxel and carboplatin (Carbo/Taxol). The number of cycles administered differed among patients.

The patient population is somewhat diverse in terms of surgeries. In total 25 of the 27 patients had been documented having surgery. A hysterectomy with bilateral salpingo-oopherectomy has been performed on 22 of the 27 patients. In 16 of these 22 patients the procedure was referred to as TAH/BSO, which stands for total abdominal hysterectomy bilateral salpingo-oopherectomy. For three of the patients hysterectomies were recorded, but the bilateral salpingo oophorectomy was not. One of the patients still had her uterus.

When a course of radiation treatment for a patient comes to an end, regardless of whether due to the completion of the planned course of treatment, or due to
complications, a document called Radiation Therapy End of Radiation Treatment Consultation Note is created, which summarizes the treatments that were administered. An End of Treatment Consultation Note was not found for 2 of the patients. For these patients, information was obtained from other documents as needed.

These documents were read for each of the 27 patients to determine whether EBRT was administered in addition to HDR. If EBRT was administered in addition to HDR for a particular patient, the total prescribed dose, dose per fraction, number of fractions, and length of treatment in days each due to EBRT were recorded, when available.

These documents were also read in order to find relevant information on HDR treatment, and the following information was recorded: total dose, dose per fraction, number of fractions, and days of treatment, each due to HDR. Other prescription parameters such as the type of applicator, prescription depth from the surface of cylinder, active length of cylinder, diameter of cylinder, and the type of cylinder were also recorded when available.

There is diversity among the patient population also when looking at radiation treatment modalities and prescriptions. The one main common factor that all of the patients have is that they all received gynecological HDR brachytherapy treatments. Nine patients were documented to have received EBRT in addition to the HDR, and a tenth patient was found to have received EBRT at another center. Of the 27 patients in total, all but one patient, namely the one suffering from cancer of the vaginal wall, who had no surgery, received VCBT.
For the patient specific HDR VCBT courses of treatment, the total dose prescribed ranged from 12 to 37.5 Gy, the dose per fraction ranged from 300 to 750 cGy per fraction, and number of fractions ranged from three to seven.

For the documented patient specific EBRT courses of treatment pertaining to the gynecological malignancy, the total dose prescribed ranged from 30 to 50.4 Gy, the dose per fraction ranged from 180 to 200 cGy, and the number of fractions ranged from 15 to 28.

Some of the treatments were assigned a constant prescription depth, which ranged from surface of cylinder to 5 mm from surface among the patients, while other prescriptions prescribed depth to a variable depth ranging between specified depths depending on the proximity of the rectum and bladder. The active lengths of the prescription were recorded in varying ways, either specified by a fractional length of the vagina being treated or by centimeters.

The vaginal cylinder applicators which were placed within the patients by a radiation oncologist for administering the treatments included, the Varian Capri applicator, the MIAMI applicator as well as single catheter and multicatheter CT/MR cylinders made by nucletron.

2.3 Methods of Gathering Dosimetric Data on Point Dose

We are interested in measuring the dose variation at the hottest spot of the critical organ in question, which in this case is the rectum, with respect to several small range motions. By the term hottest spot we mean the physical point on the critical organ that receives maximal point dose. The hot spot was located by the following procedure: The
dose volume histogram (DVH) was printed to a text file (.txt) using the built-in commands in the Oncentra TPS. The maximum dose value that a nonzero volume of the rectum received was recorded. An isodose curve corresponding to the value previously found was then created in brachyplanning mode. Following this, the CT slices depicting the transversal view with respect to the central axis of the applicator were scrolled through and the very small regions where rectum contour intersects that of the isodose line were visually identified. Patient points can then be placed within these small regions and the dose calculation output for these points that the Oncentra TPS yields can be viewed. The maximal point dose that was found by inspecting these was designated to be the hottest spot. We call this point $P_{\text{max}}$ and the dose at this point we call $D_{\text{max}}$ for reference purposes. Without much difficulty one can accurately find the point on the rectum receiving the maximal dose in this manner.

Figures 8 through 12 are intended to show how the point dose data can be gathered sequentially for one patient treatment plan.
Figure 8. Picture of the rectum contour intersecting the 480 cGy isodose curve. The point P1 on the image depicts this point to which we may refer to as the "hottest spot" on the rectum.

