DESIGN OF 3D-PRINTED MULTI-CATHETER GYNECOLOGICAL BRACHYTHERAPY APPLICATORS WITH CUSTOMIZABLE CATHETER POSITIONS

by

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This thesis is dedicated to my Grandfather Penney

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ABSTRACT

Brachytherapy patients are often planned with vendor-supplied applicators and templates. For asymmetric gynecological targets, the applicator of choice is often the Miami or MUPIT applicator, depending on the tumour size. This applicator comes in different diameters however the catheter positions are fixed. This research designed multi-catheter customizable applicators with patient-specific catheter positions, which could be created using a 3D printer. The patient-specific catheter locations are based on the patient's specific anatomy. In this retrospective Research Ethics Board (REB) approved study, twenty-five past patients who received vaginal brachytherapy at the QEII Cancer Centre were chosen. Using Oncentra Brachy treatment planning system, the catheter positions were reconstructed according to the patient's anatomy. DVH parameters from the patient-specific applicator plans were then compared to the original applicator treatment plans. The high dose regions for all plans showed a decrease for the patient-specific with V_{200} decreasing from 7.4% to 3.3% ($p<0.0001$), for an intracavitary applicator. For the interstitial plans, V_{150} decreased from 38.6% to 34.0% ($p<0.0006$) for the patient-specific applicators. The patient-specific applicator plans showed a statistically significant decrease in the dose delivered to the OARs. The quality indices were statistically better for the patient-specific plans. Patient-specific intracavitary and interstitial/intracavitary hybrid applicators with customized catheter locations showed a more homogeneous and conformal target coverage. When comparing applicator design, a patient-specific, 3D-printed applicator resulted in better coverage of the CTV, with improved sparing of the OARs.

LIST OF ABBREVIATIONS USED

EBRT	External beam radiation therapy
DNA	Deoxyribonucleic Acid
MLC	Multi Leaf Collimator
LDR	Low-Dose Rate
HDR	High-Dose Rate
Ir-192	Iridium-192
TPS	Treatment Planning System
MUPIT	Martinez Universal Perineal Interstitial Template
CT	Computed tomography
MRI	Medical Resonance Imaging
SCC	Single Channel Cylinder
CTV	Clinical Target Volume
OAR	Organ At Risk
MCC	Multi-Channel Cylinder
PTV	Planning Target Volume
3D	Three-Dimensional
IPSA	Inverse Planning Simulated Annealing
DTDC	Dwell Time Dose Constraint
GO	Graphical Optimization
DVH	Dose Volume Histogram
ABS	American Brachytherapy Society

CI	Conformity Index
DHI	Dose Homogeneity Index
DNR	Dose Non-Uniformity Rate
OI	Overdose Index
EQD2	Equivalent Dose in 2 Gy Fractions
LQ	Linear Quadratic
REB	Research Ethics Board

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CHAPTER 1 INTRODUCTION

1.1 Gynecological Cancer

Gynecology is the branch of medicine concentrating on the diagnosis and treatment of the female reproductive organs, including the uterus, ovaries, fallopian tubes, cervix, vulva, and vagina.[1] A diagram of the female reproductive system is shown in Figure 1.1.

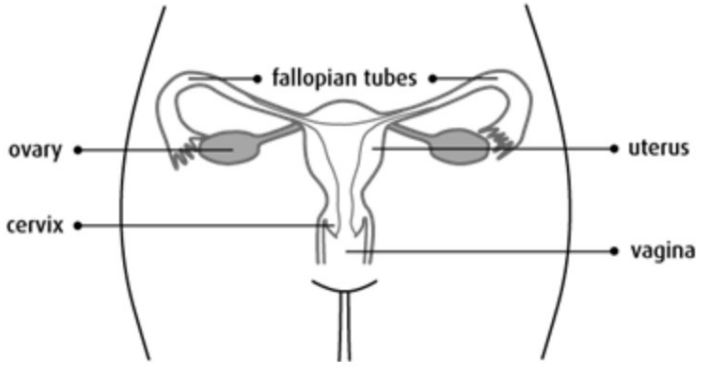


Figure 1.1 Diagram of female reproductive system.[2]

A tumour is a collection of abnormal cells that can start in any one of the trillions of cells in the body. Tumours behave differently depending on whether they are cancerous (malignant) or non-cancerous (benign). Malignant tumours spread and grow into nearby tissues and may travel to distant parts of the body, in a process known as metastasizing. To differentiate cancerous tumours, staging can be used to assess the tumour. Staging is based on a physical exam, blood test, imaging test and a biopsy.[3] A cancer with a lower stage reflects a smaller tumour that has not metastasized.

Cancer can form in any segment of the gynecological system. Fallopian tube cancer is a rare and difficult disease to cure. The main treatment is surgery with a combination of external beam

radiation therapy, further known as EBRT.[4] Ovarian cancer is the most lethal of gynecological cancers, with 5-year survival rates of less than 50%.[5] Surgery and platinum-based chemotherapy drugs, such as carboplatin or cisplatin are usually used to treat ovarian cancer.[5] There can also be a role for targeted and hormonal therapy in combination with chemotherapy, or as a maintenance therapy. The role of EBRT in the treatment of ovarian cancer has greatly diminished due to the large amount of acute and late toxicities that occur in patients. Vulvar cancer is primarily treated surgically, with radiation therapy or chemoradiation delivered before or after the surgery.[6] The remaining gynecological cancer sites (cervical, uterine, and vaginal) are commonly treated with radiation therapy, with EBRT and/or brachytherapy.

1.1.1 Cervical Cancer

The cervix is the passageway that connects the uterus to the vagina. Symptoms are dependent on the stage of the disease, with no symptoms present in early disease and various symptoms such as vaginal discharge and bleeding in advanced disease stage.[6] Squamous cell carcinomas represent 80-90% of all cervical cancer.[6] In Canada, an estimated 1450 patients were diagnosed with cervical cancer in 2022 and its ranked as the fifteenth most common type of new cancer in those assigned female at birth.[7] A description of each stage and the corresponding treatment option is shown in Table 1.1. Sections 1.2 and 1.3 will go into further detail regarding the individual treatment modalities for the gynecological cancers commonly treated with radiation.

Stage	Description	Treatment Option
I	Confined to uterus	Surgery alone, radiation therapy alone, brachytherapy alone, brachytherapy with EBRT
II	Invades beyond uterus but not to pelvic wall or to lower third of vagina	Surgery alone, radiation therapy alone, brachytherapy alone, brachytherapy with EBRT
III	Extends to pelvic wall and/or involves lower third of vagina	EBRT with chemotherapy and brachytherapy
IV	Distant metastasis	EBRT with chemotherapy and brachytherapy

Table 1.1: Cervical cancer staging and treatment options.[6]

1.1.2 Uterine Cancer

Uterine cancer is the most frequently diagnosed gynecological cancer.[6] In 2022, 8100 patients were projected to be diagnosed with uterine cancer, accounting for 7% of all new female cancers in Canada.[7] Uterine cancer was also expected to be the sixth leading cause of female cancer mortality, after ovarian cancer.[7] A description of each grade and the corresponding treatment option can be seen in Table 1.2.

Stage	Description	Treatment Option
I	Confined to uterus	Surgery sometimes followed by radiation therapy
II	Invades beyond uterus, but not to pelvic wall or to lower third of vagina	Surgery sometimes followed by radiation therapy
III	Extends to pelvic wall and/or involves lower third of vagina	Surgery followed by radiation therapy
IV	Spread beyond pelvis Metastasized	Rarely surgery, chemo/radiation to take away pain and symptoms

Table 1.2: Uterine Cancer staging and treatment options.[6]

1.1.3 Vaginal Cancer

Vaginal cancer accounts for 2% of gynecological malignancies.[8] The vagina is the passageway from the cervix to the outside of the body. In 2018, 1075 Canadian women were diagnosed with vaginal cancer.[7] Symptoms are comparable to those of cervical cancer and typical treatment of this cancer includes surgery and radiation therapy. A description of each grade and the corresponding treatment option can be seen in Table 1.3.

Stage	Description	Treatment Option
I	Tumour is localized to the vaginal wall	Brachytherapy alone
II	Involved the subvaginal tissue but has not extended pelvic wall	Brachytherapy + EBRT
III	Invades pelvic wall	EBRT
IV	Extended beyond pelvis	EBRT to control symptoms

Table 1.3 Vaginal cancer staging and treatment options.[6]

1.2 Gynecological Cancer Treatment Modalities

Once diagnosed with gynecological cancer, patients are often offered treatment with multiple modalities, including surgery, chemotherapy, and radiation therapy. For cancers of the vulva, uterus, and cervix, surgery is most effective when the cancer is well-localized and has not metastasized. Surgery is used to remove the tumour volume as well as surrounding tissue to limit the chance of recurrence.

Chemotherapy is a treatment option employed to kill as much of the cancer as possible or to shrink the primary tumour. Chemotherapy is typically used as systemic therapy; the drug will travel through the bloodstream and can attack cancer cells anywhere within the body.[9] An

example of a chemotherapy drug used for gynecological cancer is cisplatin, a platinum-based drug.[5] Chemotherapy uses powerful drugs that can cause side effects for the patient, such as nausea, vomiting, diarrhea, extremity weakness/swelling, drowsiness, and hearing issues..[9] As seen in Tables 1.1-1.3, chemotherapy can be used alone, or concurrent with EBRT.

Another commonly used treatment is radiation therapy. Like surgery, it is a localized treatment. The goal is to destroy the cancer cells but allow the normal cells nearby to recover. Radiation therapy can be delivered through EBRT and brachytherapy. EBRT uses high energy particles to destroy cancer cells by damaging the cell's carrier of genetic information, known as deoxyribonucleic acid (DNA), so that the cancer is no longer able to grow.[3] A common machine used for this is known as a linear accelerator, or linac. One of the linacs used at the QEII Cancer Centre in Halifax, Nova Scotia is shown in Figure 1.2.

Figure 1.2 One of the linacs currently used at QEII Cancer Centre in Halifax, NS.

A linac uses microwaves to accelerate electrons to high energies, 4 to 25 MeV.[3] The electrons are then collided with a tungsten target to produce high energy x-rays. As these rays exit the linac, multi-leaf collimators (MLCs) are used to shape the beam to conform to the shape of the target volume.[10] MLCs can also be used to modulate the fluence exiting the linac treatment head, to deliver intensity-modulated radiation therapy.

EBRT treatment is fractionated, meaning the prescription dose is delivered over multiple days. A small amount of radiation is delivered during each appointment, known as a fraction, with all fractional doses adding to the prescription dose. Fractionating radiation therapy results in a better therapeutic ratio, which is the relationship between the probability of tumour control and likelihood of normal tissue damage.[3] A common fractionated treatment for most gynecological cancers is 45 Gy delivered over 25 fractions.[11]

Brachytherapy is an internal radiation therapy technique, where radioactive sources are placed inside the body, either directly into or in proximity to the tumour. The radiation treatment options are dependent on the location and stage of the primary tumour and nodal volumes to be treated.[11]

1.3 Gynecological Brachytherapy

Following the discovery of radium and its radioactive properties by Pierre and Marie Curie, in 1903 Alexander Graham Bell suggested "… there is no reason why a tiny fragment of radium sealed in a fine glass tube should not be directly inserted into the very heart of the cancer, thus directly upon the diseased material…"[11] Graham Bell was one of the many who contemplated the treatment potential of radioactive radium, and in 1904, Pusey and Caldwell undertook the first trial treatment for cervical cancer by inserting a glass capsule of radium directly into the

tumour.[8] This was followed by the creation of the first gynecological applicator in Frickein, Manchester, in 1905.[8] The key objective of brachytherapy has remained unchanged over more than a century - as a cancer modality that employs radioactive sources near or directly inserted into the tumour volume.

Brachytherapy treatments can be differentiated based on the dose rate of the source. Two of the most common dose rates delivered clinically are classified as low (< 2 Gy/hour) and high dose rate (> 12 Gy/hour). Currently, in the developed world, low dose rate (LDR) brachytherapy treatments use small seed-like sources (hereafter referred to as “seeds”) that are manually implanted permanently into the patient permanently. The seeds can be seen within a prostate patient can be seen in Figure 1.3.

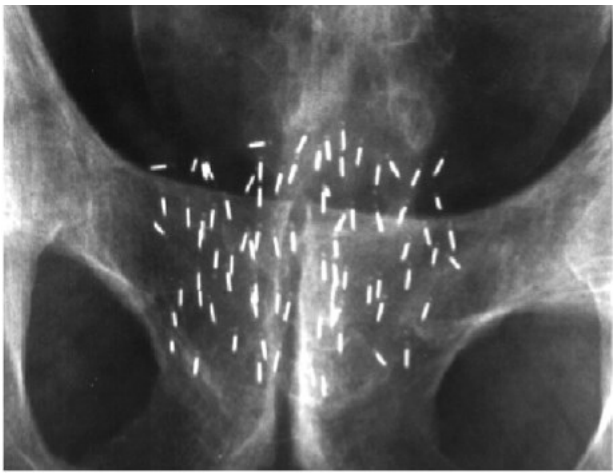


Figure 1.3 An x-ray showing LDR brachytherapy sources implanted in a prostate.[12]

The prescribed dose will be delivered over the lifetime of the source, until the source chosen has decayed completely.[11] This technique is primarily used for low-risk prostate cancer, but in the past, LDR sources treated all gynecological brachytherapy patients. For gynecological

cancers treated in the developed world, high dose rate (HDR) brachytherapy is now the clinical standard.

1.3.1 High Dose Rate Brachytherapy

The most commonly used HDR brachytherapy isotope is Iridium-192 (Ir-192), with a half-life of 73.8 days and an average energy of 380 keV.[11] For HDR gynecological brachytherapy, the radioactive sources are inserted into the patient via intracavitary or interstitial catheters. The delivery of the source is temporary, with the dose delivered over a brief period, stepping through preprogrammed positions within the catheters for set times, both as determined by the treatment planning system (TPS). The source can stay in a particular location within each catheter (known as dwell position), for a certain time (known as dwell time), until the treatment plan is delivered completely. The remote afterloader, shown in Figure 1.4, houses and controls the source. The afterloader connects directly to the catheters implanted in the patients via source transfer tubes, with the source attached to a stainless-steel cable that steps through the transfer tubes to the dwell positions in the catheter, as determined by the TPS. The afterloader translates those instructions and carries them out to allow for the delivery of a consistent and reproducible treatment plan while also minimizing the exposure to radiation for hospital staff.[9]

Figure 1.4 The remote afterloader used at the QEII Cancer Centre in Halifax, NS

The source is then retracted back into the remote afterloader. Figure 1.5 shows the remote afterloader connected via a transfer tube to a vaginal cylinder used at the QEII Cancer Centre in Halifax, NS.

Figure 1.5 Remote afterloader connected with a transfer tube to a gynecological cylinder applicator at the QEII Cancer Centre in Halifax, NS

The entire delivery procedure is computer-guided with communication between the treatment console and the afterloader. The catheters allow for safe housing of the source, allowing it to not encounter bodily fluids of the patients and therefore be reused for many treatments over a period of months.

Before treatment begins, a “dummy”, or fake, source that is larger than the radioactive source, is sent through each catheter to ensure there are no obstructions. An obstruction during treatment could cause the source to become lodged in the catheter/transfer tube or detach from the stainless-steel cable, creating an emergency for both the patient and staff. Once it is confirmed that there are no obstructions, the treatment may begin. Figure 1.6 shows a 3D printed surface applicator that was created at the QEII Cancer Centre for the treatment of a basal cell carcinoma tumour. Each flexible plastic catheter is numbered and inserted within the applicator to connect to the remote afterloader via the corresponding numbered transfer tube.

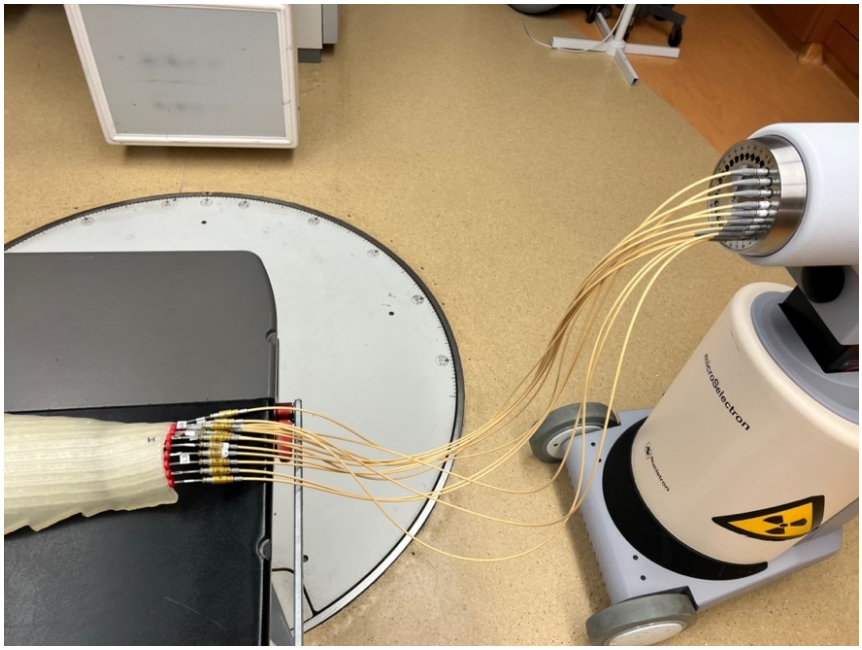


Figure 1.6 3D printed skin applicator connected via transfer tubes to remote afterloader at QEII Cancer Centre in Halifax, NS

Brachytherapy applicators vary depending on the anatomical site and the goal for the treatment. The decision of which type of applicator to use is dependent on the configuration of the tumour-bearing organ, as well as on the size and shape of the tumour.[11] Gynecological brachytherapy employs both interstitial and intracavitary applicators.

1.3.2 Interstitial Gynecological Brachytherapy

Needles are inserted directly into the tumour volume in interstitial brachytherapy, under general or regional anaesthesia.[9] A Martinez Universal Perineal Interstitial Template, MUPIT, shown in Figure 1.7, is an applicator that is designed for the placement of interstitial needles. It can be used to treat the vagina, perineum, or rectum.[13]

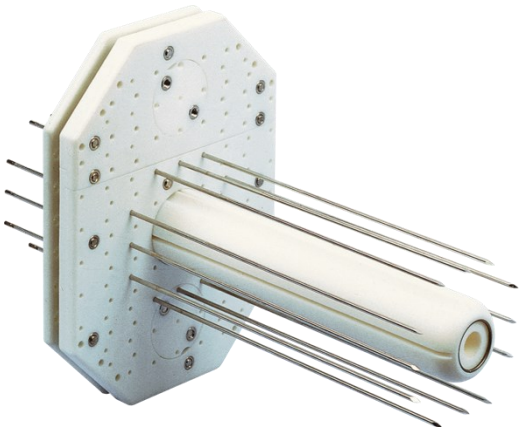


Figure 1.7: A MUPIT applicator used for interstitial gynecological brachytherapy treatment. The applicator consists of a template for the needles to travel, and a cylinder to provide better stability.[13]

The template has angled holes to allow the needles to reach the widest target volumes. A vaginal cylinder is placed in the centre of the template to provide better stability of the template.[13] This creates a fixed geometry at the insertion point and may be used to guide the needles.[14] The needles are fixed in the template by screws and if necessary, and the template is sutured to the skin. Interstitial applicators are ideally CT and/or MR compatible, as imaging for treatment planning purposes ensures the correct needle geometry. MR compatibility will aid in accurate target contouring. (Note that the MUPIT applicator is not MR safe, but other interstitial applicators may be.) Physicians may also insert the needles into the tumour volume without a template, or “freehand”.