The displacements whose dosimetric effects were simulated were superior inferior motion, medial lateral motion, and rotational motion. All anatomical directions are taken with respect to the central axis of the applicator. Since these simulated displacements are with respect to the central axis of the applicator, before simulating any motions of the applicator, it is important to align the coordinate system of the three dimensional CT model in such a way that one of the coordinate axes coincides with the central axis of the applicator.
The measurement of dose variation at $P_{\text{max}}$ due to simulated $1 \text{ mm}$ of displacement in the superior inferior direction was found in the following manner for each patient plan: the CT image of the transverse plane containing the point $P_{\text{max}}$ was found. Then a point $1 \text{ mm}$ above this point was found by scrolling up slices in the transverse plane, until a difference of $1 \text{ mm}$ is obtained from the coordinate reading of the slice being viewed and that of the slice containing $P_{\text{max}}$. A patient point is added in the same place on the slice $1 \text{ mm}$ above $P_{\text{max}}$ as $P_{\text{max}}$ was in the original slice containing it and the calculated dose given by Oncentra is recorded. We call this point $P_{\text{sup}}$ and the dose at this point $D_{\text{sup}}$ for reference purposes. This can be done with ease, since the location of the point $P_{\text{max}}$ in its respective slice can still be seen while viewing the slice that is $1 \text{ mm}$ above it. The point that lies $1 \text{ mm}$ directly below $P_{\text{max}}$ can be found in a similar manner, by scrolling in the opposite direction. We call this point $P_{\text{inf}}$ and the dose at this point $D_{\text{inf}}$ for reference purposes. Thus to calculate the variation in dose at $P_{\text{max}}$ due to the simulated superior inferior displacement of $1 \text{ mm}$ the following formula was used:

$$100\% \times \frac{|D_{\text{sup}} - D_{\text{inf}}|}{D_{\text{max}}}$$ (4)
Figure 9. Three images obtained by editing screenshots of Oncentra TPS depicting how the measurements of dose variation due to 1 mm displacements in the superior inferior direction were gathered for a specific fraction of treatment for a specific patient. **Left:** An area of the slice 1 mm above the hotspot is shown. Note that the slice indicates the corresponding location of P1 in the slice 1 mm below, namely the one shown in Figure 8. **Middle:** A patient point P2 is placed appropriately in the slice in such a way that it is directly above the point P1. **Right:** A patient point, in this case labeled P3 is placed in the slice 1 mm below in such a way that it is directly below P1.

The measurement of dose variation at $P_{\text{max}}$ due to a simulated 1 mm displacement of the applicator in the medial lateral direction was found in the following manner for each patient plan: The CT image of the transverse slice containing $P_{\text{max}}$ was found. Using a built in tool of Oncentra called distances and measures, a line segment having the point $P_{\text{max}}$ as one endpoint and the center of the applicator in the transverse slice as the other endpoint was created. Then using distances and measures again, a segment having 1 mm distance from the point $P_{\text{max}}$ along this line segment towards the center of the applicator was constructed. A patient point was placed on the endpoint of this segment 1 mm from
\( P_{\text{max}} \), and the dose calculated by Oncentra at that point was recorded. We call this point \( P_{\text{med}} \) and the dose at this point \( D_{\text{med}} \). In a similar manner the point that is 1 mm away from \( P_{\text{max}} \) in the opposite direction was found and the dose calculated by Oncentra was recorded. We call this point \( P_{\text{lat}} \) and the dose at this point \( D_{\text{lat}} \). Thus to calculate the variation of dose at \( P_{\text{max}} \) due to the simulated 1 mm of medial lateral displacement, the following formula was used:

\[
100\% \times \frac{|D_{\text{med}} - D_{\text{lat}}|}{D_{\text{max}}}
\] (5)
Figure 10. Two images obtained by editing screenshots of Oncentra TPS are shown depicting how the measurements of dose variation due to 1 mm displacements in the medial lateral direction were gathered for a specific fraction of treatment for a specific patient. **Left:** After taking the superior and inferior measurements as depicted in Figure 9, the Oncentra TPS overlaps the points P1, P2, P3 within the view in the slice containing P1. The number in the image that is hard to make out is really the numbers 1, 2 and 3 overlapped. **Right:** 1 mm distances are drawn, the orange indicating 1 mm towards the applicator, and the yellow indicating 1 mm away from the applicator. Patient points P1 and P4 as shown are the points where dose is calculated for the purpose of evaluating dose variation due to 1 mm displacements in the medial lateral direction.

The measurement of dose variation due to a displacement of five degrees of rotation along the central axis of the applicator was found in the following way for each patient plan: The CT image of the transverse plane containing P_{max} was found. Using the Oncentra tool distances and measures, an angle of 5 degrees was measured.
counterclockwise, having $P_{\text{max}}$ as one of its endpoints and having the center of the applicator in the slice containing $P_{\text{max}}$ as its vertex was constructed. Using distances and measures again, the distance from $P_{\text{max}}$ to the vertex of the angle was measured. A line segment of this same distance was constructed in the direction of the other leg of the angle, originating from the vertex of the angle. A patient point was placed at the endpoint of this line segment that is not the vertex of the angle, and the dose calculated by Oncentra was recorded. We call this point $P_{\text{ccw}}$ and the dose at this point $D_{\text{ccw}}$. Repeating this procedure with the exception of rotating clockwise we can define $P_{\text{cw}}$ and the dose at that point $D_{\text{cw}}$. The dose variation at $P_{\text{max}}$ due to the simulated 5 degree rotational motion was calculated using the following formula:

$$100\% \times \frac{|D_{\text{cw}} - D_{\text{ccw}}|}{D_{\text{max}}}$$ (6)
**Figure 11.** Images obtained by editing screenshots of the Oncentra TPS depicting how measurements involving dose variation due to a hypothetical rotational motion of five degrees are made after completing the medial lateral measurements shown in Figure 10. Both images above depict the slice containing the hottest spot. **Left:** Using the Oncentra tool distances and measures, an angle of 5 degrees was measured counterclockwise, having $P_1$ as one of its endpoints and having the center of the applicator in the slice containing $P_1$ as its vertex was constructed. The second endpoint of the angle is chosen to be far away to make it convenient to construct an angle of exactly 5 degrees graphically. **Right:** Using distances and measures again, the distance from the hottest spot to the vertex of the angle was measured, which in this case is 16.4 mm.
Figure 12. Images obtained by editing screenshots of the Oncentra TPS depicting how measurements involving dose variation due to a hypothetical rotational motion of five degrees are made after completing those shown in Figure 11. **Left:** A line segment originating from the center of the vaginal cylinder in the transverse planar slice containing the hottest spot is constructed along the leg of the 5 degree angle not containing P1 in such a way that the other endpoint of the line segment and the hottest spot are equidistant from the center of the vaginal cylinder. **Right:** A five degree angle constructed in the opposite direction in a similar way is shown in addition along with patient points labeled by Oncentra TPS as P6 and P5. If the applicator were to make a motion counterclockwise (from this point of view in the figure), the point dose calculated by Oncentra TPS that was at point P6 would move to the “hottest spot”. It is important to note that this assumption is valid since the point dose is calculated in a homogenous medium.
This method of gathering data senses dose variation in the following way: since the method that the Oncentra TPS uses to calculate dose does not take into account heterogeneities of any kind, it follows that a displacement of the applicator would yield the same displacement of the dose distribution pointwise. For example, if the applicator were to move five degrees clockwise, the point $P_{\text{max}}$ would be getting the dose $D_{\text{ccw}}$.

Air in the rectum near the hotspot and its possible effect on dose variation was another variable of interest. The patients were divided into two categories, namely Air and No Air, depending upon whether or not air was present at the rectum near the hottest spot. This was evaluated by looking at the slice of the rectum on the transverse plane containing the hottest spot and visually approximating whether or not a contiguous volume of air of 0.1 cc in the rectum or more goes through that slice. If more than 0.1 cc was found then the patient was placed in the Air category.
Figure 13. This image was obtained by editing a screenshot of the Oncentra TPS. The "hottest spot" on the rectum is indicated by P1. A volume of air within the rectum of the patient can be seen very close to P1.

2.4 Other Methods of Normalization for Calculations of Percent Differences

The values that were calculated according to the previous section were examples of percent differences. There are various ways to calculate percentage differences. Instead of normalizing the percent difference to the hottest spot, one could normalize to the prescription dose, or to the average of the endpoints, or perhaps even another meaningful value. Another method of calculation that was chosen to be performed on the data of this study was to normalize the percentage difference to the average of the endpoints of the dose. For example, when calculating the percentage difference in dose
due to a 1 mm hypothetical displacement of the applicator in the superior inferior direction, in addition to using Eq (4) as described earlier, we also calculate

$$100\% \times \frac{|D_{sup} - D_{inf}|}{D_{sup} + D_{inf}}$$

(7)
3. RESULTS AND DISCUSSION

3.1 Point Dose Variation Data

The purpose of this section is to summarize the point dose data that were obtained in this study. Discussions involving both clinical and statistical significance will follow.

3.1.1 Methods of Calculating Percent Difference Practically Coincide

In the methods and materials section, two methods of normalization for the calculation of percentage difference were used. The first method of calculation normalized the percentage to the calculated point dose at the hottest spot, whereas the second normalized the percentage to the average of the endpoints. From a clinical perspective, these two methods of calculation yield nearly identical values. A general formula denoting the normalization to the average of the endpoints is the following:

\[ 100\% \times \frac{|D_+ - D_-|}{(D_+ + D_-)/2} \]  

(8)

Where \(D_+\) denotes the dose resulting from the displacement under consideration in one direction and \(D_-\) denotes the dose resulting from the displacement under consideration in the opposite direction as that of \(D_+\).

The advantage of normalizing to the endpoints is that the respective formula depends on only two input values whereas the other depends on three. Thus for calculations of percentage uncertainties of dose used for the data, the normalization to the average of the endpoints shall be used.
3.1.2 Point Dose Variation in Superior Inferior Direction

For the 55 patients whose point dose data were gathered, dose variation at the hottest spot due to a simulated 1 mm displacement in the superior inferior direction calculated by normalizing to the average of the endpoints was found to have a minimum value of 0.02%, a maximum value of 12.66%, with an average value of 1.50%, and a standard deviation of 2.04%.

Figure 14. From a clinical perspective, two methods of normalization for the calculation of percentage difference yield nearly identical values in the case of simulated 1 mm displacements in the superior inferior direction.
3.1.3 Point Dose Variation in Medial Lateral Direction

Dose variation at the hottest spot due to a simulated 1 mm displacement in the medial lateral direction calculated by normalizing to the average of the endpoints was found to have a minimum value of 12.22%, and a maximum value of 22.71%, with an average value of 16.95% and a standard deviation of 2.77%.

**Figure 15.** From a clinical perspective, two methods of normalization for the calculation of percentage difference yield nearly identical values in the case of simulated 1 mm displacements in the medial lateral direction.
3.1.4 Point Dose Variation due to Rotational Motion

The measurement of dose variation due to a displacement of one degree of rotation along the central axis of the applicator was found to have a minimum value of 0.00\%, a maximum value of 2.76\%, with an average value of 0.64\% and a standard deviation of 0.62\%. It is a remarkable observation that the standard deviation and the mean nearly coincide.

**Figure 16.** From a clinical perspective, two methods of normalization for the calculation of percentage difference yield nearly identical values in the case of simulated 1 degree rotational displacements of a vaginal cylinder applicator.
The measurement of dose variation due to a displacement of five degrees of rotation along the central axis of the applicator was found to have a minimum value of 0.06%, a maximum value of 13.71% with an average value of 2.21% and a standard deviation of 3.01%.

Figure 17. From a clinical perspective, two methods of normalization for the calculation of percentage difference yield nearly identical values in the case of simulated 5 degree rotational displacements of a vaginal cylinder applicator.
3.1.5 Tables summarizing the point dose data

Tables 1, 2, and 3 summarize the point dose variation data for all of the motions studied for the population as a whole and also for both the Air and No Air categories.

Table 1: Results of dose variation due to the hypothetical motions that were simulated retrospectively for the 55 patient plans when calculating percent difference by normalizing to the average of the endpoints.

<table>
<thead>
<tr>
<th>Displacement type</th>
<th>Rectum dose variation %</th>
<th>Average %</th>
<th>Standard deviation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>±1mm medial/lateral:</td>
<td>12.22 - 22.71</td>
<td>16.95</td>
<td>2.77</td>
</tr>
<tr>
<td>±1mm superior/inferior</td>
<td>0.02 - 12.66</td>
<td>1.50</td>
<td>2.04</td>
</tr>
<tr>
<td>±5° rotation</td>
<td>0.06 - 13.71</td>
<td>2.21</td>
<td>3.01</td>
</tr>
<tr>
<td>±1° rotation</td>
<td>0.00 - 2.76</td>
<td>0.64</td>
<td>0.62</td>
</tr>
</tbody>
</table>
**Table 2:** Results of dose variation due to the hypothetical motions that were simulated retrospectively for the 32 patient plans within the Air category when calculating percent difference by normalizing to the average of the endpoints.

<table>
<thead>
<tr>
<th>Displacement type</th>
<th>Rectum dose variation %</th>
<th>Average %</th>
<th>Standard deviation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>±1mm medial/lateral:</td>
<td>12.22 – 22.71</td>
<td>17.19</td>
<td>2.90</td>
</tr>
<tr>
<td>±1mm superior/inferior</td>
<td>0.02 - 12.66</td>
<td>1.71</td>
<td>2.46</td>
</tr>
<tr>
<td>±5° rotation</td>
<td>0.09 - 11.97</td>
<td>2.56</td>
<td>3.18</td>
</tr>
<tr>
<td>±1° rotation</td>
<td>0.00 – 2.76</td>
<td>0.68</td>
<td>0.68</td>
</tr>
</tbody>
</table>

**Table 3:** Results of dose variation due to the hypothetical motions that were simulated retrospectively for the 23 patient plans within the No Air category when calculating percent difference by normalizing to the average of the endpoints.

<table>
<thead>
<tr>
<th>No Air group</th>
<th>Rectum Dose variation %</th>
<th>Average %</th>
<th>Standard Deviation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>±1mm medial/lateral:</td>
<td>12.43 - 21.69</td>
<td>16.63</td>
<td>2.61</td>
</tr>
<tr>
<td>±1mm superior/inferior</td>
<td>0.03 - 4.28</td>
<td>1.18</td>
<td>1.23</td>
</tr>
<tr>
<td>±5° rotation</td>
<td>0.06 - 13.71</td>
<td>1.71</td>
<td>2.74</td>
</tr>
<tr>
<td>±1° rotation</td>
<td>0.02 - 1.81</td>
<td>0.59</td>
<td>0.53</td>
</tr>
</tbody>
</table>
3.2 Clinical Significance of Point Dose Study

The clinical significance of point dose is not entirely known at present, and there seems to be some uncertainty in the literature. According to Levitt\(^6\), “There is some question as to whether point doses are meaningful clinically, and perhaps maximum dose should be reported for the dose averaged over a small but clinically significant volume” and Halperin et. al.\(^10\) agrees by stating that “There is some question as to whether a single point in the 3D dose matrix is meaningful clinically; typically, the maximum dose averaged over a small but clinically significant volume is more meaningful”, while Chao\(^11\) also agrees.

On the other hand, a plan evaluation metric that is recorded for treatment plans at SFRO that is “almost” like a point dose is D0.01cc i.e. the dose corresponding to the “hottest” 0.01 cm\(^3\) of rectum. Thus, from an everyday clinical perspective, it appears that the concept of point dose has a clinical meaning in the context of the rectum being the critical organ.