Needle implantation can take place in a single plane or multiple planes, as determined by the thickness of the target volume. A target thickness with a maximum of 12 mm can often use a single plane.[14] Implantation in two planes is recommended for target volumes with a minimum of 10 mm to a maximum of 25 mm. When the target is greater than 25 mm, the tumour should be treated with multiple rows of needles, in an arrangement of a triangle or rectangle.[14] To ensure proper treatment of the entire target volume, the length of the needle must be clearly longer than

the length of the target volume, and the number of needles used must be sufficient to cover the entire target volume. If the target is treated with a smaller number of needles, areas of high dose occur around the needles, known as a “hot spot”.[14] Hot spots can result in considerable side effects to the patient, such as necrosis.

1.3.3 Intracavitary Gynecological Brachytherapy

Intracavitary brachytherapy is used for a tumour that has formed on an organ with a cavity nearby. Intracavitary treatment for gynecological cancer is best for treatment to the vagina, vaginal cuff, and cervix.[14] The placement of an intracavitary gynecological brachytherapy applicator relies on the use of the vaginal cavity. The correct placement of the applicator within the patient is important, ensuring no air gaps between the applicator and target volume, with a tight fit.

In brachytherapy, the dose fall off is very fast, with dose that reduces with respect to the change in distance according to an inverse square law effect. Introducing an airgap of even 1-2 mm can result in dose reductions to the tumour volume.[15] This can also result in the failure to treat all the microscopic cancer cells, increasing the risk for recurrence.[16] Various applicators are commercially available, and the choice of one over another is dependent on the location and characteristics of the tumour.

1.3.3.1 Ring and Tandem Applicator

When the cancer is located within the cervix, uterus and upper 1-2 cm of the vagina, a ring and tandem applicator may be used (Figure 1.8).[14] The “tandem” is the central tube, inserted into the uterine canal, and the “ring” is surrounding the tandem, placed against the cervix.[11] The applicator is connected to the afterloader, and the source is programmed to stop

and deliver dose at different dwell positions within the ring and tandem.[11] The positioning of the sources is especially important because of the proximity of the applicator to the target and the nearby organs at risk - bladder, rectum and sigmoid.

Figure 1.8: A ring and tandem applicator. The tandem is the central tube with the ring surrounding.[13]

1.3.3.2 Vaginal Cylinder Applicator

For those who require irradiation to the vaginal cuff and those who have had a hysterectomy, a vaginal cylinder is used.[14] A vaginal cylinder provides isotropic irradiation to the vagina, with a single central source path of possible dwell positions.[11] An example of a single channel cylindrical (SCC) applicator is shown in Figure 1.9. The applicator is available to purchase from the brachytherapy vendor in different diameters, often ranging from about 20 mm to 40 mm. CT and MR-compatible HDR brachytherapy cylinders are composed of plastic and carbon fiber to minimize artifacts during imaging.[14] The cylinder shown in Figure 1.9 is not MR-compatible as it contains metal components.

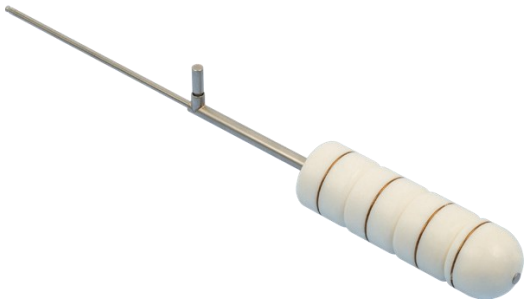


Figure 1.9: Single channel cylinder (SCC) applicator. This is not MR-compatible due to its metal components.[13]

One downside of the SCC applicator is its limited ability to sculpt the clinical target volume (CTV) and organs at risk (OARs) due to its single source path. The dose distribution of a SCC can be seen in Figure 1.10. Note the applicator in Figure 1.10 is not a SCC applicator, it is a multi-channel cylindrical applicator with dwell positions activated to resemble a SCC applicator. The single source path follows the basic dose distribution plan and is used for post-operative endometrial cancers, vaginal carcinomas, or recurrences that require symmetric treatment to the vagina.

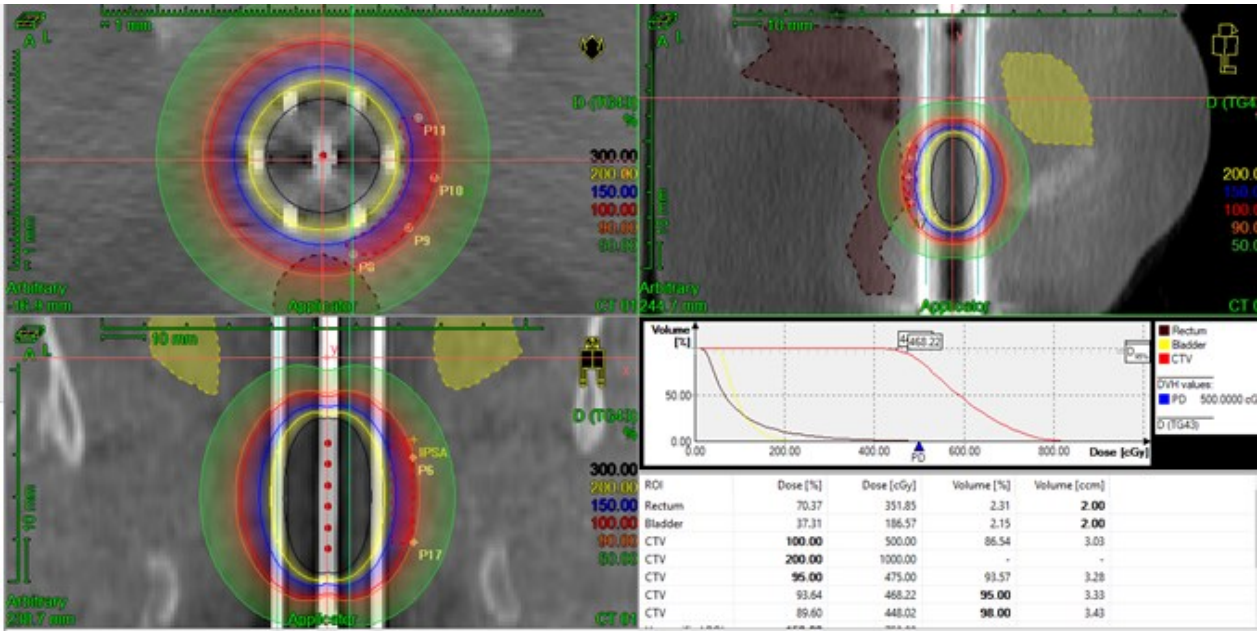


Figure 1.10 Dose Distribution, representative of a Single Channel Cylinder. The applicator in the image is a MCC applicator with only a single central catheter activated. The target volume is the red dashed line, with the rectum and bladder in brown and yellow, respectively.

A multichannel cylinder (MCC) applicator presents an applicator with catheter channels on the periphery of the applicator. A common commercially available multi-channel cylinder applicator is called the Miami, named after the location of its creation - the University of Miami. The MCC possesses a single central channel and six peripheral channels. (Figure 1.11) The applicator has a core that houses all seven channels, and different diameter cylindrical sleeves to achieve the best fit for the patient to ensure no air gaps exist between the applicator and vaginal mucosa.

Figure 1.11: Commercially available Miami applicator, the central channel may be inserted into the uterus.[13]

The additional channels at the periphery support a conformal dosimetry that can better shape the dose distribution to limit the dose to the OARs and can create an asymmetric dose distribution. The addition of extra channels allows the reduction of dose to the OAR's when compared with the cylinder dose distribution. The dose distribution can be seen in Figure 1.12.

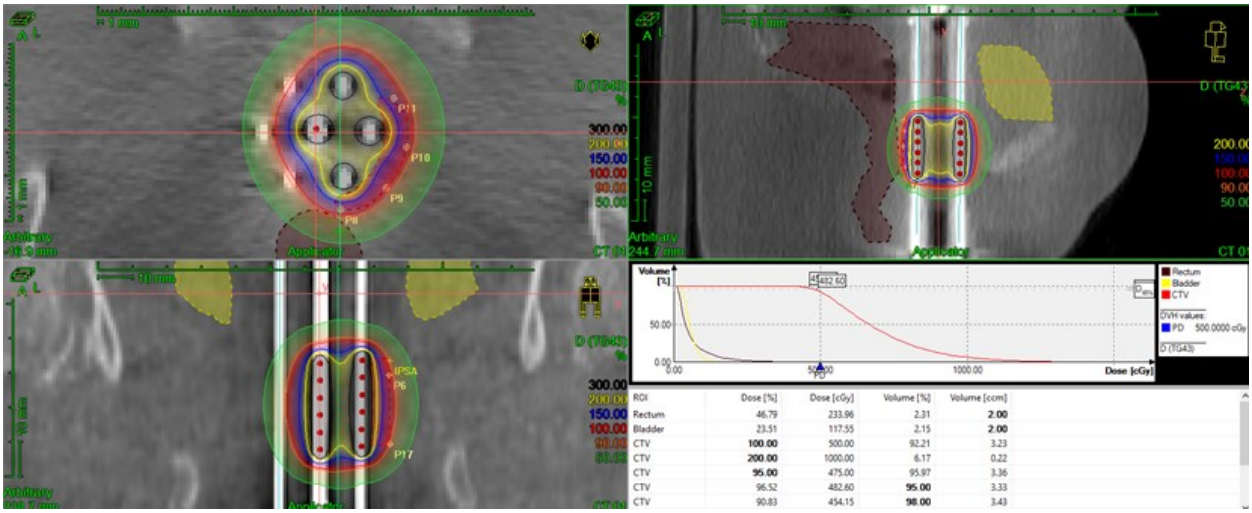


Figure 1.12: Miami applicator dose distribution, with the same dataset as Figure 1.12 to compare the MCC applicator dose distribution to that of the SCC applicator. The target volume is the red dashed line, with the rectum and bladder in brown and yellow, respectively.

1.4 Vaginal Brachytherapy Treatment Planning

Treatment planning requires a team of radiation oncologists and medical physicists to work together and create a plan to best treat every patient. The radiation oncologist first determines the

diagnosis and treatment options. When treating many gynecological cancers, EBRT and brachytherapy combination is a common modality. For endometrial cancer, a SCC applicator is used, to deliver a symmetric dose adjuvant to the entire vaginal cuff, prescribed to the vaginal surface or a depth of 5 mm. When the diagnosis is primary vaginal cancers and recurrences of endometrial cancer, the targets are commonly asymmetric.

Primary vaginal cancer is a rare cancer.[17] Over the last decade, vaginal cancer guidelines have been developed, with a focus on interstitial treatment.[18] Primary vaginal cancer resembles cervical cancer in terms of risk factors, with human papillomavirus (HPV) infection being most significant. Other factors include age, immunosuppression, and cigarette smoking.[19] This has led to the adaption of treatment techniques similar to those for locally advanced cervical cancer, for which there is extensive evidence.[17]

Vaginal recurrences of endometrial cancer commonly begin in the post hysterectomy scar but can also develop at other sites of the vaginal wall.[18] During treatment for these recurrences, one goal is organ preservation, with physicians tending to treat the recurrent site with EBRT and/or brachytherapy. Re-irradiating recurrences in women who previously received radiation therapy can lead to significant symptoms and treatment caused illnesses.[18] Employing treatment techniques that can adapt to the patient's anatomy is a useful tool when managing these cases.

For the treatment of vaginal cancers and recurrences, multi-catheter intracavitary applicators and hybrid interstitial/intracavitary applicators have been used. They both have shown improved coverage of the target while also sparing organs at risk for asymmetric targets, as discussed in the preceding sections.[20]

When contouring the target volumes, the CTV includes the gross tumour volumes and surrounding at risk tissues. When the target volume is large, this can lead to increased dose to the entire vaginal cavity. The prescription dose is applied to the entire CTV. Common dose schedules are 45 Gy in 25 fractions of EBRT, with a brachytherapy schedule of 6 Gy times 4 fractions, or 7 Gy times 3 fractions.[20] When the target volume involves the upper vagina, which has a higher tolerance to radiation, or a higher staged tumour, the prescription dose can increase. For tumours in the lower vagina, fractionation schemes should be given in a lower dose per fraction to reduce potential for complications.[20]

The applicator used can be intracavitary and/or interstitial, depending on the size and location of the CTV.[20] Target volumes with a width of less than 5 mm, may be treated with an intracavitary applicator. These cancers are usually asymmetric and require dose be delivered to a certain side of the vagina. Therefore, a MCC applicator, like the Miami, is used. When a target is thicker than 5 mm, an interstitial applicator, such as the MUPIT, is used.

1.5 Treatment Planning Systems (TPS)

A computerized TPS is a specialized software that uses algorithms to develop a treatment plan for the patient. A TPS can take images from CT and/or MR scans to contour target volumes and calculate dose. Oncentra Brachy (Elekta AB, Stockholm, Sweden) is the TPS that is currently used to plan brachytherapy treatments in the Department of Radiation Oncology at the QEII Health Sciences Centre (also known as the QEII Cancer Centre). This software can be used to contour the main target volumes and OARs. A description of the main target volumes can be seen in Table 1.4.

Target Volume	Description
Gross Target Volume (GTV)	The visible and clinically demonstrable, location and extent of the tumour volume
Clinical Target Volume (CTV)	Volume that contains the GTV and includes a volume of surrounding tissue with a high risk of microscopic, subclinical disease
Planning Target Volume (PTV)	Geometrical expansion of the CTV to account for geometric and dosimetric uncertainties

Table 1.4 Definition of target volumes.[14]

In intracavitary brachytherapy, the planning target volume (PTV) does not expand from the CTV and the terms may be used interchangeably because of the limited target motion with respect to the applicators that ultimately dictate the dose delivery. The catheters that contain the HDR source are within or next to the CTV. Applying the additional margin for the PTV, may result in an increased dose throughout the CTV and OARs.[14] When treating with a MCC, the OARs are the bladder, rectum and sigmoid, and bladder, rectum, and urethra for MUPIT.

The user can reconstruct the applicator on the images through direct reconstruction by contouring the visible applicator, the proxy radiopaque markers inserted into the visible applicators for visualization, or by the overlay of a library of applicators that the user matches to the visible imaging. On the CT/MRI scans, the position of each catheter or “dummy” markers are visible. Figure 1.13 shows a radiopaque marker within a ProGuide Sharp needle guide. The radiopaque marker shows the available dwell positions of the source within the applicator. This allows for reconstruction of the catheters in the correct position within the applicator or the correct position for the needles within the patient.

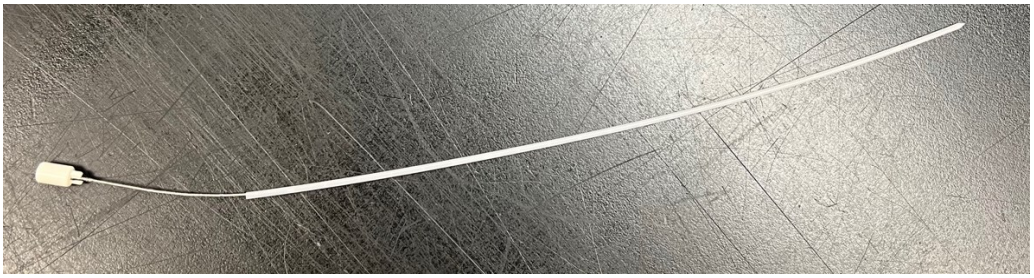


Figure 1.13 Radiopaque marker in a ProGuide Sharp Needle guard

At the QEII Cancer Centre, the radiation oncologist contours the target volume and OAR. The treatment planner, a medical physicist, reconstructs the catheters as seen on simulation imaging and activates the appropriate dwell positions. Once a plan is created, it is further optimized by the planner to achieve the dose constraints, leading to a high-quality treatment plan.[14]

1.6 Optimization of Treatment Plan

Treatment plan optimization is the act of obtaining an optimal dose distribution to maximize the prescription dose coverage to the target and minimize dose to the organs at risk.[3] To optimize a treatment plan, manual planning or an optimization algorithm can be used. Manual planning is a forward-directed, trial and error method where the choices are made to alter the dose distribution through adjustments of controllable parameters, such as dwell weights and times.[14] The dwell positions are restricted to the catheters, needles, or applicator. The dwell times can be iteratively changed at a minimum of 0.1 s time increments until the desired dose distribution is achieved.[14] It can be time consuming, and the quality of the plan is heavily dependent on the experience and skill of the planner. The planning goals can be complex, with several planning goals competing against each other, and endless possibilities for source positions.[14]

An inverse planning technique is more common for planning gynecological brachytherapy implants with more than three catheters. As opposed to forward planning, inverse planning starts with inputting the clinical objectives for the plan and an algorithm determines the treatment parameters that will fulfill the objectives. Inverse planning works to determine a set of dwell positions and times that satisfy the clinical dose objectives. Graphical optimization is the manual manipulation of the isodose lines and can be used to "fine tune" the dose distribution (see Section 1.5.2)

1.6.1 IPSA

The Inverse Planning Simulated Annealing, or IPSA, optimization algorithm is widely employed within clinics. IPSA is an inverse planning algorithm that is based on contoured anatomy and optimizes source dwell times using a simulated annealing algorithm, based on the work by Kirpatrick *et al.*[21] and developed for brachytherapy applications by Lessard and Pouilet.[22] The algorithm requires contoured patients' anatomy from the CT or MR imaging, with the applicator in place, and the user enters a series of surface and/or volumetric prescribed dose constraints. The constraints are set by the user at the time of treatment planning. IPSA gives an acceptable conformal plan in a matter of seconds by providing the distribution of the dwell times within the catheters, activating only the dwell positions of catheters created within the targets of the plans.[23]

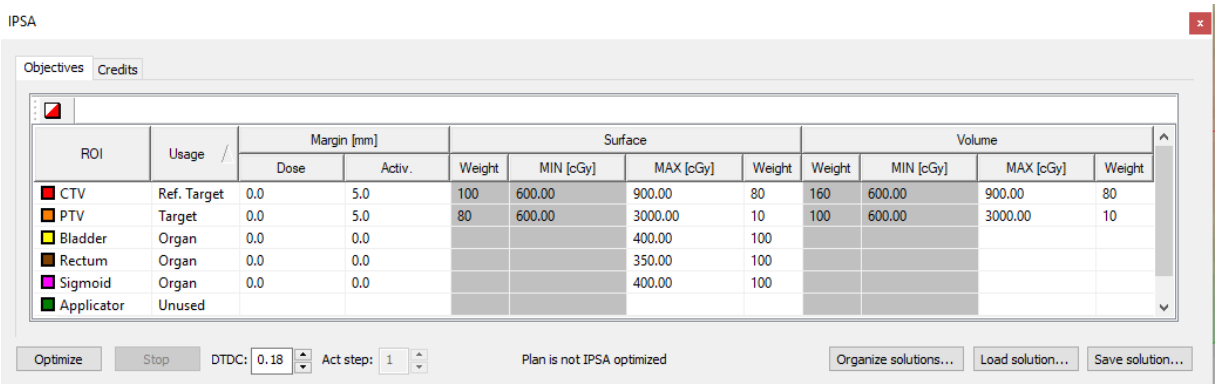


Figure 1.14 IPSA Dose Objectives for a vaginal brachytherapy plan

To use IPSA, the planner must enter the dose constraints, such as minimum and maximum dose to target volumes and OARs, with a corresponding weight. A cost function is used to quantify the values of the dose within the treatment plan to meet its clinical objectives. The cost function W_i, calculates the dose (D_i) at a point i is converted into a penalty value through the following relation:

$$W_i = \begin{cases} m^{min}\left|D_i - D^{min}\right| & if\ D_i < D^{min} \\ m^{min}\left|D_i - D^{max}\right| & if\ D_i > D^{max} \\ 0 & if\ D^{min} \le D_i \le D^{max} \end{cases} \quad \text{(Equation 1.1) [23]}$$

Where D^{min} and D^{max} represent the lower and upper range of acceptable doses. When the dose is within the specified range, the penalty is zero. If the dose to point i is above or below the specified range, the penalty increases at rates of m^{min} and m^{max}. This equation is used for both CTV and OARs. The goal of each optimizer is to minimize or maximize the cost function by changing the dose distribution within the constraints of clinical dose limits. The "best" plan constitutes from minimal cost. If clinical objectives are not met, the planner can adjust the importance or weighting factor of each constraint, or the value of the minimum/maximum doses

to ensure that the dose distribution achieved will meet the dose requirements. Ultimately, the decision that a plan is clinically acceptable and can be used to treat a patient is a decision made by the physician.