“The prostate brachytherapy literature has consistently demonstrated that very small volumes of the rectum can tolerate very high doses of radiation, which is an important consideration in this era of highly conformal dose escalation”\(^12\). There are also studies, which relate the maximal point dose to the rectum to clinical endpoints involving rectal toxicities\(^13,14\). A dose limitation of rectal point dose < 70 Gy based on 2D planning is mentioned in Hansen\(^4\).

In Waterman and Dicker’s study\(^13\), maximal point dose to the rectum is studied with respect to the clinical endpoint of RTOG grade ≥ 2 late rectal morbidity, which is
ulceration/bleeding. An even more recent study has also investigated the clinical significance of the maximal point dose to the rectum as a plan evaluation metric, this time considering as a clinical endpoint the Grade 1 late rectal bleeding (greater than 90 days after radiation therapy) which is evaluated according to Common Terminology Criteria for Adverse Events v 4.0. Thus, it appears that the point dose in this study does have some clinical context that it can be compared to. It is with respect to these rectal toxicities that we can compare the dose difference data from our study to, which shall be done in the following subsections.

Since from the previous section it can be seen that the dose variations due to medial lateral motion are the greatest, it is the effect of these variations that we shall study with respect to the rectal toxicities.

3.2.1 Late Rectal Toxicities (Grade greater than or equal to 2)

In this section it shall be discussed how the data gathered in our study indicates that dose variation due to medial lateral 1 mm motions of the gynecological applicator does not appear to cause RTOG grade 2 or greater late rectal toxicity in patients receiving HDR alone or HDR followed shortly after EBRT based on a literature comparison and some calculations involving the data, which are described below in more detail.

Multiple studies cited in Constine have researched dose volume relationships predicting late rectal bleeding toxicities of grade 2 or higher as defined by either RTOG or SOMA-LENT, and made recommendations for DVH statistics based on their findings. According to Constine “Dose-volume constraint
recommendations are only slightly altered when all forms of late rectal toxicity are included in the outcomes analysis.” This indicates that grade 2 bleeding toxicity of the rectum is clinically a very significant outcome.

Constine\textsuperscript{12} also states that “the maximum point dose to the rectum after brachytherapy is [also] predictive of RTOG \( \geq 2 \) bleeding, with a 0.4\% toxicity rate for a maximum point dose of 150 Gy, a 1.2\% toxicity rate for a maximum point dose of 200 Gy, and a 4.7 % rate for a maximum point dose of 300 Gy\textsuperscript{13}.” However, these doses predicting toxicity in Waterman and Dicker’s study\textsuperscript{13} were obtained in the context of I-125 prostate brachytherapy, which is a low dose rate (LDR) brachytherapy treatment modality. However, due to radiobiological effects, such as sublethal damage repair, an LDR dose of 150 Gy does not necessarily have the same biological effects as HDR, so this LDR 150 Gy dose constraint should in one way or another be “translated” to HDR. Comparisons between LDR and HDR remain somewhat controversial. Thus, we wish to create from this literature value a very conservative constraint value that the data from our study shall be compared with, in order to put the results into some kind of clinical perspective.

For crudely translating results into the context of HDR from LDR reference \textsuperscript{21} recommends multiplying by a number within the range of 0.66 to 0.75. In the interest of being conservative, we pick 0.66, and compare our data to \((150 \text{ Gy})^{*}(0.66) = 99 \text{ Gy}\).

As summarized in the methods and materials section, the patients in our retrospective study had a wide variety of dose fractionation prescriptions, with some patients having HDR alone and others having HDR followed shortly after EBRT. In order
to compare these data to our 99 Gy dose, we can calculate the EQD2 for each patient, who received HDR brachytherapy alone, or HDR shortly after EBRT. The patients who had received multiple courses of EBRT and or HDR were omitted from this particular clinical comparison.

According to the literature\(^1\) the BEDs of HDR and EBRT may be added together, and it follows from straightforward mathematics that the EQD2s in these cases can also be added together. For calculations of EQD2s, since we are interested in late effects, the alpha beta ratio parameter was set equal to 3.

To calculate the EQD2 of the EBRT treatments for a specific patient, in the interest of being conservative we use the maximum rectal point dose that was obtained from DVHs of treated courses for the dose per fraction parameter. Note that for all of the patients who received EBRT in this study, the maximum point dose to the rectum from the DVH was greater than the prescription dose to the rectum.

To calculate the EQD2 of the HDR treatments for a specific patient, the maximum of the prescribed dose per fraction and \(D_{\text{med}}\) points for each fraction for which data was gathered for that patient was taken to be the value of the dose per fraction in the interest of being conservative. For the dose variation data gathered the \(D_{\text{med}}\) was sometimes above and sometimes below the prescribed dose per fraction value for a given patient. Since this point dose study is a preliminary study investigating dose variation, the point dose data was not gathered for every planned fraction of every patient (for HDR every fraction of every HDR treatment with a gynecological applicator is re-planned at SFRO). Including the prescribed dose per fraction in the set that the maximum is taken over for
the value of dose per fraction in the EQD2, makes the value of EQD2 a bit more conservative.

The total EQD2s were obtained for each patient by using the EQD2 for HDR alone for patients who received only HDR, and by adding the EBRT EQD2 to the HDR EQD2 for the patients who received EBRT shortly after HDR.

The values of the total EQD2s remained under 90 Gy for every patient who received either HDR brachytherapy only or HDR shortly after EBRT. Thus, based on this crude clinical comparison, the dose variation caused by the hypothetical 1 mm motions of the applicator do not appear to cause RTOG ≥ 2 rectal morbidity. The prescription ranges of the doses of the HDR alone and those of HDR followed shortly after EBRT seem to be low enough to allow for these small variations to occur without the grade 2 rectal toxicity.

3.2.2 Late Rectal Toxicities (Grade ≥ 1)

In this section, a literature value will be compared to our data along with some calculations in order to discuss how medial lateral dose variation due to 1 mm motions could potentially affect or exacerbate grade 1 rectal toxicity as evaluated by Common Terminology Criteria for Adverse Events v 4.0.

In a study by Ishikawa et. al., a dose constraint recommendation of $D_{\text{max}} < 74.1$ Gy along with other DVH statistics were determined as cutoff values for of rectal wall DVHs for grade ≥ 1 late rectal toxicities. The patients had been treated for prostate cancer with 74-GY 3DCRT by using the 7 fields technique. The daily dose was administered 5 days a week at 2.0 Gy per
fraction. Note that this means that the EQD2 for this study is 74.1 Gy and that it does not need to be calculated. Thus, the 74.1 Gy maximum point dose is a parameter that the data from our study can be compared to using the total EQD2s.

The values of the total EQD2s as calculated in section 3.2.1 were chosen to be conservative, since in that section it was to be demonstrated that RTOG grade 2 or greater toxicity is unlikely, due to the nature of most patient prescription ranges falling far below the 99 Gy constraint. However, with the method of calculation described in section 3.2.1, several patients have total EQD2s above the 74.1 Gy maximal point dose constraint, including patients from both the HDR only group, and the HDR followed by EBRT group. One can think of the total EQD2s which were calculated in section 3.2.1 as a way of screening out which patients have prescriptions or variations of dose that hypothetically could affect the rectal toxicities based on a given literature point dose value. In the following subsection, a much more detailed retrospective dosimetric analysis shall be shown on the case of one patient who received HDR brachytherapy alone and for whom dose variation measurements were made retrospectively for every fraction.

3.2.2.1 Specific Patient Case Analysis

The parameters in section 3.2.1 were chosen very conservatively to demonstrate that reaching the 99 Gy dose constraint does not happen. To explore clinical relevance searching for evidence as to whether or not hypothetical effects could happen, it makes sense to pick less conservative parameters for a retrospective analysis exploring the case of an individual patient.
Table 4 shows the set of medial lateral point dose measurements in cGy which were retrospectively gathered for each fraction of treatments that had been administered for one particular patient along with the EQD2 corresponding to the heterogeneous fraction sizes in each row.

**Table 4:** The medial lateral point dose measurements retrospectively gathered for each fraction of treatments that had been administered for one particular patient, along with the EQD2 corresponding to the heterogeneous fraction sizes in each row.

<table>
<thead>
<tr>
<th>Anonymous</th>
<th>Fx1 (cGy)</th>
<th>Fx2 (cGy)</th>
<th>Fx3 (cGy)</th>
<th>Fx4 (cGy)</th>
<th>Fx5 (cGy)</th>
<th>EQD2 heterogenous (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dmed</td>
<td>604.98</td>
<td>760.34</td>
<td>616.77</td>
<td>630.08</td>
<td>618.23</td>
<td>61.5</td>
</tr>
<tr>
<td>Dmax</td>
<td>553.72</td>
<td>679.86</td>
<td>570.32</td>
<td>583.55</td>
<td>551.51</td>
<td>52.4</td>
</tr>
<tr>
<td>Dlat</td>
<td>513.22</td>
<td>615.60</td>
<td>531.83</td>
<td>545.55</td>
<td>498.42</td>
<td>45.7</td>
</tr>
</tbody>
</table>

We consider several hypothetical situations along with their dosimetric effects expressed in terms of EQD2. In the following hypothetical scenarios we make an assumption that the hotspots coincide throughout the fractions, although the accuracy of this assumption would need to be clinically investigated further.
If hypothetically, the applicator had remained perfectly still throughout each treatment, the resulting EQD2 taking into account the heterogeneous fraction sizes for the hottest point dose would be 52.4 Gy which remains under the 74.1 Gy grade 1 late rectal toxicity literature value constraint.

If hypothetically, the applicator had moved 1mm towards the hottest spot in the medial direction throughout each treatment, the resulting EQD2 taking into account the heterogeneous fraction sizes for the hottest point dose would be 61.5 Gy, which remains under the 74.1 Gy grade 1 late rectal toxicity literature value constraint.