An original disadvantage of IPSA was that it was not initially designed to include a smoothness function. Therefore, the distribution of a single dwell time with respect to adjacent ones can sometimes show a large difference. The Dwell Time Deviation Constant (DTDC) parameter was introduced to restrict the dwell time deviation in each catheter.[24] This controls potential hot spots around each dwell position. The DTDC value can be set from 0.0 to 1.0 where 0 is an unrestricted optimization and 1 is homogeneous dwell times. Cunha *et al.* increased the DTDC value from 0 to 1.0, in 0.1 increments, for patients with prostate and gynecological tumours. In all cases, a DTDC value that was not zero caused an increase in the penalty function over the unmodified IPSA plan.[25] A DTDC of 1 resulted in nearly equal dwell times for all dwell positions in each catheter.[25] The study resulted in using a smaller value, as higher values can lead to significant degradation to the metrics.[25] IPSA can then create an optimized dose distribution based on the contoured CTV and OARs.

1.6.2 Graphical Optimization

Graphical optimization (GO) is an interactive method of optimization where the user can manually manipulate the dose distribution.[23] The isodose lines in the dose distribution on the transverse, sagittal and coronal CT images are adjusted manually. The dwell positions and weights of the sources are calculated to achieve the new dose distribution, and with a slider bar between local optimization (isodoses only in the vicinity of the mouse click are adjusted) and global optimization (isodoses throughout the volume are adjusted). GO is a fast method that can

improve the coverage of the target while decreasing hot spots. GO is not calculated based on patient's anatomy, it is simply the movement of isodose lines around the contoured target volumes to increase or decrease the dose to the volumes.[26]

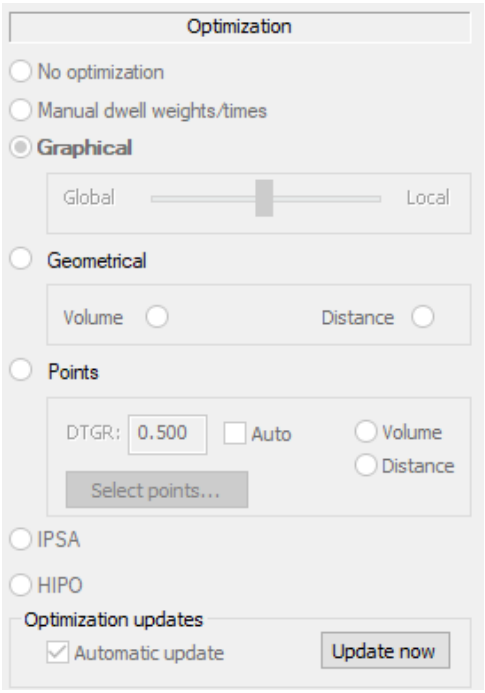


Figure 1.15 Optimization tool bar, with graphical optimization selected. Other optimization methods shown here, such as geometrical or point optimization were not used in this study and will not be discussed.

1.7 Evaluation of a Treatment Plan

Once a treatment plan has been created on the TPS, the oncologist must assess dose to target volume and the OARs. The plan is optimized until an ideal treatment plan is created to ensure the patient is receiving the best possible plan. Plan analysis is completed by evaluating dose distributions, dose volume histograms (DVH), and dose homogeneities.

1.7.3 Dose Distributions

Dose distributions are a series of isodose curves or color-coded washes that provide detailed spatial dose information. Dose distributions allow the planner to see regions of uniform dose, as well as hot spots. They are also useful for showing the minimum and maximum doses that will be delivered to the CTV and OARs. Dose distributions are used to view the overall pattern of the dose. Figure 1.16 shows the dose distribution for Patient 4 of this study for the original treatment plan used for treatment. The red isodose line is the 100% dose line. For each plan, ideally this is covering the CTV. The blue and yellow line, 150% and 200% respectively, represent the hotter regions of dose, known as hot spots. Ideally, these lines are not entering the tissue and remain within the applicator.

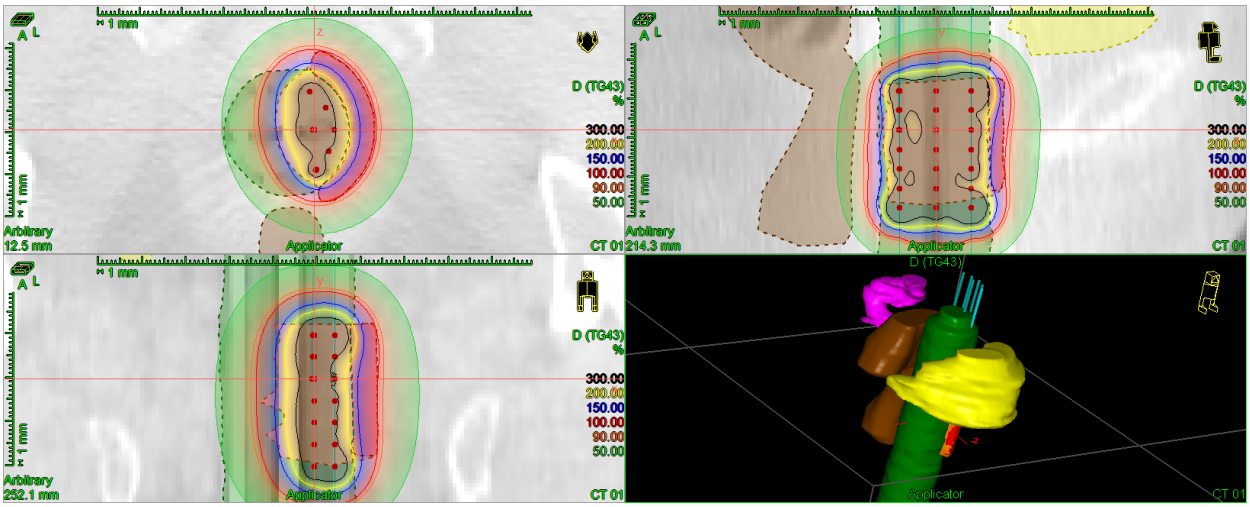
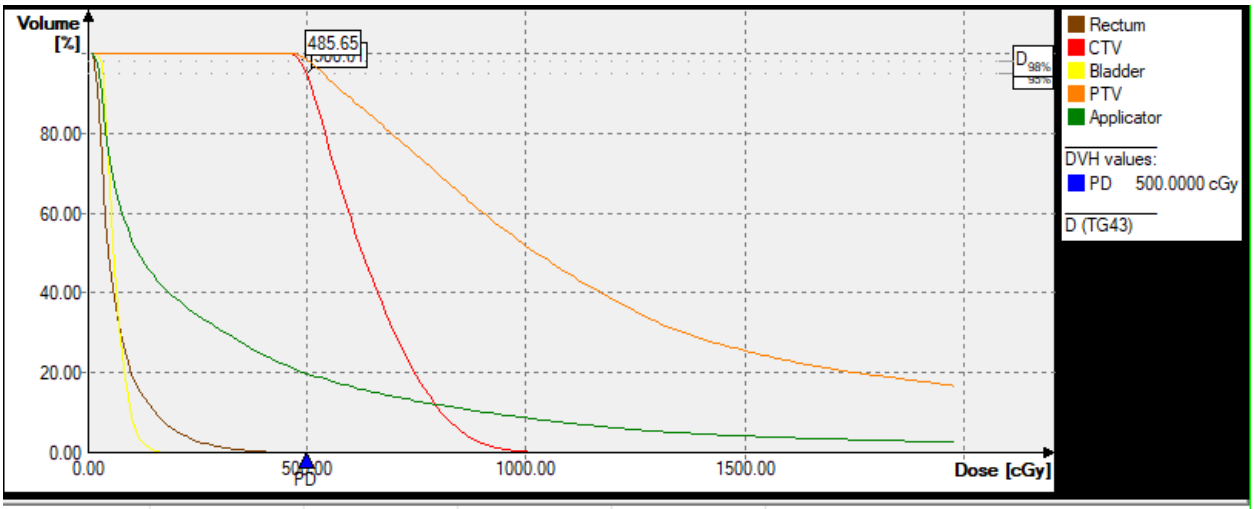


Figure 1.16 A sample dose distribution from Oncentra Brachy for Patient 4. The target volume is represented by the dotted red line, the applicator is the dotted green line, the rectum is the dotted brown line, and the bladder is the dotted yellow line. The isodose lines are represented by the solid lines.

1.7.4 DVH

Although the dose distributions show complete information about dose deposition within the patient, there is a need for a more focused evaluation pertaining to specific structures. The TPS condenses the vast amount of information contained within the plan into a single 2-

dimensional plot that is quick to analyze. Dose volume histograms (or DVHs) evaluate defined volumes by using an ordered list of all the dose voxels within a volume.[27] Cumulative DVHs are the most common type of DVH used in plan evaluation, with the dose voxels binned by an increment dose value, and the number of voxels within that dose bin or greater is tabulated. DVH curves are assessed, and the treatment plan parameters can be adjusted until the dose to regions within the volume have been deemed acceptable by meeting the planning constraints.[27] DVHs for the CTV and the nearby OARs are reviewed for all radiation therapy plans.



ROI	Dose [%]	Dose [cGy]	Volume [%]	Volume [ccm]
Rectum	53.22	266.12	2.31	**2.00**
Bladder	25.54	127.72	2.15	**2.00**
CTV	**100.00**	500.00	95.00	3.33
CTV	**150.00**	750.00	19.34	0.68
CTV	**200.00**	1000.00	0.20	0.01
CTV	**95.00**	475.00	99.22	3.48
CTV	100.00	500.01	**95.00**	3.33
CTV	97.13	485.65	**98.00**	3.43

Figure 1.17 Sample DVH showing cumulative DVH plots for the rectum, bladder, CTV and PTV.

Every histogram for each structure starts by covering 100% of the volume. The coverage then decreases at higher doses until leveling off at smaller volumes. The curve indicates how much dose is absorbed within the structure.[14] The interplay of target coverage and dose to OARs are seen visibly when plotted.

From a DVH, the percentage of volume receiving a particular dose and the dose delivered to a certain volume can be analyzed. American Brachytherapy Society (ABS) provides recommendations for which values to report for vaginal cancer or recurrent cancer in the vagina. They recommend reporting the percentage of volume receiving 100%, 150%, and 200% of the dose - V_{100}, V_{150} and V_{200} respectively. As well as the minimum dose received by the hottest 98% and 95% of the target volume, D_{98}, D_{95}, respectively. For the OARs, they suggest dose constraints for the minimum dose that is delivered to the most irradiated 2 cubic centimeters of the organ, D_{2cc}. D_{2cc} is used as a maximum dose evaluation tool for OARs.

1.7.5 Dose Homogeneity of CTV

The dose to the CTV can be evaluated further using different quality parameters.

1) Conformity Index (CI); this is defined as the ratio of volume receiving ≥ 95% of the prescription dose to the total CTV. The ideal index is 1.[28]

$$CI = \frac{V_{95}}{V_{CTV}} \quad \text{(Equation 1.2)}$$

2) Dose homogeneity index (DHI); this is defined as a ratio of volume receiving between 100% and 150% of the prescription dose to total CTV. A larger DHI shows a homogeneous dose distribution in target.[29]

$$DHI = \frac{V_{100-150}}{V_{CTV}} \quad \text{(Equation 1.3)}$$

3) Dose non-uniformity rate (DNR); this is defined as a ratio of volume receiving at least 150% of prescription dose to that receiving at least 100% of prescription dose. A smaller DNR shows a lower region of unequal dose within the target.[30]

$$DNR = \frac{V_{150}}{V_{100}} \quad \text{(Equation 1.4)}$$

4) Overdose Index (OI); this is defined as a ratio of volume receiving at least 200% of the prescription dose to that receiving at least 100% of this dose. Ideal OI is 0.[31]

$$OI = \frac{V_{200}}{V_{100}} \quad \text{(Equation 1.5)}$$

1.7.6 Dose Constraints of OARs

When evaluating the organs at risk, the ABS recommends reporting the dose to organs at risk as the summation of EBRT and brachytherapy doses by preforming a calculation of biologically equivalent dose in 2 Gy per fraction, EQD2.[32]

The Linear Quadratic (LQ) model is one of the many cell survival models that are based on the kinetics of cellular damage production and repair and is the most used model in clinical studies. [14] The linear quadratic model is most often used to evaluate cell survival represented by Equation 1.6. The LQ model in its simplest form describes the average fraction, *S,* of cells surviving a clinical dose, *D.*

$$S(D) = e^{-\alpha D - \beta D^2} \quad \text{(Equation 1.6)}$$

where *S(D)* is the fraction of cells surviving dose *D,* α is a constant that describes the initial slope of the cell survival curve, and β is a constant that describes the quadratic component of cell killing.[3] The LQ model can be manipulated to create an equation for EQD2. The exponent of the LQ model can be converted to calculate EQD2 using the following equation:

$$EQD2 = D\left\{\frac{d+\frac{\alpha}{\beta}}{2+\frac{\alpha}{\beta}}\right\} \quad \text{(Equation 1.7)}$$

Where D is the total prescription dose, d is the fractional dose, and $\frac{\alpha}{\beta}$ is a ratio that describes the cell's radiosensitivity to dose fractionation.[14] Cells with a higher $\frac{\alpha}{\beta}$ are less sensitive to the sparing from fractionation schemes. EQD2 is used to compare the relative effectiveness of different dose fractionation schemes, and for determining other fractionation schedules to match the cell killing of a known fractionation scheme.[14] The ABS recommends an EQD2 D_{2cc} of the bladder as a cumulative dose of less than 65 Gy and less than 80 Gy to the rectum.[32]

For an EQD2 calculation, the dose is calculated using both EBRT and brachytherapy treatments in using Equation 1.7. For each patient in this study, the EBRT fractionation scheme was assumed to be 45 Gy in 25 fractions, 1.8 Gy per fraction. EQD2 is used for OAR dose calculation, where $\frac{\alpha}{\beta}$ is 3 Gy, as the OAR tissue have a later response to radiation. For EBRT, we can calculate:

$$EQD2 = 45\left[\frac{1.8+3}{2+3}\right] = 43.2\ Gy$$

For Patient 1 of our study, we achieved a dose to the bladder for the original applicator plan of 1.60 Gy from the TPS. The brachytherapy prescription was 6 Gy times 4 fractions, 24 Gy total. Then we can calculate the EQD2 for brachytherapy:

$$EQD2 = 6\left[\frac{1.6+3}{2+3}\right] = 5.89\ Gy$$

To get the total EQD2 for Patient 1, the EQD2 for EBRT and brachytherapy must be added together, giving a total EQD2 dose of 49.09 Gy for the original applicator.

1.8 Applications of 3D Printing in Radiation Therapy

Three-dimensional (3D) printing techniques, also referred to as additive manufacturing, have become increasingly popular in the medical field. 3D printing can create 3D objects using computer software without complex and time-consuming human-lead processes. To manufacture a product, a digital model is generated by 3D design software and partitioned into two-dimensional cross sections layer by layer.[33]

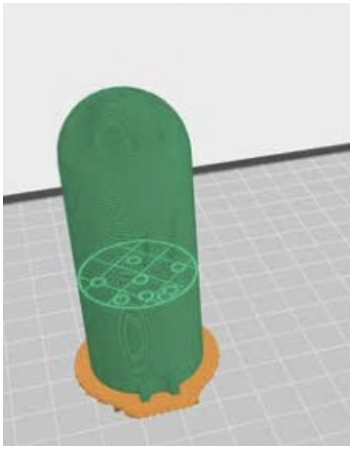


Figure 1.18 Model of a gynecological brachytherapy applicator on MakerBot Print (version 3.0, MakerBot Industries, USA) [34]

Afterwards, the computer will design the path information for each layer based on the cross sections. The computer will guide the printer layer by layer to print a 3D model.

At the QEII Cancer Centre, 3D printing technologies have resulted in the development of individualized skin boluses for electron and photon radiotherapy. The bolus can help reduce hot spots caused by the electron beam for electron treatments and to create a more conformal dose for the target volume. Creating bolus' offer a practical advantage because neither the patient nor the staff have to be present during the fabrication process.[35]

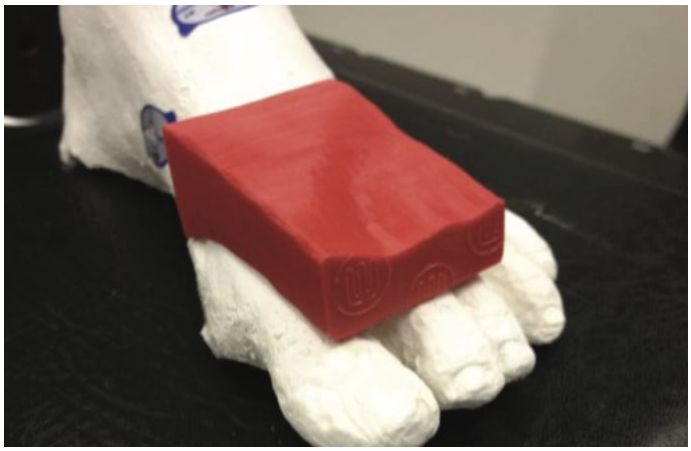


Figure 1.19 Picture of foot phantom with bolus on surface.[35]

Another study developed a patient specific HDR brachytherapy applicator for administrating radiation to superficial lesions, as shown in Figure 1.20.[36] This applicator was not used to treat the patient due to its close proximity of the target volume to the ipsilateral eye, and the resulting high dose to that OAR.