If hypothetically the applicator had moved 1mm away from the hottest spot in the lateral direction throughout each treatment, the resulting EQD2 taking into account the heterogeneous fraction sizes for the hottest point dose would be 45.7 Gy, which remains 74.1 Gy grade 1 late rectal toxicity literature value constraint.

However, if we were to assume that a motion of 1 mm such as that resulting in the 760.34 cGy would occur repeatedly throughout each fraction, the EQD2 in that case would be 80.6 Gy which would be above the 74.1 Gy grade 1 rectal toxicity literature value constraint. Under these assumptions this grade 1 toxicity could occur, or be exacerbated due to these small range 1 mm displacements.

Considering the first three hypothetical situations above, two observations can be made: The EQD2 value consistently remained under the 74.1 Gy value, which is a good thing, but the difference between the extreme cases due to 1 mm motions is $74.1 - 45.7 = 28.4$ Gy which is quite a bit of uncertainty. However, in the fourth hypothetical situation above, the 74.1 Gy cutoff value is overpassed.
While these exact assumptions above are a bit unrealistic and perhaps unlikely, it is important to keep in mind that the differences of EQD2 for point dose that we are considering are due to hypothetical motions of 1 mm and that in an actual clinical situation the applicator might move even more. The above discussion is simply meant for these results to be put into some kind of clinical perspective.

The conclusion that can be made based on the above discussion, is that an investigation into both magnitude and distribution of interfractional and intrafractional motions of the gynecological applicators is warranted, i.e. how much the applicators move from insertion in CT room to treatment in HDR suite, and how much the applicator placement differs from insertion to insertion, and whether these displacements are completely random in terms of direction, or whether the applicators have a tendency to consistently exhibit a particular motion in a particular direction.

3.3 Statistical Analysis of Point Dose Study

We are interested in seeing whether or not the presence of air within the rectum, or the type of applicator make any statistically significant difference to the point dose variation due to these hypothetical motions. Despite the fact that these differences from a clinical perspective may appear to be very small, just based on inspection of the means, there may still be statistically significant differences.

In order to determine an appropriate statistical test, one useful piece of information is to determine whether the distributions of dose variations due to these various types of motions are normal. To do so we may use the Shapiro-Wilk normality test to the data set obtained for each type of motion. This test was applied to each dataset
by implementing the command `Shapiro.test()` built into the R statistical language. The results of the test are summarized in Table 5.

**Table 5:** The test statistic and corresponding p-value resulting from applying the Shapiro-Wilk normality test to the population data set for each type of motion.

<table>
<thead>
<tr>
<th>Displacement type:</th>
<th>Test Statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial lateral</td>
<td>W = 0.9658,</td>
<td>p-value = 0.1183</td>
</tr>
<tr>
<td>Superior inferior</td>
<td>W = 0.6269</td>
<td>p-value = 1.435e-10</td>
</tr>
<tr>
<td>Five degree rotation:</td>
<td>W = 0.6013</td>
<td>p-value = 5.672e-10</td>
</tr>
<tr>
<td>One degree rotation</td>
<td>W = 0.8628</td>
<td>p-value = 1.591e-05</td>
</tr>
</tbody>
</table>

The null hypothesis for the Shapiro-Wilk test is that the dataset in question is normally distributed. For small p-values such as those less than 0.005, we can reject the null hypothesis at the 99% confidence level. Thus we may conclude that the data in the case of the superior-inferior and the case of rotational motions are most likely not normally distributed. However, with 90% confidence we cannot reject the null hypothesis that the distribution of dose due to medial lateral motion is normal since the p-value > 0.10 in this case. In any case, it seems unlikely that any of the distributions are normal and thus the results that would be obtained from a standard two-way ANOVA which makes use of the assumption that the data are approximately normal may be misleading.

Possible options for further analysis of statistical significance would include either applying a Box-Cox transformation followed by a two-way ANOVA to the dataset
involving each type of motion, or perform one-way ANOVAs for each of the two desired variables. Yet another option would be to perform the Kruskal-Wallis tests instead of the one-way ANOVAs. According to 22, the oneway ANOVA is not very sensitive to deviations from normality and the Kruskal-Wallis test causes a loss of information since ranks are substituted for actual data values, which is a reason to prefer the oneway ANOVA.

With the statistical analysis performed in this study, no statistically significant conclusion can be made, other than that the population distributions of dose variations are not normal in the case of the hypothetical superior inferior and rotational displacements. An in depth statistical analysis of performing a multi factor ANOVA on these two categorical variables among other variables of interest, by utilizing the Box-Cox transformation with an optimal value of lambda as a remedial method for the missing assumption of normality of the population should be carried out. However, standard statistical software such as R does not appear to have a built in way of finding the optimal parameter of lambda. As a future project, in house software should be written to carry out this remedial method so that an analysis of statistically significant results could be carried out appropriately.
4. CONCLUSION

The point dose variation due to hypothetical 1 mm medial lateral displacement of a vaginal cylinder applicator might make a difference in terms of grade 1 late rectal toxicity as defined by Common Terminology Criteria for Adverse Events v 4.0 in some patients receiving HDR VCBT alone or shortly after EBRT.