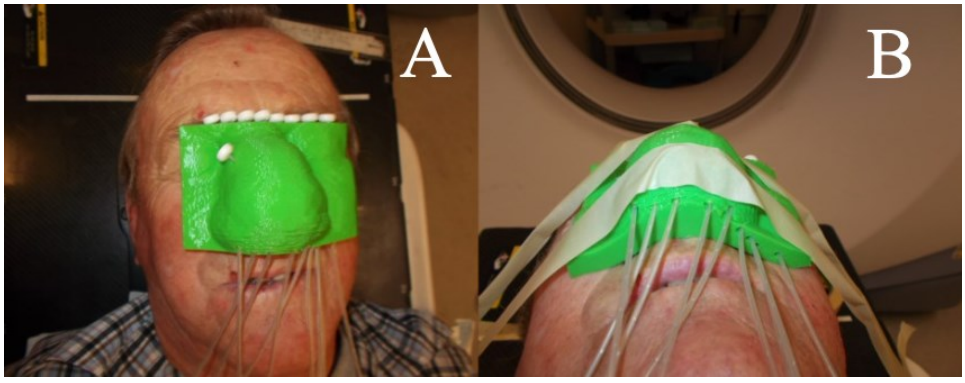


Figure 1.20 3D printed applicator designed for patient with basal cell carcinoma of the nose at the QEII Cancer Centre.[36]

For gynecological brachytherapy specifically, 3D printing can be used to create a vaginal cylinder to customize the fit to the individual patient, particularly if the treatment volume does not conform to the commercially available sizes. One of the first reports of using 3D printing for

gynecological brachytherapy was to create a custom version of the ring and tandem applicator. A cap was created to mount on the ring component of the tandem and ring, allowing interstitial needles to be inserted through the cap ring.[37] Sethi *et al.* demonstrated the clinical use of several custom-sized cylinders that were better able to fit the patient than what was commercially available.[38]

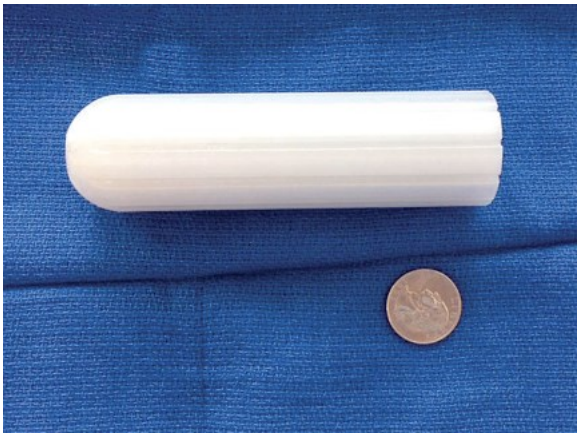


Figure 1.21 Picture of 3.5 cm diameter 3D printed vaginal cylinder with 10 external catheter channels and one centra channel for tandem for use with a patient that has a wide vaginal vault.[38]

Several other groups have reported 3D printing individualized applicators for gynecological brachytherapy. Yan *et al*. compared the dosimetric differences between a standard MCC applicator with a 3D printed applicator. The patients must have received a hysterectomy and then required brachytherapy. The lesions must have been less than 10 mm thick. The patient dataspace was made up of endometrial cancer, cervical cancer, and recurrences in those regions.[15] The catheters were designed with a catheter in the centre and the outer catheters placed approximately 5 mm away from the applicator surface, with 10 mm space between each catheter. The applicators were customized to the patient's specific vaginal cavity using a vaginal packing with gauze that was CT friendly. The 5 types of vaginal morphologies can be seen in Figure 1.22. The most common configuration was the dome-column for 21 out of 48 patients,

this is a cylindrical applicator.[15] The least common was ‘up wide and low narrow’. The difficulty with applicators D and F can be during insertion, as the upper end of the applicator is thicker and can cause pain to the patient when inserting the larger upper part into the smaller lower region of the cavity. To avoid this, the 3D-printed applicator can be inserted in two halves, causing less overall pressure to the patient during insertion.[15] Overall, the results showed that the 3D-printed applicator delivered a higher dose to a larger volume while also offering a more conformal and homogeneous dose to target.[15] Further research on the configuration of the vaginal cavity needs to be completed to help further understand which patients would require a 3D-printed applicator.

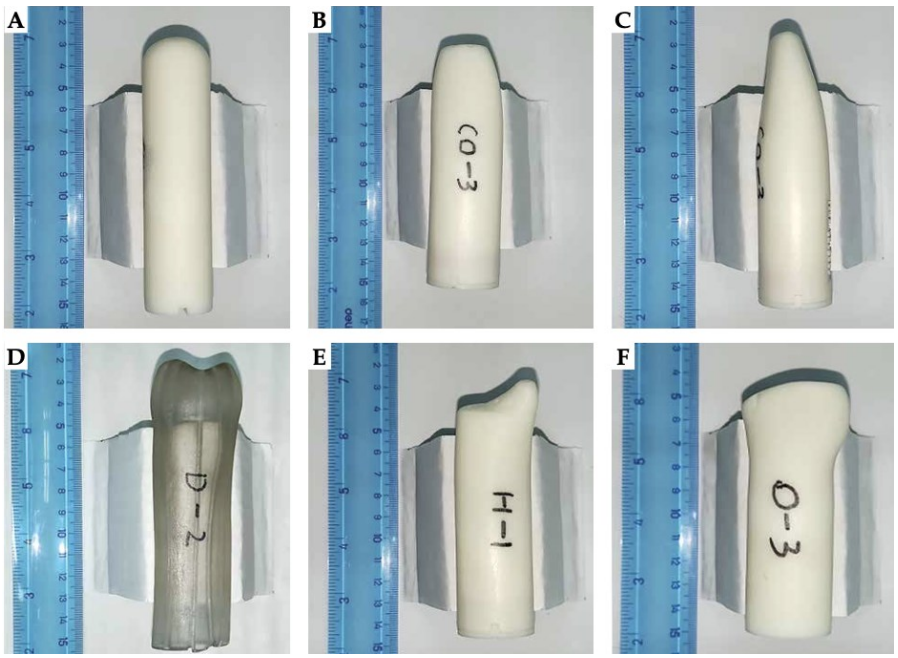


Figure 1.22 Photos of 3D printed applicators with various configurations. A) Dome-column B) Coronal view of the Gothic arch-column C) sagittal view of Gothic arch-column D) Two dog ears-column E) One dog ear column F) “Up wide and low narrow”[15]

Another study investigated hypothetical improvements to a the gynecological HDR brachytherapy applicator by using shielding to improve dose distribution and organ at risk

sparing during treatment.[39] They tested various biocompatible 3D printing bio compatible materials to use as the shielding segments via Monte Carlo. The work is on-going, focusing on the appropriate thickness required for sufficient shielding when using 3D printed steel.

For interstitial gynecological brachytherapy, the templates can be customized using 3D printing. 3D-printing also introduces the idea of hybrid applicators, combining the intracavitary cylinder applicator with needles that exit the applicator and into the target volume. Zhao *et al*. designed individualized applicators with oblique needles for cervical cancer patients and showed that the use of oblique needles delivered a higher target dose, improved target coverage and reduced dose for organs at risk.[40]

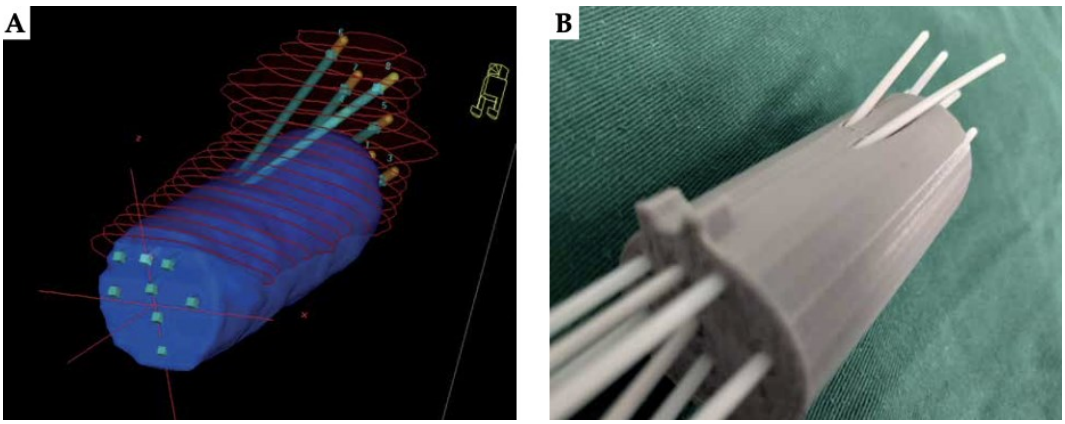


Figure 1.23 3D printing of cylindrical applicator with oblique needles. A) 3D Graphics in planning phase B) applicator after 3D printing.[40]

A recently published study by Kudla *et al*. assessed an in-house modelling and 3D printed patient-specific cylindrical template for use in vaginal cancer brachytherapy.[41] The applicators consisted of flexible intracavitary and interstitial needles. The patient dataspace consisted of 10 patients, chosen to show a range of vaginal tumour location and geometries. Vaginal targets at the top of the vaginal vault can be difficult to treat with a single channel

cylinder applicator and free hand needles.[41] The coverage of the high-risk target volume can achieve only an adequate dose distribution, shown in Figure 1.24 A. This case was proven to have an increased dose coverage of the high-risk target volume when treated with a patient-specific applicator, shown in Figure 1.24 B.

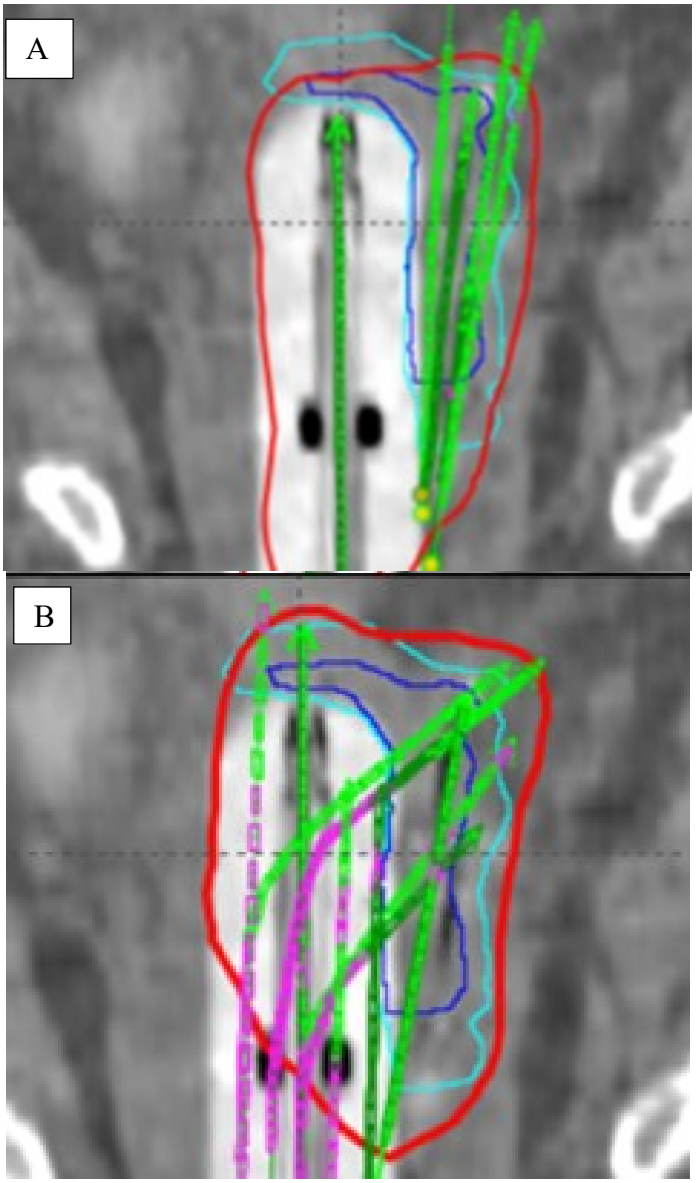


Figure 1.24 Dose distribution for A) original treatment applicator and B) patient-specific applicator. The HRCTV is represented by cyan, the GTV in blue, the 100% isodose line in red. The digitized needles are represented by the green lines. B) shows an improvement in the dose coverage for the HRCTV at the top of the vault.[41]

For a 3D printed gynecological brachytherapy applicator to be used in a clinical setting, the material of the applicator must be compatible with the brachytherapy workflow.[42] It must be biocompatible, sterilizable, and safe for CT scans that produce images with little artifacts. Cunha *et al.* evaluated PC-ISO (Stratasys, Eden Prairie, MN) as a material for the applicator.[42] It is a commercially available material that is FDA-approved, biocompatible, thermoplastic and can be sterilized. PC-ISO showed equivalent dose properties to water at HDR brachytherapy energies and was compatible with brachytherapy planning system and workflow, with no artifacts when imaged with CT.[42] The results of their study showed that cylinder applicators printed with PC-ISO improved treatment, in terms a more patient specific treatment plan.

While 3D printing applicators can provide a customized treatment plan that better suits each patient, the work to produce the applicator according to images is time-consuming work, as contouring the applicator within the TPS is dependent on the contouring skills of the planner.[34] The applicator is contoured through one modal image, such as a CT scan. Therefore, the contour of the applicator may affect the contouring accuracy The materials used in 3D printing techniques are also expensive, which can lead to difficulty in applying this technique clinically.

Risk analysis and patient comfort are critical factors that also must be assessed. When 3D printing the applicator, the channels for the catheters must be circular and consistent to ensure needle access. The roughness of the exterior of the applicator must be smooth to reduce friction and improve patient quality.[38] Patient comfort is number one priority during applicator insertion and removal.

1.9 Research Goals

Every patient's target volume, OARs and disease make-up is unique and may be best served with a unique solution tailored to their disease. Current vaginal brachytherapy patients at the QEII Cancer Centre are treated with vendor supplied applicators, such as the Miami. The Miami applicator comes in different diameters; however, the catheter positions are pre-set within the applicator. Patients treated with interstitial gynecological brachytherapy are typically treated with a MUPIT applicator. The MUPIT applicator allows for template needle placement, with the template sutured to the patient and needles implanted through the perineum and inserted until they traverse the tumour.

These intracavitary and interstitial plans with vendor supplied applicators can be optimized to decrease dose to OARs and increase dose to the CTV as much as possible. A 3D-printed patient-specific multi-channel cylindrical applicator with catheter positions placed strategically throughout the applicator may allow the asymmetric cancers of the vagina to be treated more effectively. A hybrid interstitial/intracavitary applicator can also be created, where the needles enter the patient through the applicator and then leave the applicator to enter the target volume.

The purpose of this study is to design patient-specific gynecological brachytherapy applicators with custom catheter positions to create better treatment plans by increasing dose coverage to the CTV and reducing dose to OARs. Twenty-five past patients of the QEII Cancer Centre were de-identified and replanned using the applicators they were originally planned with. The patients were then planned again with patient specific catheter positions, with dose objectives compared between the two plans. It is our hypothesis that a customized, patient-specific applicator will improve the dose distribution compared to the plan with the applicator that was used during treatment.

CHAPTER 2 METHODS AND MATERIALS

In the work presented in this thesis, gynecological brachytherapy applicators with patient-specific catheter positions were created in the brachytherapy treatment planning system, Oncentra Brachy 4.6.2. Both intracavitary and intracavitary/interstitial hybrid applicators were designed to generate a new treatment plan to compare to a treatment plan calculated with the original applicator.

2.1 Patient Selection

In this retrospective Research Ethics Board (REB) approved study, the patient cohort was made up of 25 patients that have received brachytherapy treatment at the QEII Cancer Centre in Halifax. The patient selection criteria were as follows:

1. The patient received gynecological brachytherapy treatment with a Miami or MUPIT applicator.
2. The patient must have had CBCT or CT imaging for planning purposes.
3. The patient was not a typical a post-hysterectomy patient who would have received symmetric treatment to the vaginal cuff with a single channel cylindrical (SCC) applicator.
4. The patient was one of the last 25 patients who were treated at the QEII Cancer Centre, who also met the above criteria.

Out of the 25 patients that met the conditions, 12 patients were treated with the Miami applicator, and 13 were treated interstitially with the MUPIT. Stage II was the most common. The characteristics of the patients can be seen in Table 2.1.

Characteristics	Number of patients (n=25)
Brachytherapy Applicator	
Miami	12
MUPIT	13
Treatment	
EBRT + brachytherapy	24
Brachytherapy alone	1
Primary	17
Recurrence	7
Secondary Malignancy	1
Stage	
I	8
II	8
III	5
IV	1
Unknown	3
Primary diagnosis	
Endometrial Cancer	9
Vagina	14
Ovarian	1
Cervix	1

Table 2.1 Patient characteristics from chart review of past patients receiving gynecological brachytherapy at the QEII Cancer Centre

Oncentra Brachy Version 4.6.2 (Elekta) was used in this study. The patient plans were exported and anonymized using Oncentra, then reimported into the TPS and assigned a number, from 1 to 25. Patients 1 to 12 were treated originally with the Miami applicator and Patients 13 to 25 were treated with the MUPIT applicator. Under each patient case in the TPS, the original treatment plan was duplicated, with the original catheters deleted to allow the creation of a new plan that had customized catheters based off the location of the patient's CTV. The workflow of this study is straightforward and duplicated for each of the twenty-five patients.

2.2 Study Goals

The dose goals for this study are based off the ABS consensus guidelines for interstitial brachytherapy for vaginal cancer. The ABS guidelines recommend a D_{90} of greater than or equal to 100%.[32] To try and improve the dose delivered to a larger part of the CTV, our dose goal to achieve when optimizing a plan was established to be D_{95} of 100%. The high dose regions are analyzed by V_{150} and V_{200} for the CTV volume. Our goal is V_{150} of less than 50% and V_{200} of less than 15%, adapted by the study of brachytherapy for malignancies of the vagina using 3D printing.[43] For the cumulative dose for the bladder and rectum, ABS recommends an EQD2 D_{2cc} of less than 65 Gy and 80 Gy, respectively.[32]

2.3 Study Workflow

The workflow of the study is shown in in Figure 2.1. The first step of the process is contouring the applicators, followed by placing new catheters on the duplicated plans, based on the patient's anatomy. IPSA and graphical optimization were then used to achieve the goal of dose to 95% of the volume equal to the prescription dose (D_{95} = 100%). The dose distributions and DVH analysis were collected from the planning system. Quality indices described in Chapter 1.6.5 were calculated, and the OAR D_{2cc} dose was converted to EQD2.

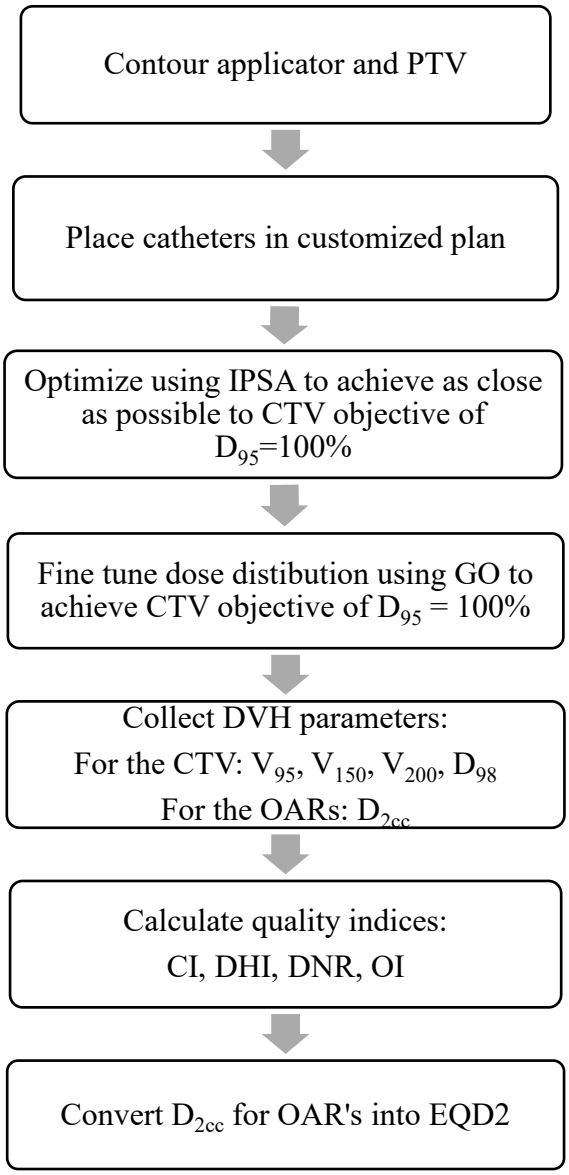


Figure 2.1 Workflow of the study

2.3.1 Contouring

Oncentra Brachy has a target definition tool that allows the user to easily define target volumes in the images. For each patient, the CTV and OARs were previously contoured from the treatment. The CTV was contoured in red. The OARs for all patients included the bladder and rectum. In Patient 1 to Patient 12, the sigmoid was contoured in the original dataset for 3 out of 12 plans, therefore, the sigmoid was not included in the analysis, but it was used in the IPSA

optimization when present. For Patient 13 to Patient 25, the urethra was contoured as an OAR in 4 out of 13 plans, like the sigmoid, the urethra was not included in analysis but was used in IPSA optimization when present. The bladder was contoured in yellow and the rectum in brown.

The applicator could be seen clearly on all the images. The contouring of the applicator was done using the pearl tool to ensure a perfectly cylindrical applicator resembling what was used for treatment, shown in Figure 2.2.

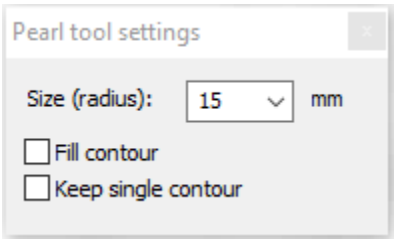


Figure 2.2 Pearl tool for contouring on Oncentra Brachy TPS. The radius is the size of the circle, which provides a perfectly cylindrical applicator, just like the original applicator.

A PTV was also contoured for each case. The PTV in this study does not fall under the usual definition of a planning target volume. The PTV was used as a planning construct to ensure that the source positions outside the CTV can be activated. The PTV was a copy of the CTV, adding ¾ of the applicator so that catheters within the applicator but not within the CTV are able to be activated. A comparison of the CTV and PTV for one of the patients can be seen in Figure 2.3.

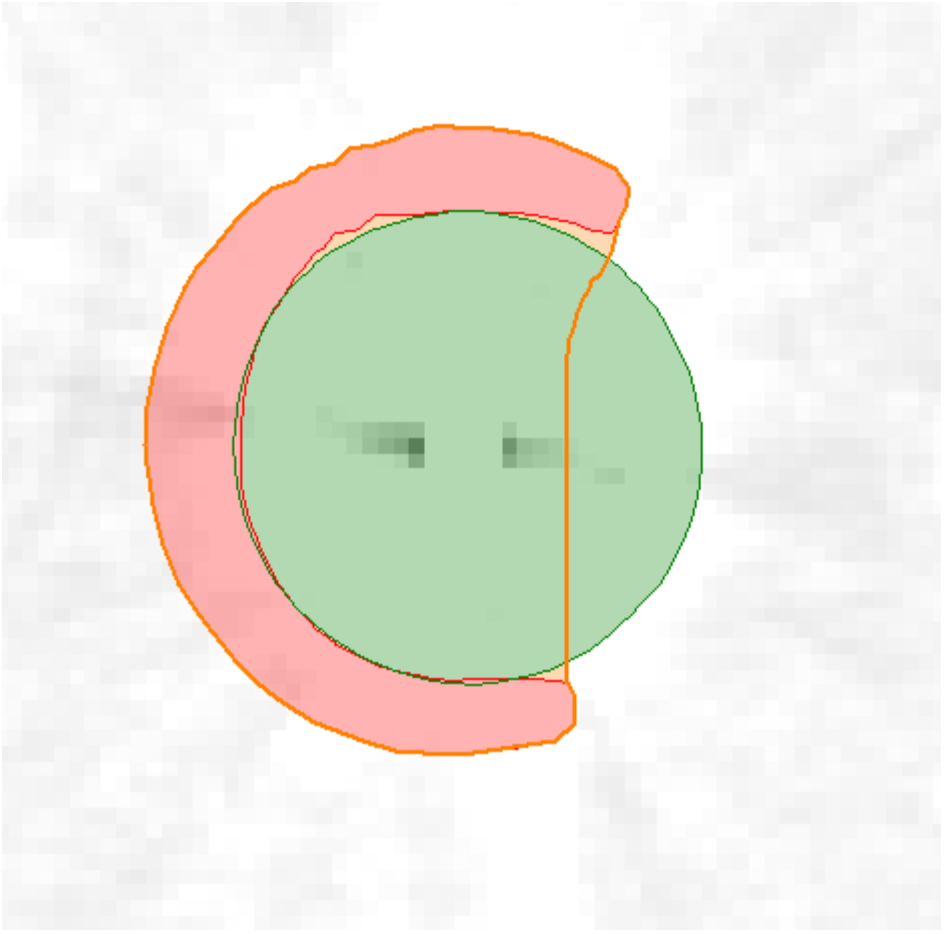


Figure 2.3 CTV versus PTV. The CTV is indicated by the red target surrounding the applicator (green). The PTV is indicated by the orange line, a copy of the CTV and including part of the applicator for optimization purposes.

The PTV must be contoured for use as an optimization structure for IPSA, as per Section 1.5.1. IPSA can only activate dwell positions within the target structures, with an activation margin, during optimization.[23] Once the applicators and PTV were contoured for each patient, the catheters can be reconstructed for each customized patient-specific plan.

2.3.2 Catheter Placement

For the original treatment plan, the catheters were already placed in their respective location that were used for treatment, as viewed on the planning images. These catheters were not edited, and the plan was only re-optimized using IPSA and GO with the same dose goals as

the patient specific plan, as discussed in Section 1.5. The catheter reconstruction function in Oncentra Brachy enables customized, patient-specific plans to be created. The catheters can be placed anywhere within the applicator, with the goal of creating a more homogeneous dose and conformal target coverage.

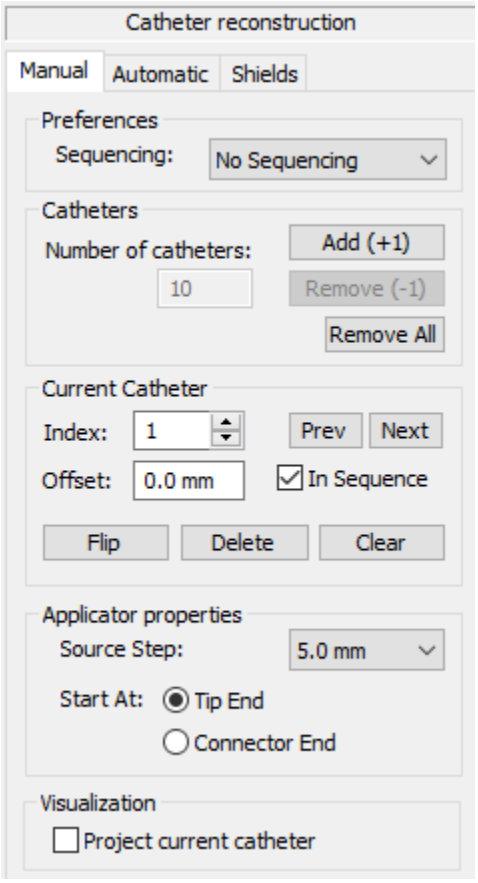


Figure 2.4 Catheter reconstruction tool on Oncentra Brachy

The catheter is placed on a slice beyond the superior end of the applicator, then followed down the length of the applicator using the project catheter tool, until the inferior end of the applicator was reached. In the TPS software, there is no limit on the number of catheters that can be placed, or the distance between each catheter as it is all just digital reconstruction.

With the existing equipment available for the afterloader at the QEII Cancer Centre, the choice of 6F (6-French) Flexible catheter with a 2 mm diameter was chosen for placement within the hypothetical 3D printed applicator. Previous work by another group found that when 3D printing an applicator, the tunnel which the catheter will enter must be 3.3 mm in diameter.[36] This is to ensure that the catheter can fit in the respective hole without force or kinking. This led to the discovery of the minimum allowable distance between each catheter. To account for the 3.3 mm tunnel, each catheter must be at least 5 mm apart, from the middle of the tunnel to the middle of the tunnel. This is to ensure that the tunnels will not overlap, and each catheter will have its own tunnel. The minimum distance between the catheter and the edge of the applicator, also referring to previous work, was determined to be at least 5 mm.[36]

On the patient-specific plans, the reconstruction tool was used to place catheters within the applicator for Patient 1 to Patient 12. For Patient 13 to 25, as well as Patient 5, for reasons outlined in Chapter 3.1.1, a hybrid interstitial/intracavitary applicator was created. Every interstitial catheter began within the applicator, then exited the applicator and entered the CTV. The measure tool was used to determine the width of each CTV. The measure tool measures the distance between two points on image. It is indicated by the colored stripped lines connecting each catheter in Figure 2.5.

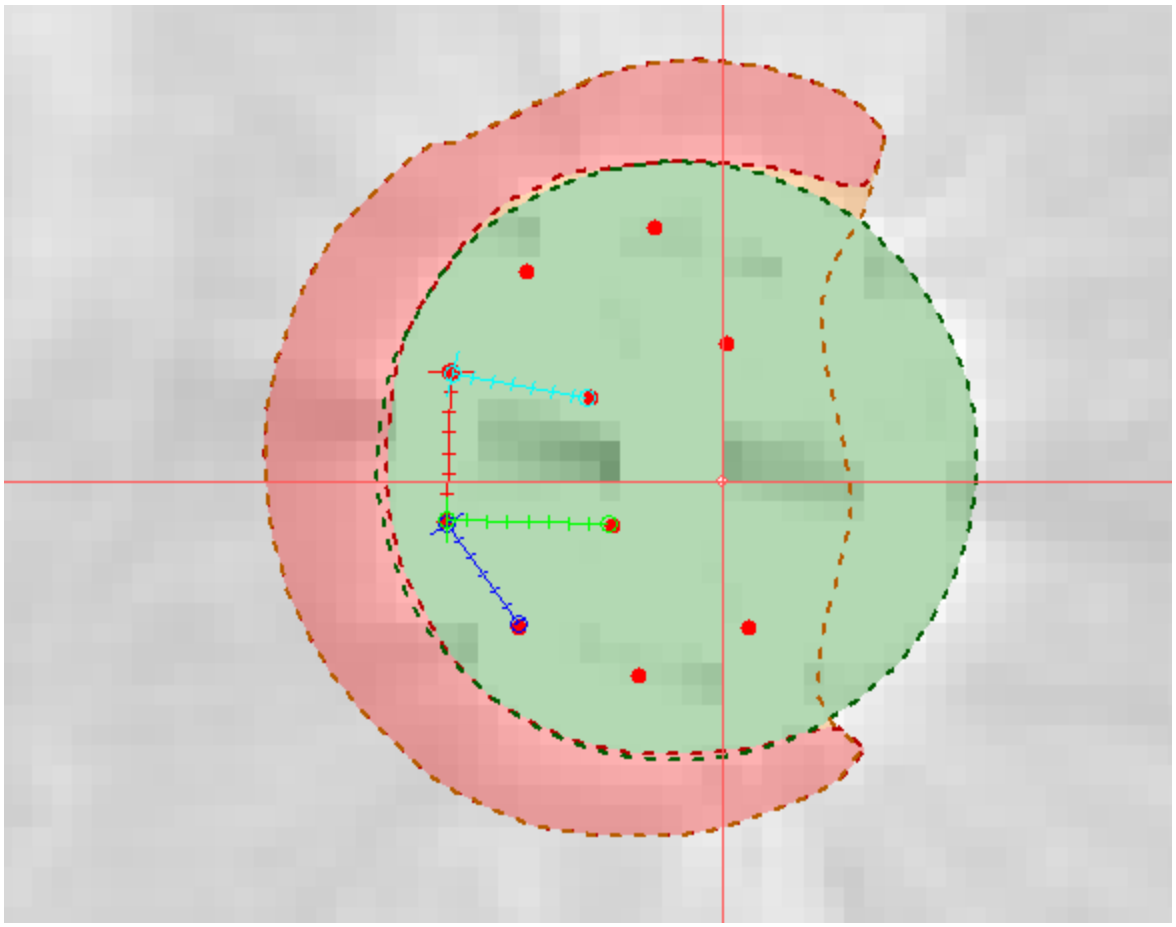


Figure 2.5 Measure tool in Oncentra Brachy. The catheter positions are represented by the red dots. The stripped lines between the catheters are the measurements.

2.3.2.1 Intracavitary Catheter Placement

For Patient 1 to Patient 12, catheters were placed only within the applicator. The image rotation crosshairs were placed so that both ends of the target volume were 180 degrees apart. This is seen in Figure 2.6. A catheter was placed at each end of the CTV.

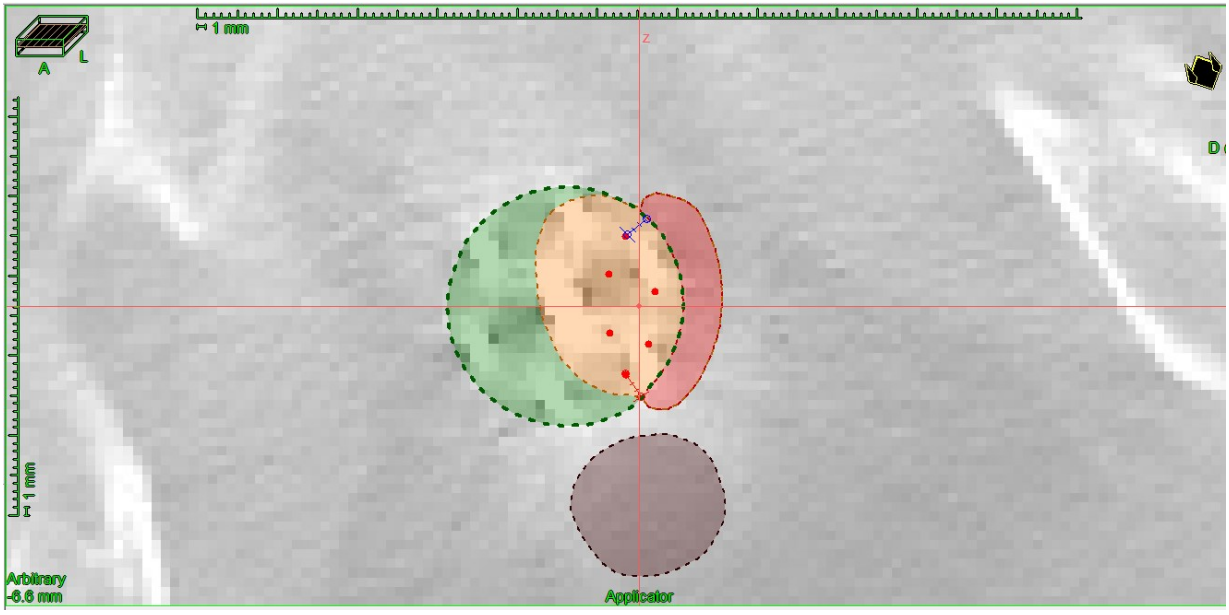


Figure 2.6 The image rotation cross hairs are indicated by the solid red lines in the whole image. These are lined up with the edges of the CTV, then using the measure tool, a catheter is placed on either end. For this case, two rows of catheters were placed.

If the width of the tumour was less than 5 mm, a single row of catheters was digitized along the edge of the applicator, shown in Figure 2.7. If the width of the tumour was at least 5 mm, two rows of catheters were used, shown in Figure 2.8. This was determined through pre-study testing on the planning system. The pre-study test included a 3 mm, 5 mm, and a 10 mm target volume. For all target volumes, a single row of catheters and double row of catheters were placed and compared. The patient dose metrics improved for a 5 mm and 10 mm target volume with a double row of catheters. The dose metrics did not improve for the 3 mm target volume with a double row of catheters.

Before each catheter was digitized, it was checked that the distance between each catheter and the edge of the applicator was at least 5 mm. Figure 2.6 shows Patient 2 who had a target thickness of 5.8 mm. This patient's rectum was also near the target, and for this reason, a catheter was not placed at the edge of the CTV that is close to the rectum.

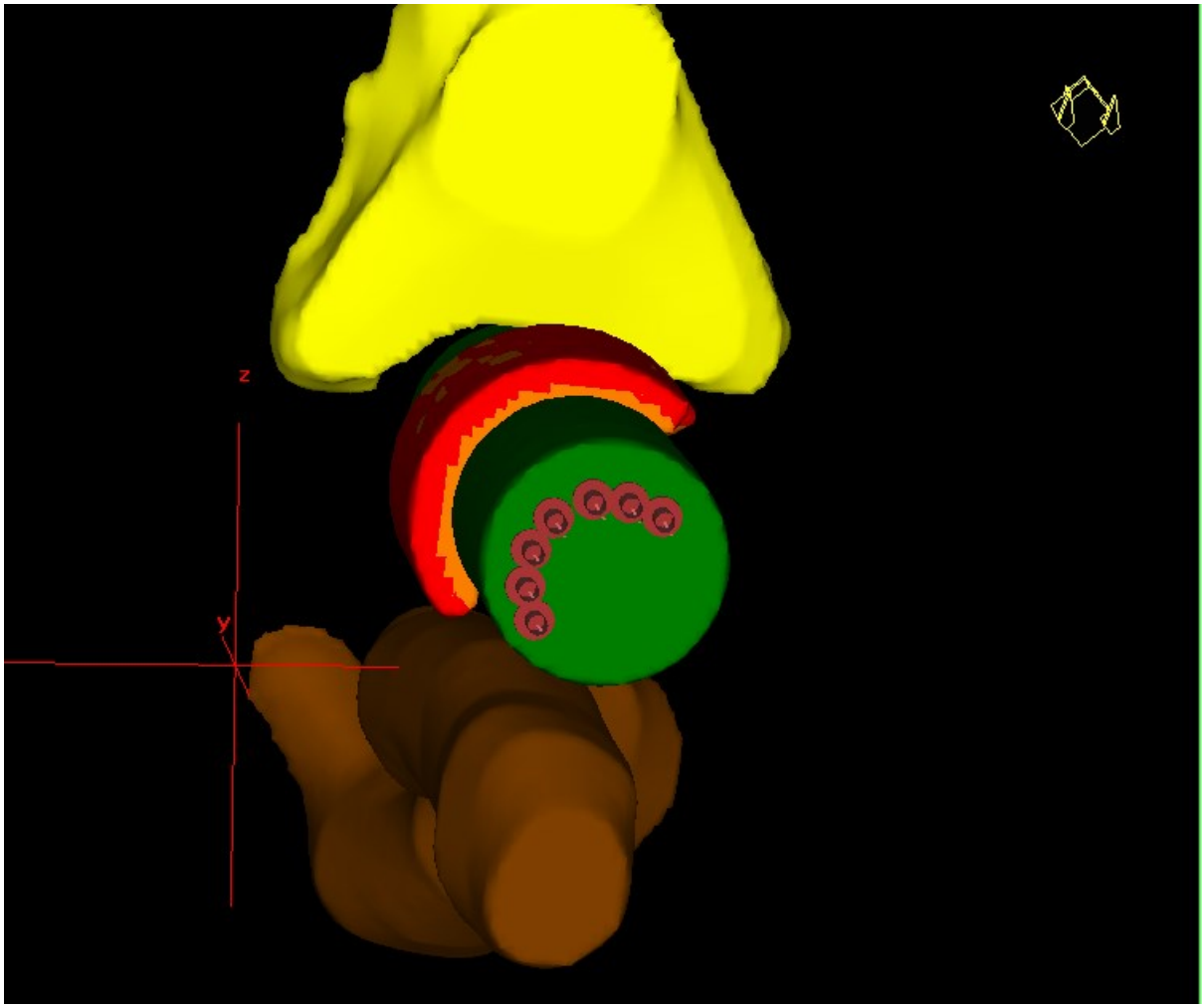


Figure 2.7 Single row of catheters for Patient 3. The applicator is green, the CTV & PTV are red and orange, rectum is brown, and bladder is yellow. The red circles on the end of the applicator represents each catheter position.