The point dose variation due to hypothetical 1 mm medial lateral displacement of a vaginal cylinder applicator, according to this analysis, did not reach a crudely obtained cutoff value for RTOG grade ≥ 2 late rectal morbidity for any of the patients receiving HDR VCBT alone or shortly after EBRT.

As part of future work, an investigation into both magnitude and distribution of interfractional and intrafractional motions of the gynecological applicators is warranted. There is also plenty of literature published about DVH statistics other than point dose such as D2cc that are recommended as dose volume constraints. As part of future work a more in depth study of dose variation due to small range hypothetical motions should be carried out, looking not only at the hottest spot, and manually taking point dose measurements but instead by shifting the reconstructed catheters in the TPS retrospectively by aid of computer software such as MATLAB to make the acquisition of any desired DVH statistics both feasible and efficient. Further future work also includes performing a multi-factor ANOVA on these dose variations due to small range hypothetical displacements, with categorical factors of interest including prescription
depth, prescription length, diameter of cylinder, applicator type and presence of air within the hotspot, by using the Box-Cox transformation with an optimal value of lambda to correct for the missing assumptions of normality of the population distribution, in order to make statistically significant conclusions.
This appendix will provide a brief overview of the AAPM report no. 51 dose calculation formalism, which has been updated by AAPM report no. 84 and is used to calculate dose rate distributions. The general, two-dimensional (2D) dose-rate equation from the 1995 TG-43 protocol is:

\[
\dot{D}(r, \theta) = S_K \cdot \Lambda \cdot \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} \cdot g_L(r) \cdot F(r, \theta)
\]  

In the equation, \( r \) denotes the distance (in centimeters) from the center of the active source to the point of interest where the dose is being calculated, \( r_0 \) denotes the reference distance which is specified to be 1 cm in report no. 84, \( \theta \) denotes the polar angle relative to the source longitudinal axis specifying the point of interest where the dose is being calculated, namely \( P(r, \theta) \). The reference angle \( \theta_0 \) defines the source transverse plan and is specified to be 90° or \( \frac{\pi}{2} \) radians. See Figure 14. The term \( S_K \) denotes the air-kerma strength, \( \Lambda \) denotes the dose-rate constant in water, \( G_L(r, \theta) \) denotes the geometry function using line-source model, \( g_L(r) \) is the radial dose function using line-source geometry, and \( F(r, \theta) \) is the 2D anisotropy function.

The geometry function using the line source model provides an effective inverse square-law correction based on an approximate model of the spatial distribution of radioactivity within the source while neglecting scatter and attenuation and is defined as
\[ G_L(r, \theta) = \begin{cases} \frac{\beta}{Lr \sin \theta} & \text{if } \theta \neq 0^\circ \\ \left( r^2 - \frac{L^2}{4} \right)^{-1} & \text{if } \theta = 0^\circ \end{cases} \]  \hspace{1cm} (10)

where \( \beta \) is the angle, in radians, subtended by the tips of the hypothetical line source with respect to the calculation point \( P(r, \theta) \) and \( L \) is either the active or effective length of the source, which needs to be chosen properly based on recommendations within report no. 84.

Figure 18. This figure which shows the coordinate system used for brachytherapy calculations, is taken from AAPM report no. 84 which is an update of report no. 51 which provided the original dose calculation formalism.

The brachytherapy dosimetry parameters, namely, \( S_K, A, g_L(r) \) and \( F(r, \theta) \) shall be briefly discussed for explanatory purposes but are discussed in much greater depth and
detail in AAPM report no.84. For a specific source model, values for $\Lambda$ and tables of values for $g_L(r)$ and $F(r, \theta)$ are generally obtained experimentally and by Monte Carlo simulations as described in AAPM report no. 84.

The air-kerma strength, $S_K$ is defined as $S_K = \dot{K}_\delta(d) d^2$ where $\dot{K}_\delta(d)$ is the air-kerma rate in vacuo at distance $d$ due to photons of energy greater than $\delta$, where $d$ is the distance from the source center to the point of $\dot{K}_\delta(d)$ specification. Typically, $d$ can be chosen to be on the order of 1 meter.

The definition of the dose rate constant in water is $\Lambda = \frac{D(r_0, \theta_0)}{S_K}$. $\Lambda$ depends on the radionuclide and the source model and is influenced by source internal design and the experimental methodology used by the primary standard to realize $S_K$.

The radial dose function $g_L(r)$ accounts for dose fall-off on the transverse plane due to photon scattering and attenuation excluding fall-off included in the geometry function and is defined as

$$g_L(r) = \frac{\frac{D(r_0, \theta_0)}{S_K}}{g_L(r_0, \theta_0) g_L(r, \theta_0)} \tag{11}$$

The 2D anisotropy function describes the variation in dose as a function of polar angle relative to the transverse plane and is defined as

$$(r, \theta) = \frac{\frac{D(r, \theta)}{S_K}}{g_L(r, \theta_0) g_L(r, \theta)} \tag{12}$$
REFERENCES


12. Constine L, Marks L, Rubin P. ALERT - Adverse Late Effects Of Cancer Treatment.