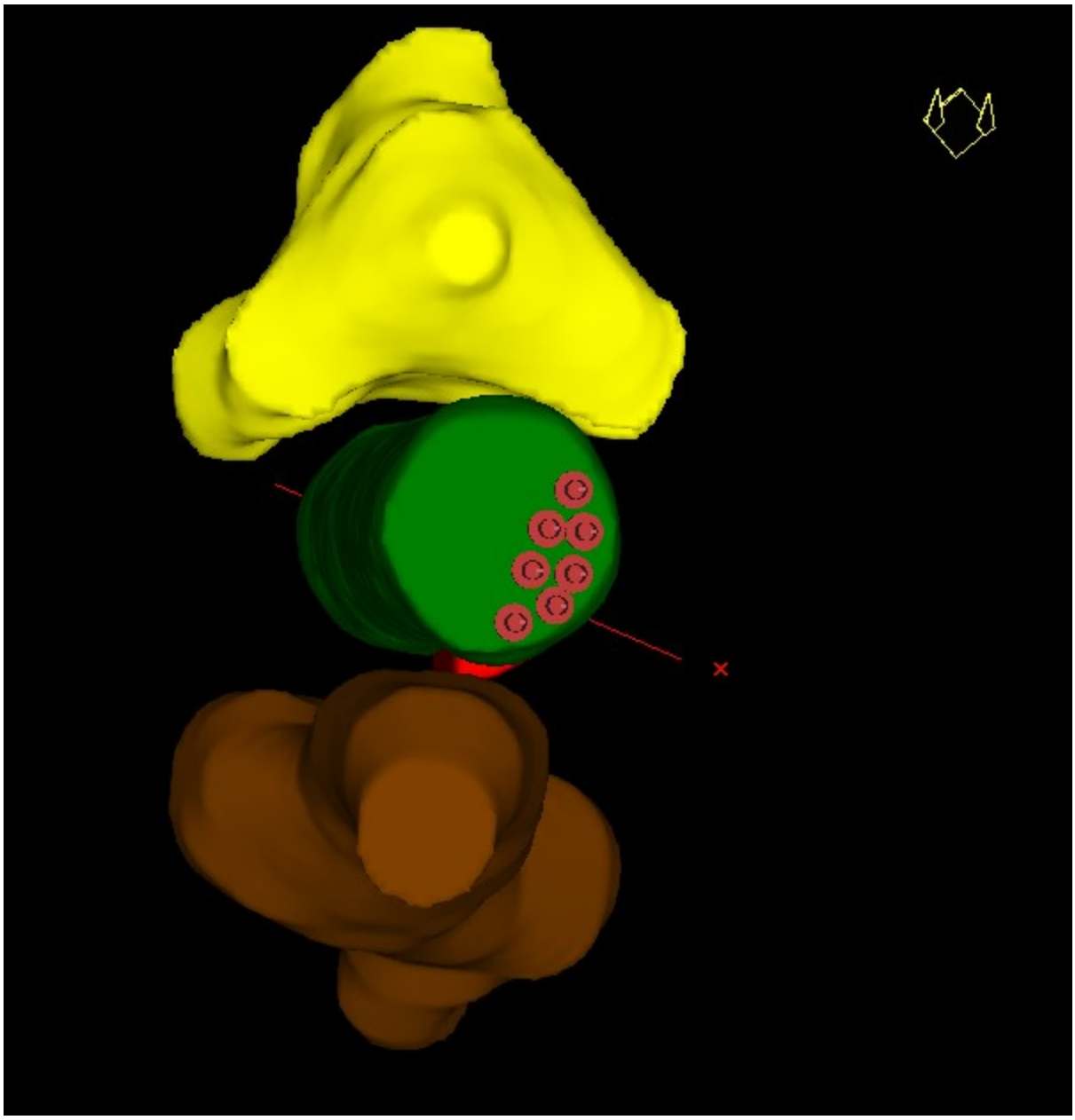


Figure 2.8 Double row of catheters for Patient 2. The applicator is green, the CTV & PTV are red and orange, rectum is brown, and bladder is yellow. The red circles on the end of the applicator represents each catheter position.

2.3.2.2 Interstitial Catheter Placement

For Patient 13 to Patient 25, the catheters were placed both within the applicator and exiting the applicator and entering the CTV. The distance requirements of 5 mm between each catheter, and between the applicator and applicator surface remained the same. The catheters that

exited into the target volume were placed strategically within the CTV to ensure dose coverage for the entire volume. Catheters were also placed within the applicator in the same matter as the intracavitary plans, with the caveat of not introducing any sharp bends during digitization that would violate the maximum curvature of the brachytherapy source. If the catheter had any paths that would be radical (and not gradual) deviations from a straight line, then there is the potential for the 6F catheters not to fit within the applicator and/or for the source to become lodged within the applicator. [36] Figure 2.9 shows Patient 25. The red dots display the catheter positions, some remain within the applicator and others enter the CTV.

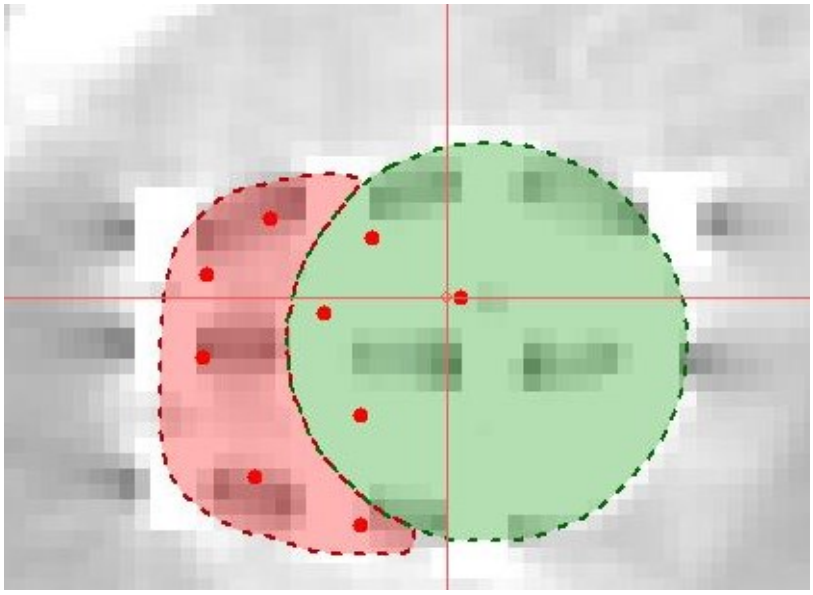


Figure 2.9 Patient 25 from the study. The red represents the CTV, and the green represents the applicator. The red dots represent each catheter position.

Figure 2.10 shows the interstitial needles that exit the applicator and enter the CTV. Some catheters also remain within the applicator.

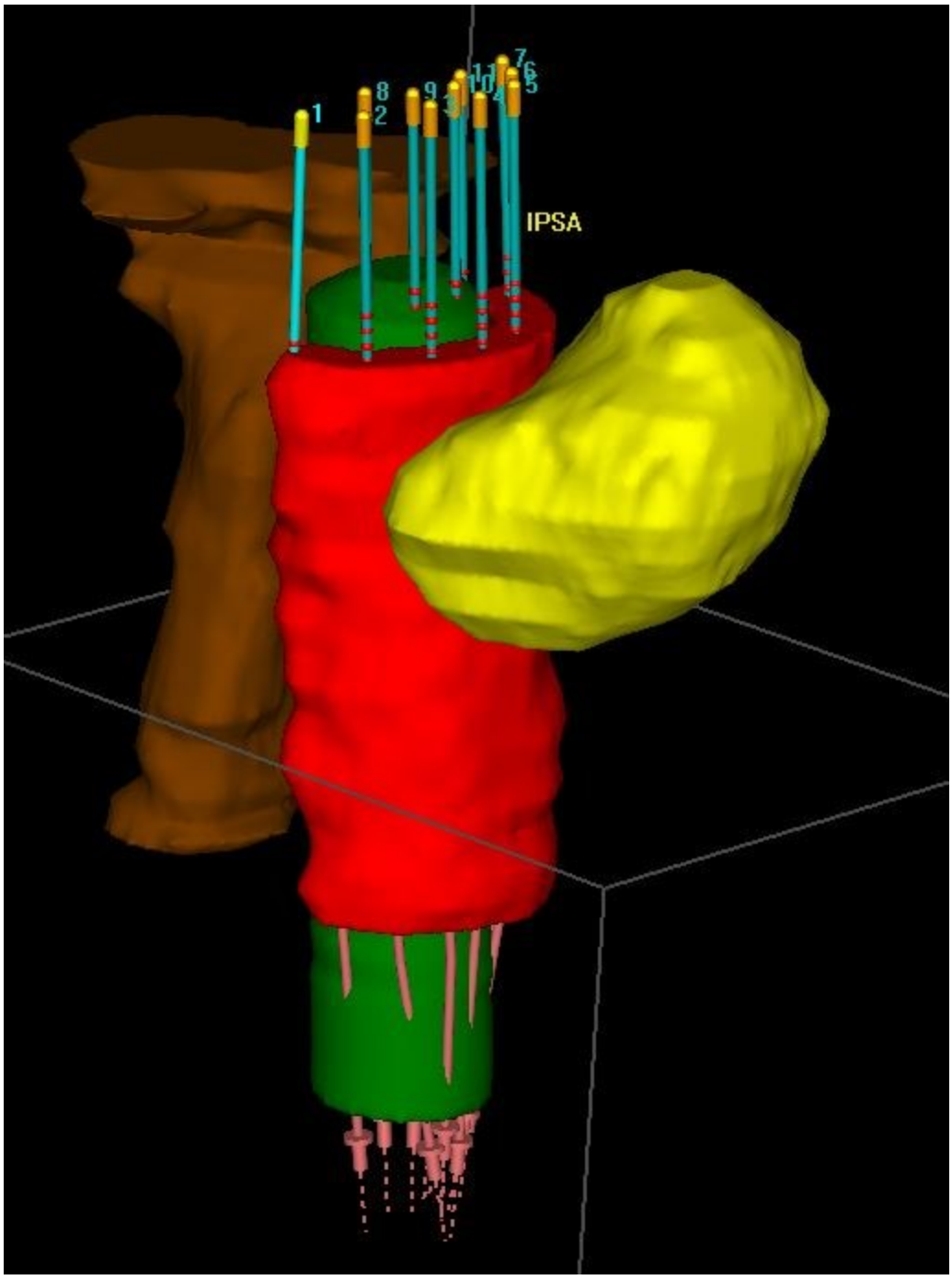


Figure 2.10 An example of an interstitial case. The applicator is green, the CTV is red, rectum is brown, and bladder is yellow. The red lines represent each catheter position.

2.4 Plan Optimization

As mentioned in Section 1.5, the dose optimization algorithms used for the study are IPSA and graphical optimization. Each plan had different dose prescriptions for brachytherapy treatment, for example, 3 fractions of 6 Gy or 3 fractions of 5 Gy, etc. The prescription can be entered using the prescription dose tab in Oncentra Brachy. (Figure 2.11) For each patient, the prescribed dose was already entered in the prescription dose tab from the original treatment plan.

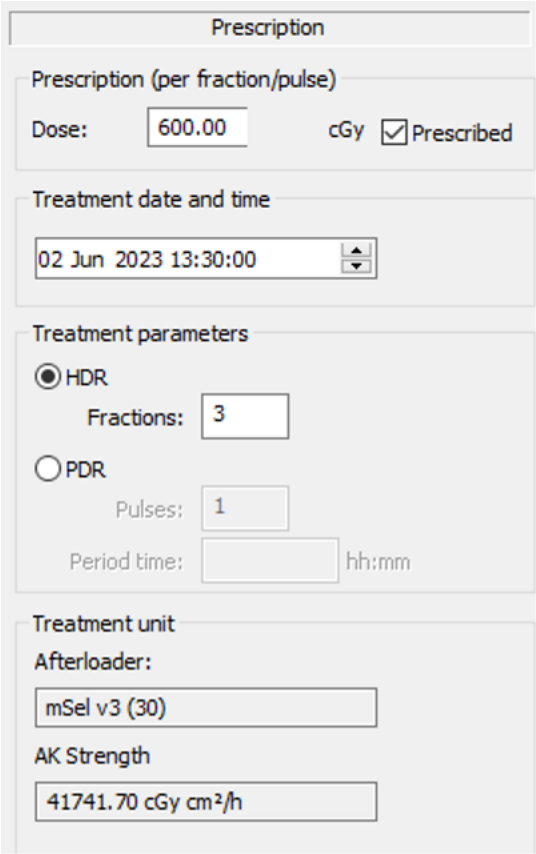


Figure 2.11 Dose Prescription tab on Oncentra Brachy TPS.

Once the catheters are reconstructed, IPSA was used to optimize each plan. The IPSA tab can be seen in Figure 2.12.

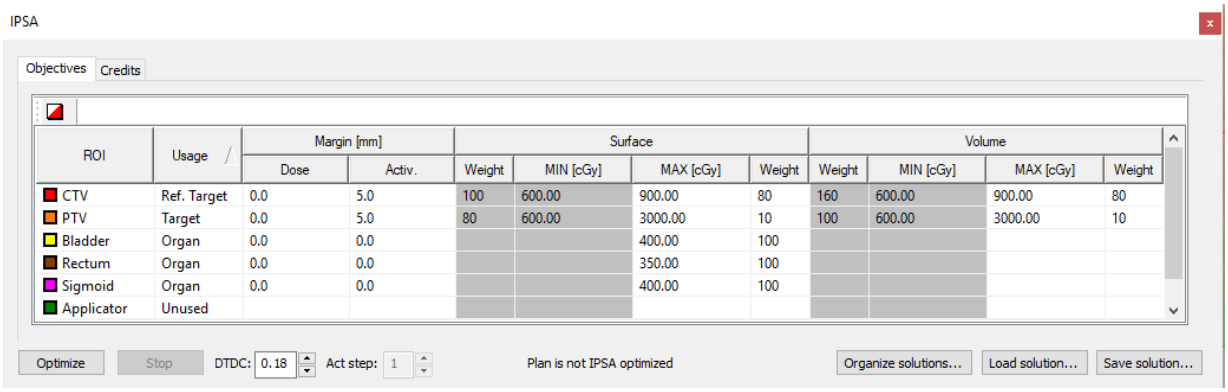


Figure 2.12 IPSA Objectives

The CTV was set as the Reference Target because this is the volume that will be treated. The PTV was set as the Target, and as discussed in Section 1.5.1, is the planning structure used only for plan optimization and not evaluation. The PTV includes all the catheters. IPSA has two distinct types of dose objectives - surface, and volume. The points on the surface, used to satisfy the surface objectives, are located near the surface of the volume and controls coverage of the CTV. The points for the volume objective are located within the target to control dose homogeneity.[23] The bladder and rectum were set as organs, and only volume dose points are optimized, because we do not want additional dose coverage of the OARs. The OARs for the surface were set to a maximum of 400 cGy for the bladder and 350 cGy to the rectum. When the sigmoid and urethra were present, a maximum surface dose of 400 cGy was used. These values were used in a study of IPSA plans by Liu *et al.*[44]

The minimum dose for the surface and volume of the CTV and PTV was set as the prescription dose, and the maximum dose was set to 150% of the prescription dose. Each objective also can have a weight, set from 0 to 200, to define its importance relative to other objectives.[23] This was adjusted as needed to optimize the plan to achieve the plan goal of D_{95} of 100%. The DTDC constraint was set to 0.18, this is the constraint used in clinic for prostate

cases, as per Section 1.5.1. The activation margin for the CTV and PTV was set as 5 mm. This is to ensure that catheters within 5 mm of the CTV and PTV can be activated and optimized. Once the plan was optimized once using IPSA, the weighting factors of the CTV, PTV and organs at risk were adjusted until the value of D_{95} was close to 100%.

Graphical optimization was used to adjust the isodose lines in areas where dose coverage was lacking, to achieve D_{95} of 100% if it was not already achieved. Graphical optimization is used by mouse-clicking and dragging an isodose line to decease or increase the dose to the surrounding area based on the direction the isodose line is dragged. When adjusting the dose with graphical optimization, the user can adjust the dose "globally" (all dwell times are affected for all dwell positions) or "locally" (only the dwell times of the dwell positions near the location of the mouse-click change) or a variable weighting of global and local.

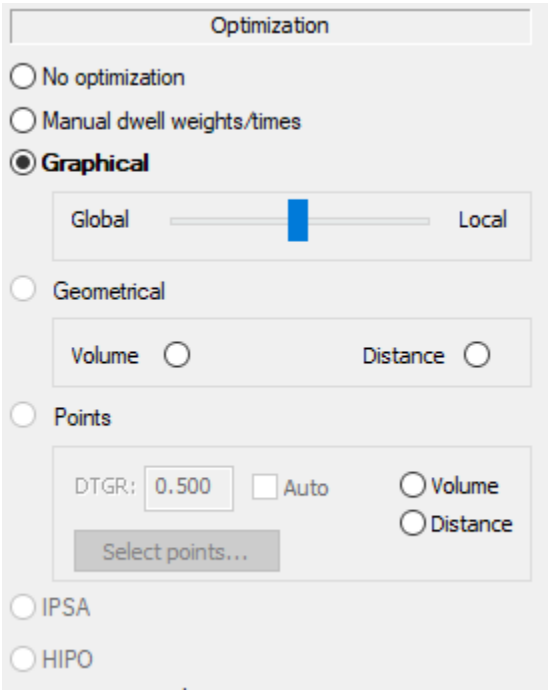


Figure 2.13 Optimization tab. Note that for this study, only graphical optimization and IPSA were used in the optimization of the plans.

2.5 Data Collection

Once each plan was optimized to achieve a D_{95} of 100%, the required data (see Table 2.2 below) was recorded from the TPS. The data was first analyzed using the dose distributions. A sample dose distribution can be seen in Figure 2.14. The 100% isodose line, in red, is defined by the prescription dose and should roughly conform to the CTV in a successful plan. The higher isodose lines, represented by 150% and 200%, should shrink around the brachytherapy sources and be limited within the CTV. The lower 50% isodose line, in green, spread outwards from the target volume, showing regions of low dose.

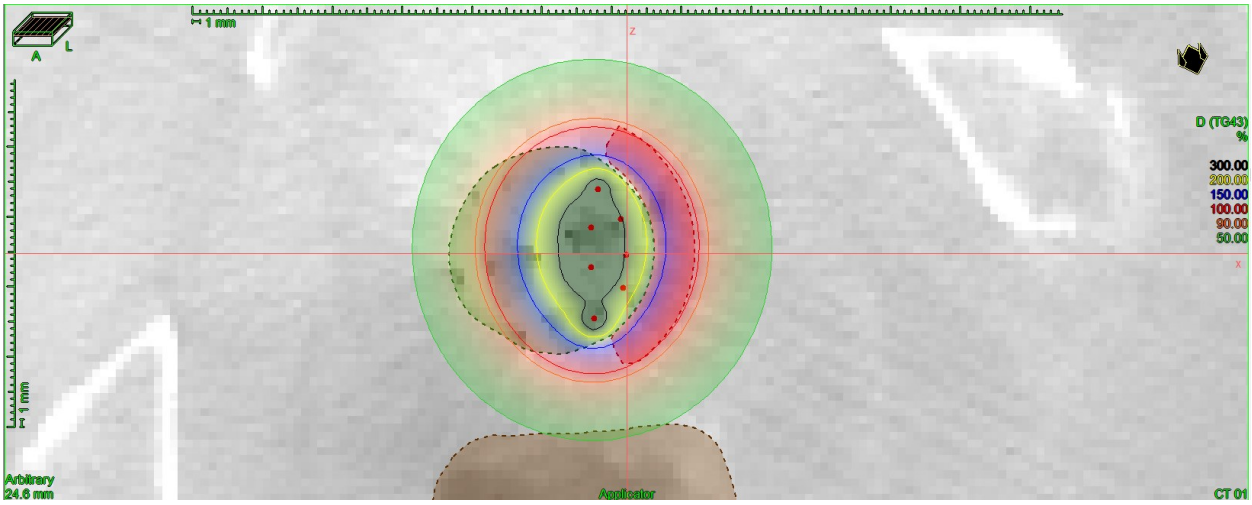


Figure 2.14 Sample dose distribution of patient 2. The applicator is shown in green, rectum in brown, bladder in yellow and CTV in red. The isodose lines are the solid lines surrounding the volumes.

The data was also analyzed using the results of DVH curves. These values provide information about the amount of dose delivered through each volume, as well as the amount of volume receiving a specific amount of dose. The values to analyze from the DVH can be seen in Table 2.2.

V_{95}	Percentage of volume receiving at least 95% of the prescription dose
V_{100}	Percentage of volume receiving at least 100% of the prescription dose
V_{150}	Percentage of volume receiving at least 150% of the prescription dose
V_{200}	Percentage of volume receiving at least 200% of the prescription dose
D_{98}	Prescription dose delivered to at least 98% of the target volume
D_{2cc}	Prescription dose delivered to 2 cubic centimeters of the target volume

Table 2.2 Definition of Dosimetric parameters

D_{98} was chosen to analyze percentage of dose to the CTV. There are no strict guidelines for D_{98} or V_{95}, so these values were simply compared between both plans. The high dose regions and plan homogeneity can be analyzed through V_{150} and V_{200}. The dose constraints of V_{150} to the CTV volume was set to be less than 50%, and the V_{200} to be less than 15%.[43]

As per ABS guidelines, the organs at risk should include descriptions of dose delivered to the volume.[32] For this study, D_{2cc} was analyzed. The ABS guidelines also recommend converting the OAR dose to equivalence dose in 2 Gy fractions (EQD2), described in Section 1.6.6. One patient did not receive external beam treatment (see Table 2.1) when they were treated in clinic, but for consistency, the EBRT prescription dose was assumed to be 45 Gy in 25 fractions for all patients, as this is the common fractionation scheme for EBRT and brachytherapy. The brachytherapy prescription dose was dependent on dose that was used for actual treatment and was found in the original plan. Based on the ABS recommendations, the goal for the rectum was a cumulative dose of less than or equal to 65 Gy and less than or equal to 80 Gy for the bladder.[32]

To calculate EQD2, Equation 7 from Section 1.6.6 was used. To account for EBRT and brachytherapy, EQD2 was calculated for both treatments and then summed. For OARs, the α/β ratio is 3 Gy since these tissues are classified as late responding. The d is represented by the dose per fraction, in Gy, and the D is represented by the total dose.

To assess the distribution of dose within the CTV, quality indices were chosen to analyze the data. Yan *et al*. compared multichannel cylinder and 3D printed applicators for vaginal cuff brachytherapy. Based on this study, it was chosen to analyze the conformity index (CI), dose homogeneity index (DHI), dose non-uniformity index (DNR), and the overdose index (OI). The conformity index describes the conformity of the target volume, and the ideal CI is 1. The dose homogeneity index describes how homogeneous the target volume is, the larger DHI value the more homogeneous the target volume. Dose non-uniformity index describes how non-uniform the dose is within the target, the lower the value the lower the non-uniform distribution within the target volume. The overdose index describes if there are any high dose hot spots within the target. The ideal parameter is 0.

For each dose parameter recorded for the plans, the Wilcoxon rank signed test was applied. The Wilcoxon rank signed test is a non-parametric statistical test to compare two means, and it is used when the data is not normally distributed. As the data in this study are not normally distributed, the Wilcoxon signed rank test is therefore an appropriate test to assess statistical significance. For example, a p-value less than 0.05 indicates there is strong evidence that there is a difference between the two plans, and there is a less than 5% chance that there is not actually a difference. A p-value of less than 0.05 was considered to be statistically significant. To be more restrictive, the clinical significance can also be assessed.

To further compare the optimized original applicator plan and the patient-specific plan, a box and whisker plot was used. A box and whisker plot shows the dispersion of the data and helps quickly identify the median value and any outliers of the data.[45] The box represents the range between the 25th and 75th percentile of scores. The median of the data is represented by the line that divides the box into two parts. The upper and lower whiskers on the box show the plans that scored outside the upper 25% and the lower 25% of scores, respectively. Outliers of the data are represented as dots on the outskirts of the whiskers.[45]

CHAPTER 3 RESULTS AND DISCUSSION

The treatment plans for the original applicator and the patient-specific applicator were analyzed and compared using Oncentra Brachy TPS. The Wilcoxon rank signed test was applied to compare the differences between each patient's plans, with a p-value of less than 0.05 considered statistically significant.

3.1 Intracavitary Patients

3.1.1 Intracavitary Patients Summary

Patients 1 to 12 were originally planned using a Miami applicator. To assess the dose coverage and dose homogeneity within the CTV, V_{95}, V_{150} and V_{200} were analyzed. The results for each patient can be seen in Table 3.1.

	V_{95} (p=0.002)		V_{150} (p=0.0002)		V_{200} (p=0.0001)	
Patient	Original Applicator (%)	Patient-specific Applicator (%)	Original Applicator (%)	Patient-specific Applicator (%)	Original Applicator (%)	Patient-specific Applicator (%)
1	98.16	98.71	24.22	26.32	3.31	1.56
2	97.33	98.02	20.23	22.80	1.63	0.13
3	98.15	97.81	24.13	21.98	4.37	2.04
4	99.03	98.33	20.67	19.34	1.20	0.20
5	97.46	98.06	44.69	42.54	16.22	15.10
6	97.03	97.63	12.13	8.69	0.25	0.04
7 CTV1	97.03	97.64	41.15	27.78	14.47	2.10
7 CTV2	98.57	98.58	25.84	25.09	4.95	0.38
8	98.58	98.81	11.18	10.13	0.61	0.60
9	98.38	98.94	64.85	65.2	37.22	22.49
10	97.27	98.29	8.31	7.57	0.04	0.00
11	96.31	97.18	4.48	3.38	0.02	0.00
12 CTV1	98.57	98.63	22.75	8.35	6.09	0.89
12 CTV2	97.27	98.29	43.26	19.17	13.55	1.06

Table 3.1 Intracavitary patient data for V_{95}, V_{150}, V_{200}

Table 3.1 shows a statistically significant difference for V_{95}, V_{150} and V_{200} for the patient-specific plans over the optimized original applicator plans. This shows the volume of 95% prescription dose that is covering the CTV is greater for the customized, patient-specific applicator plans. The high dose regions within the patient-specific applicator plans are lower. V_{150} for the original applicator plans have an average of 26.3% and the patient-specific applicator plans have an average of 22.0% (p=0.0002).

For V_{95}, Patient 3 and 4 showed a lower coverage of the target volume. Patient 1, 2 and 9 showed a higher V_{150} region within the target volume, but an increased target coverage in all three cases. These decreases in plan quality could have been resulting from suboptimal placement of the catheters within the applicator. The increase in V_{150} may be due to the increase

in coverage (V_{95}) and increased dwell times needed to achieve the coverage. The optimal catheter positions can be found in further study on the optimization of these positions. V_{200} showed superior results for all Patients for the patient specific applicator plans, with an average of 7.42% for the original applicator plans, and 3.33% for the patient-specific plans (p=0.0001).

3.1.1.1 V_{95}

V_{95} reflects the relative volume of the target volume that receives at least 95% of the prescription dose. Every patient that was treated with an intracavitary applicator achieved at least 95% for both plans. Figure 3.1 shows a plot of the original applicator plans and the customized, patient-specific plans.

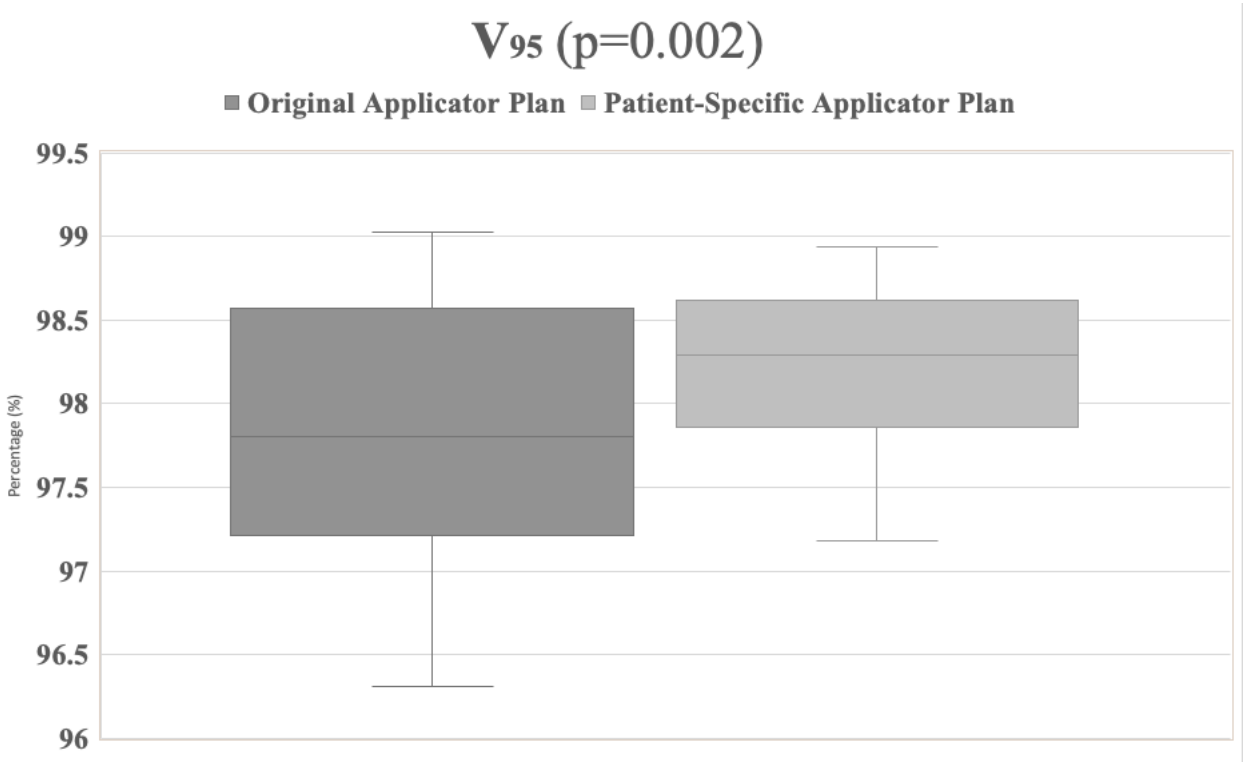


Figure 3.1 Box plot of V_{95} values for intracavitary original applicator plans and the patient-specific applicator plans.

From Figure 3.1, the median V_{95} is represented by the horizontal line within the box. The median is higher for the patient-specific plans. This shows a larger volume of the CTV received 95% of the prescription dose, resulting in improved dose coverage of the CTV. A higher number of patients with the original applicator plans achieved a V_{95} greater than the median of 97.80%, while a higher number of patients achieved a lower V_{95} than the median of 98.21% with the patient-specific plans. The patient-specific plans show statistically significant better coverage of the CTV.

3.1.1.2 *V_{150} and V_{200}*

V_{150} and V_{200} describe the volume of the CTV that contains the high dose regions. To avoid patient toxicity, the high dose regions should realistically be delivered within the applicator and limited as much as possible within the patient. The goal of V_{150} is less than 50% of the prescription dose, and less than 20% for V_{200}.

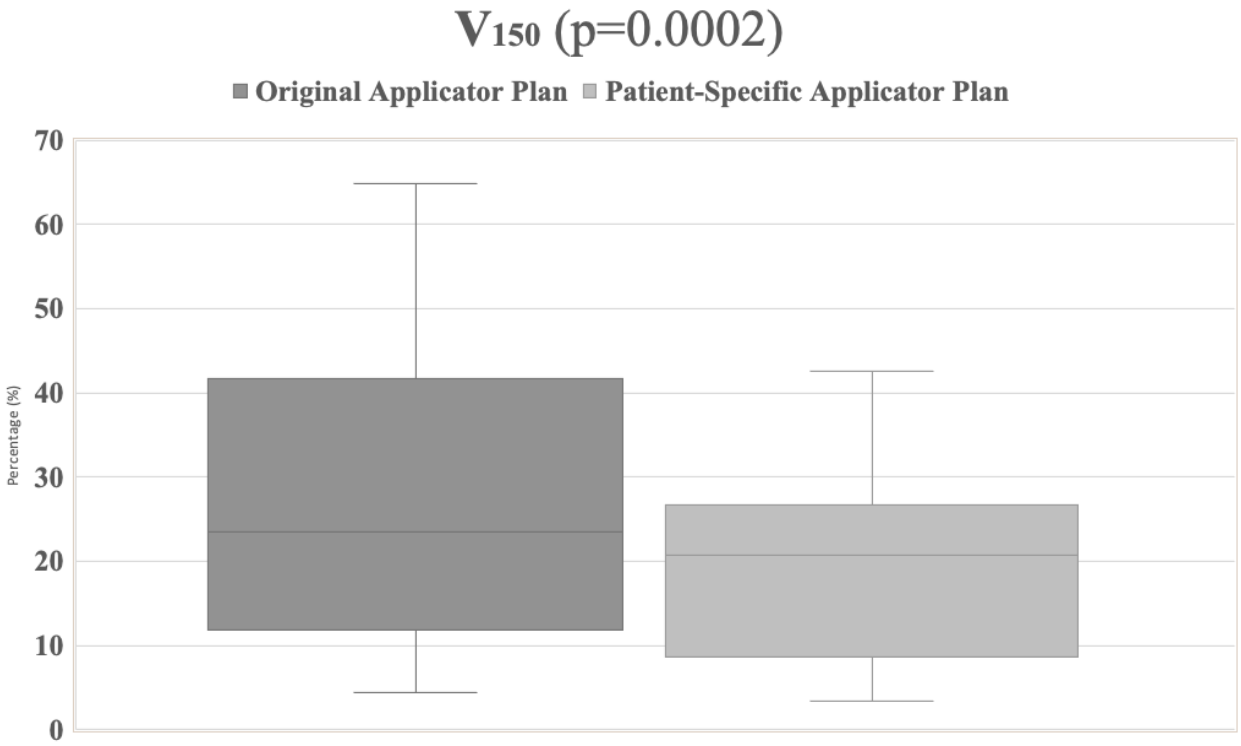


Figure 3.2 Box plot of V_{150} values for intracavitary original applicator and patient-specific applicator.

Figure 3.2 shows a box and whisker plot for the intracavitary patients for V_{150}. The patient-specific applicator plans have a lower median value, indicated by the solid line within the box. The lower median value shows that a lower high volume within the CTV is receiving 150% dose. The patient-specific plans are represented by a smaller box, indicating a less dispersed data set. For the original applicator plans, the box is larger indicating a more dispersed data set, and an average value higher than the patient-specific plans. The upper whisker shows a maximum V_{150} value for the patient-specific plans of 42.54%, while the original applicator plans have an upper whisker of 64.85%.

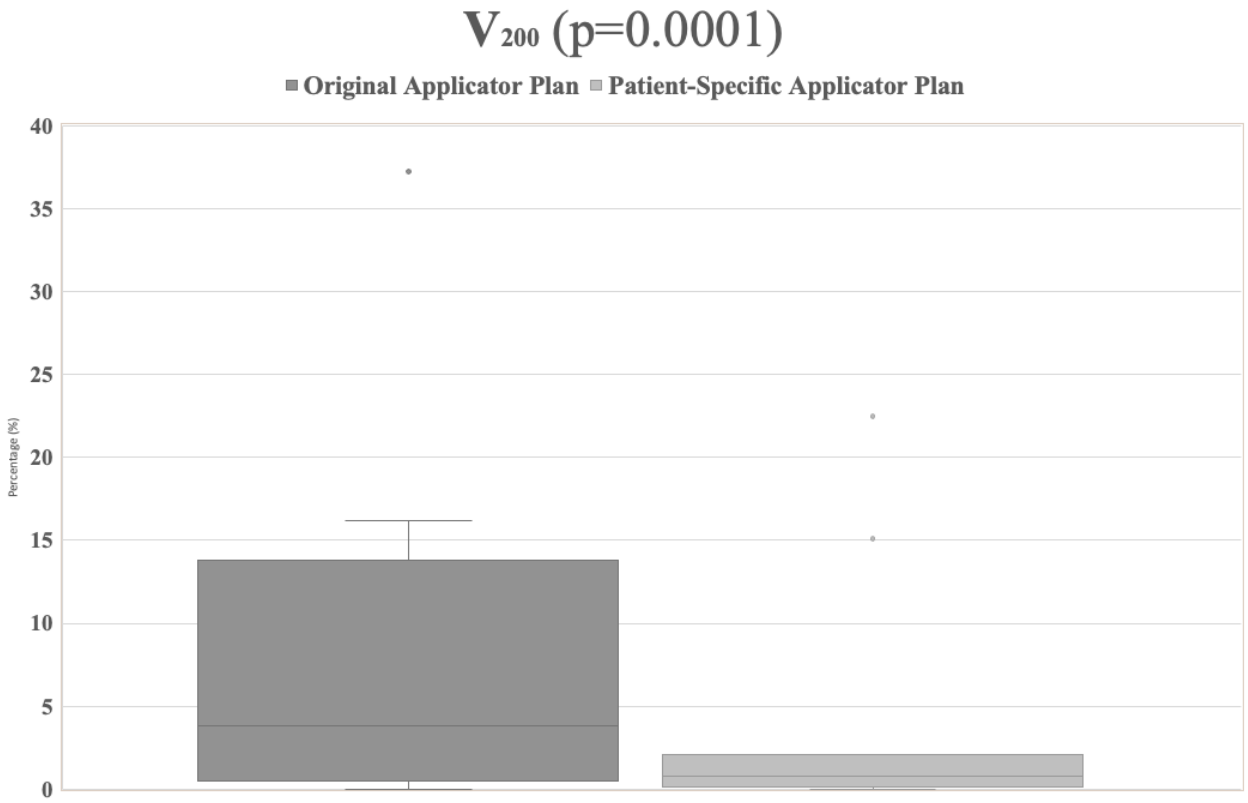


Figure 3.3 Box plot of V_{200} values for intracavitary original applicator and patient-specific applicator

Figure 3.3 shows the V_{200} values for the optimized original plans and the customized plans. The median is lower for the customized plans and again a smaller box indicating a less dispersed data set with a smaller high dose regions delivered within the CTV. The original applicator plan data has an outlier datapoint for V_{200} of 37.22%, which is the CTV1 plan for Patient 7. This patient had two CTVs, described in Section 3.1.2, and the original applicator had 7 pre-set catheter positions. The diameter of CTV1 was smaller than CTV2. When IPSA is used to optimize only one target volume can be set as the "Reference Target". For this case, the CTV2 is the larger volume so this was set as the reference. This caused overdosage to the smaller CTV1.

The outliers of the patient-specific applicator plans are 15.1%, and 22.49%, these are from these Patient 5 and Patient 9. Described in Section 3.1.1, Patient 5 had an air gap present

resulting in the V_{150} and V_{200} values to be large. Patient 9 had a CTV that surrounded the applicator, shown in Figure 3.4. This resulted in catheters needing to be digitized throughout the whole applicator. In addition, for Patient 9, the thickest part of the CTV is over 5 mm, at 6.6 mm. To decrease the V_{150} and V_{200} values, an interstitial hybrid applicator approach could potentially lower the high dose values within the CTV for Patient 9.

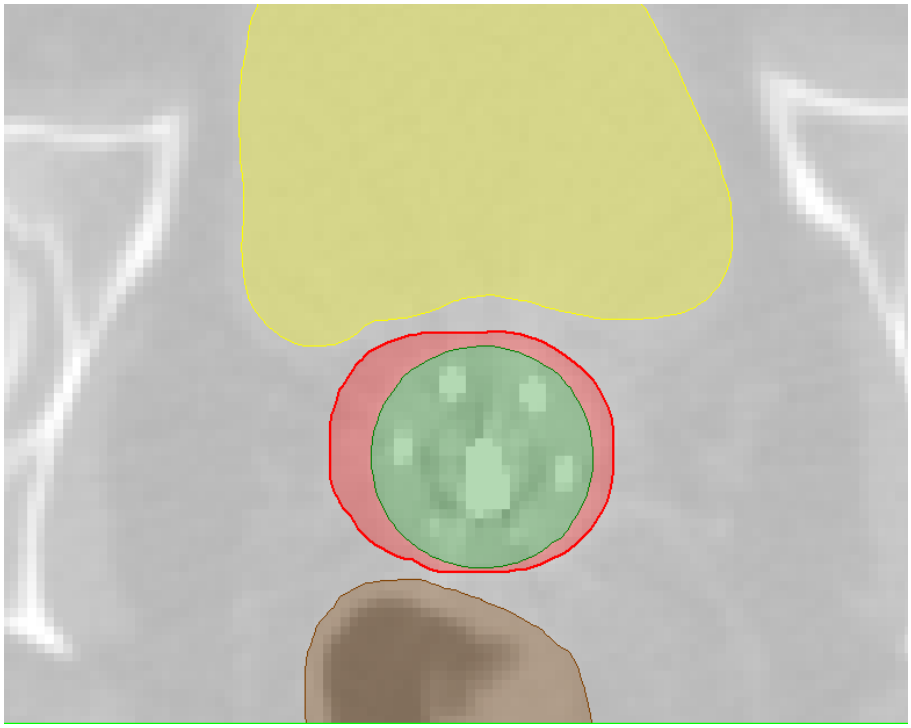


Figure 3.4 Patient 9 Contours. The applicator is in green, CTV in red, bladder in yellow and rectum in brown.

The V_{150} and V_{200} were difficult to lower when optimizing with respect to achieving a D_{95} value of 100%, as well as keeping the doses to organs at risk as low as possible.

3.1.1.3 D_{98}

To analyze the dose delivered to a higher percentage of the CTV, D_{98} was also analyzed in Figure 3.5.

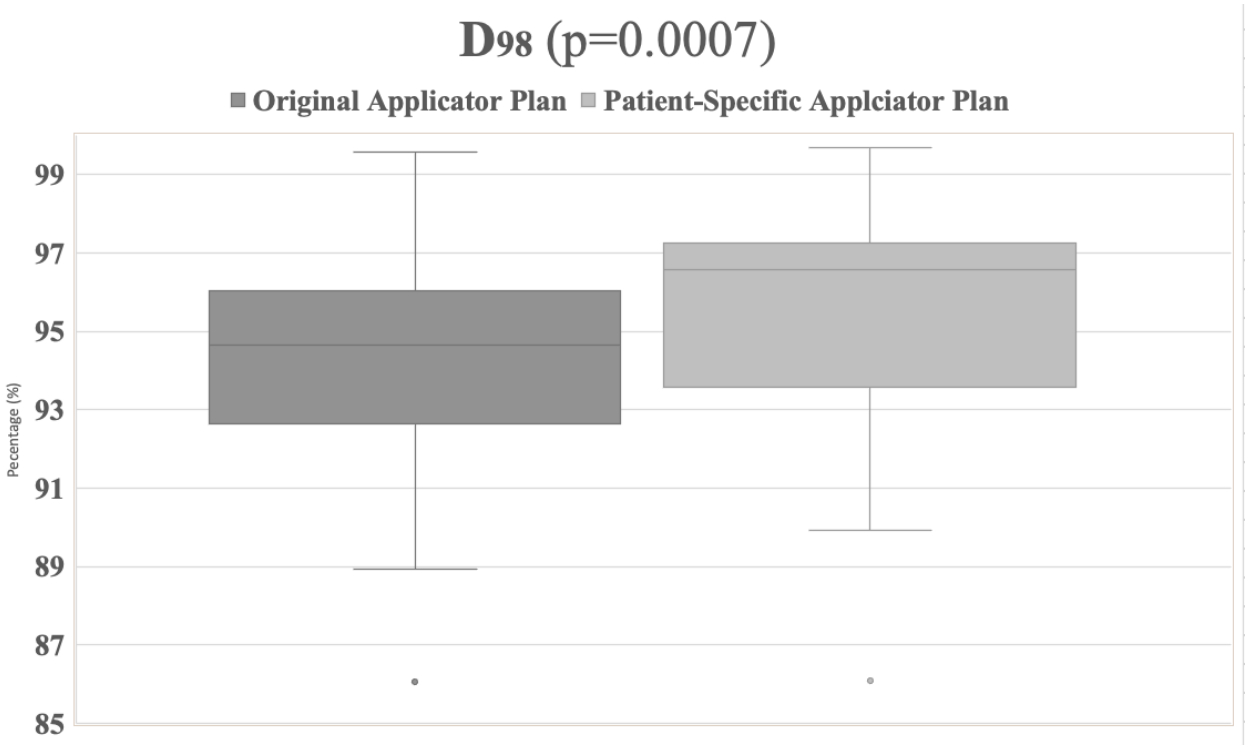


Figure 3.5: Box plot of D_{98} for intracavitary original applicator and patient-specific applicator

The patient-specific plans have a higher median, indicating that the average dose delivered to 98% of the target volume is greater for the patient-specific applicator plans. Both data sets are negatively skewed, meaning a larger number of patients are covered by a smaller D_{98} dose volume than the median. The outliers are 86.05% and 86.09% for the original and patient-specific plans, respectively. These are represented again by Patient 5 and Patient 9.

3.1.1.4 Organs at risk

Table 3.2 shows the dose delivered to the bladder and rectum.

	Bladder (p=0.001)		Rectum (p=0.001)	
Patient	Original Applicator Plan (Gy)	Patient-Specific Applicator Plan (Gy)	Original Applicator Plan (Gy)	Patient-Specific Applicator Plan (Gy)
1 6 Gy x 4 fx	1.60	1.50	3.23	2.93
2 6 Gy x 3 fx	3.95	2.76	3.62	3.07
3 6 Gy x 3 fx	2.22	2.21	3.02	2.55
4 5 Gy x 3 fx	1.76	1.28	2.93	2.66
5 5 Gy x 2 fx	5.03	4.80	5.30	4.82
6 6 Gy x 4 fx	1.33	1.41	2.72	2.67
7 6 Gy x 4 fx	4.07	3.64	3.67	3.55
8 6.5 Gy x 4 fx	0.75	0.62	3.67	3.46
9 5 Gy x 3 fx	3.45	2.91	3.77	3.23
10 5 Gy x 2 fx	3.50	3.06	4.23	4.05
11 7 Gy x 2 fx	5.41	5.10	5.30	5.40
12 6 Gy x 4 fx	3.35	2.81	3.92	3.48

Table 3.2 Intracavitary patient data for OARs. The numbers listed are the D_{2cc} values for the OAR for each plan

The dose delivered to the bladder and rectum was further assessed using EQD2. The desired dose objective for the bladder is D_{2cc} less than or equal to 80 Gy, with a dose objective of less than or equal to 65 Gy for the rectum. Table 3.3 shows the data for each patient for EQD2 D_{2cc} for both the bladder and rectum.

	Bladder (p=0.001)		Rectum (p=0.001)	
Patient	Original Applicator Plan (Gy)	Patient-Specific Applicator Plan (Gy)	Original Applicator Plan (Gy)	Patient-Specific Applicator Plan (Gy)
1	49.09	48.58	59.29	57.11
2	59.65	52.75	57.58	54.39
3	50.17	50.11	54.12	51.69
4	48.24	46.48	53.62	52.24
5	59.35	58.18	60.8	58.28
6	47.79	48.2	55.67	55.32
7	60.48	58.08	57.74	57.59
8	45.46	44.99	62.75	61.07
9	56.54	53.54	58.54	55.29
10	52.31	50.63	55.44	54.63
11	61.78	61.94	61.75	61.48
12	55.97	52.99	59.49	56.71

Table 3.3 Intracavitary patient data for the key OARs. Reported here is the D_{2cc} converted to EQD2.

In the intracavitary patients, the patient-specific applicator plans resulted in less dose to the bladder and rectum. The average for the bladder dose for the optimized original plans is 53.9 Gy and the customized plans is 52.2 Gy. For the rectum, the average is 58.1 Gy for the optimized original plans, and 56.4 Gy for the customized plans. Each of these values are lower than the dose goals.

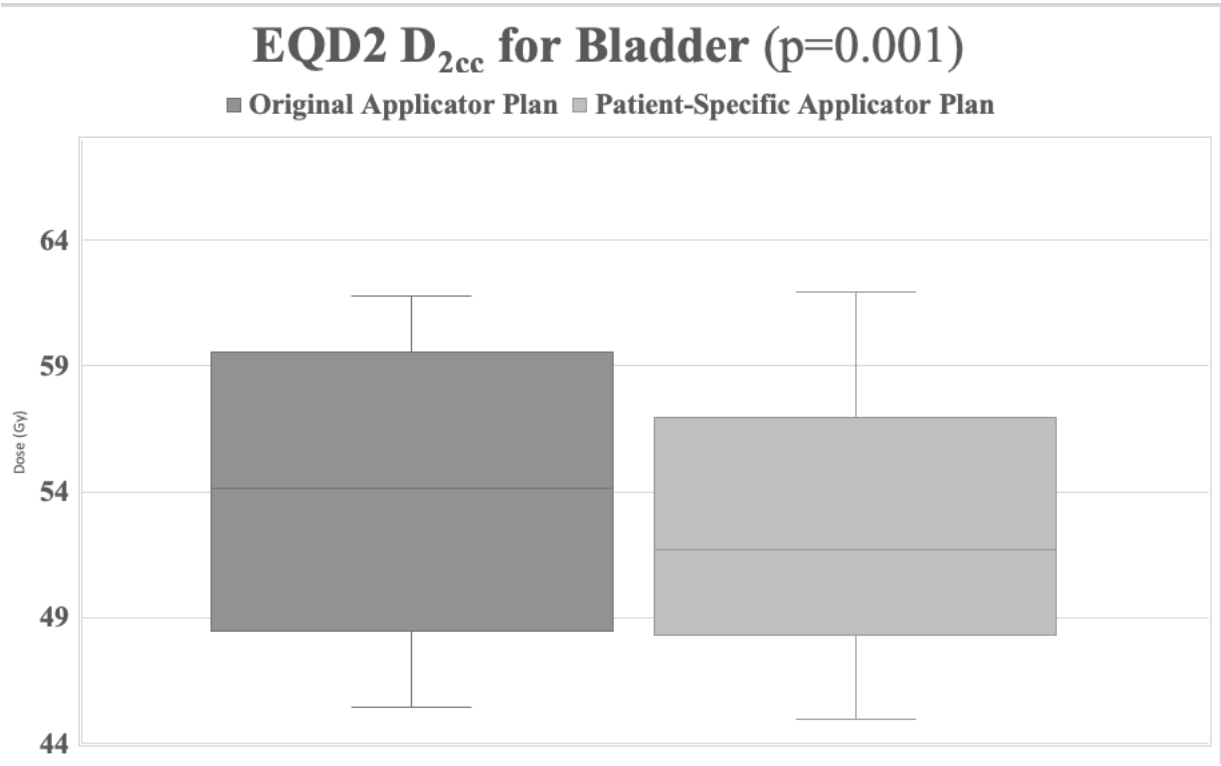


Figure 3.6 EQD2 D_{2cc} for the bladder for intracavitary original applicator and patient-specific applicator

The customized plans show a lower median value for the dose delivered to the bladder (Figure 3.6). The box for the customized plans is smaller than the optimized original plans, showing a more dispersed data set than the customized plans. The upper whisker for both datasets is higher for the customized plans, showing a more scattered dose distribution for these plans. The customized plans showed a superior bladder dose for each patient, except for Patient 6 and Patient 11. For Patient 6, the rectum at one slice is only 1.5 mm away from the CTV. For Patient 11, the rectum in one transverse slice is 2 mm away from the CTV. The short distance between the CTV and the rectum causes the optimization algorithm to try and lower the dose to the rectum, as much as possible. This can cause an increase of dose everywhere else, such as the bladder, to counteract it. For Patient 6, the increase in dose is 0.41 Gy, and 0.16 Gy for Patient

11. This is a very small increase when looking at the plan goal of D_{2cc} of less than 80 Gy to the bladder.

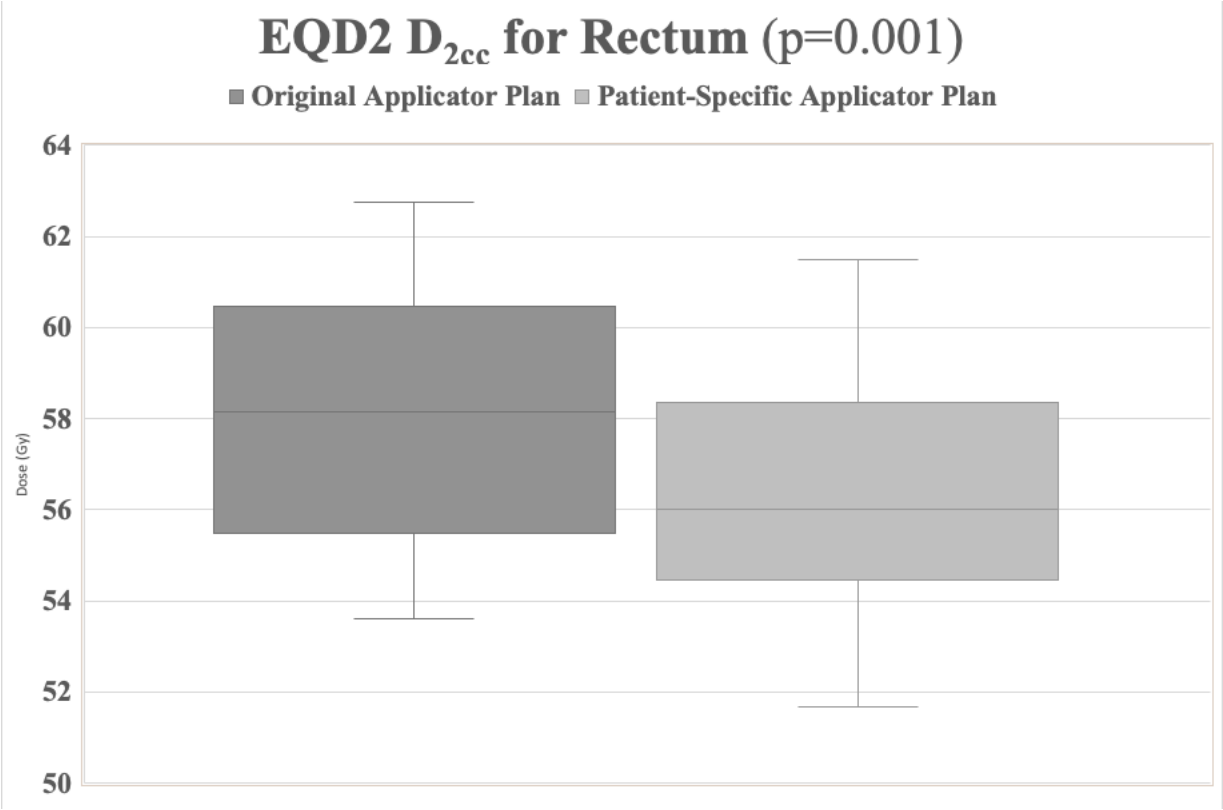


Figure 3.7 EQD2 D_{2cc} for the bladder for intracavitary original applicator and patient-specific applicator

The EQD2 dose delivered to the rectum is shown in Figure 3.7. The customized plans have a lower median value, indicating less dose would be delivered to the rectum in these plans. The lower whisker for the customized plans is a smaller value than the optimized original, indicating a lower minimum dose to the rectum for these plans, versus when treated with the optimized original treatment plans.

3.1.1.5 Quality Indices

As described in Section 1.6.5, quality indices were used to assess the dose within the CTV.

Index	Optimized Original	Customized Plan	p-value ($p<0.005$)
CI	0.977	0.984	0.0009
DHI	0.687	0.733	0.0007
DNR	0.277	0.226	0.0007
OI	0.078	0.037	0.0004

Table 3.4 Quality Indices for intracavitary patients

From Table 3.4, all quality indices show statistically significant improvement in values for the customized plans. Conformity index shows a higher statistically significant value for the customized plans, indicating a conformal dose distribution for the targets. The dose homogeneity index is also statistically higher for the customized plans, showing a more homogeneous dose within the CTV. The dose non-uniformity index is lower for the customized plans, indicating a smaller volume of non-uniform dose within the CTV for these cases. The overdose index is also statistically lower for the customized plan, describing a smaller region of overdose within the CTV.

3.1.2 Patient 5

For Patient 5, the CTV is large when compared to the other intracavitary patients, with a maximum target thickness of 12.4 mm, and a length of 95.2 mm. The bladder is also adjacent to the CTV. The prescription dose for this patient is 5 Gy times 2 fractions. A 3D representation of this patient can be seen in Figure 3.8. The applicator is shown in green, the CTV in red, the bladder in yellow and the rectum in brown.

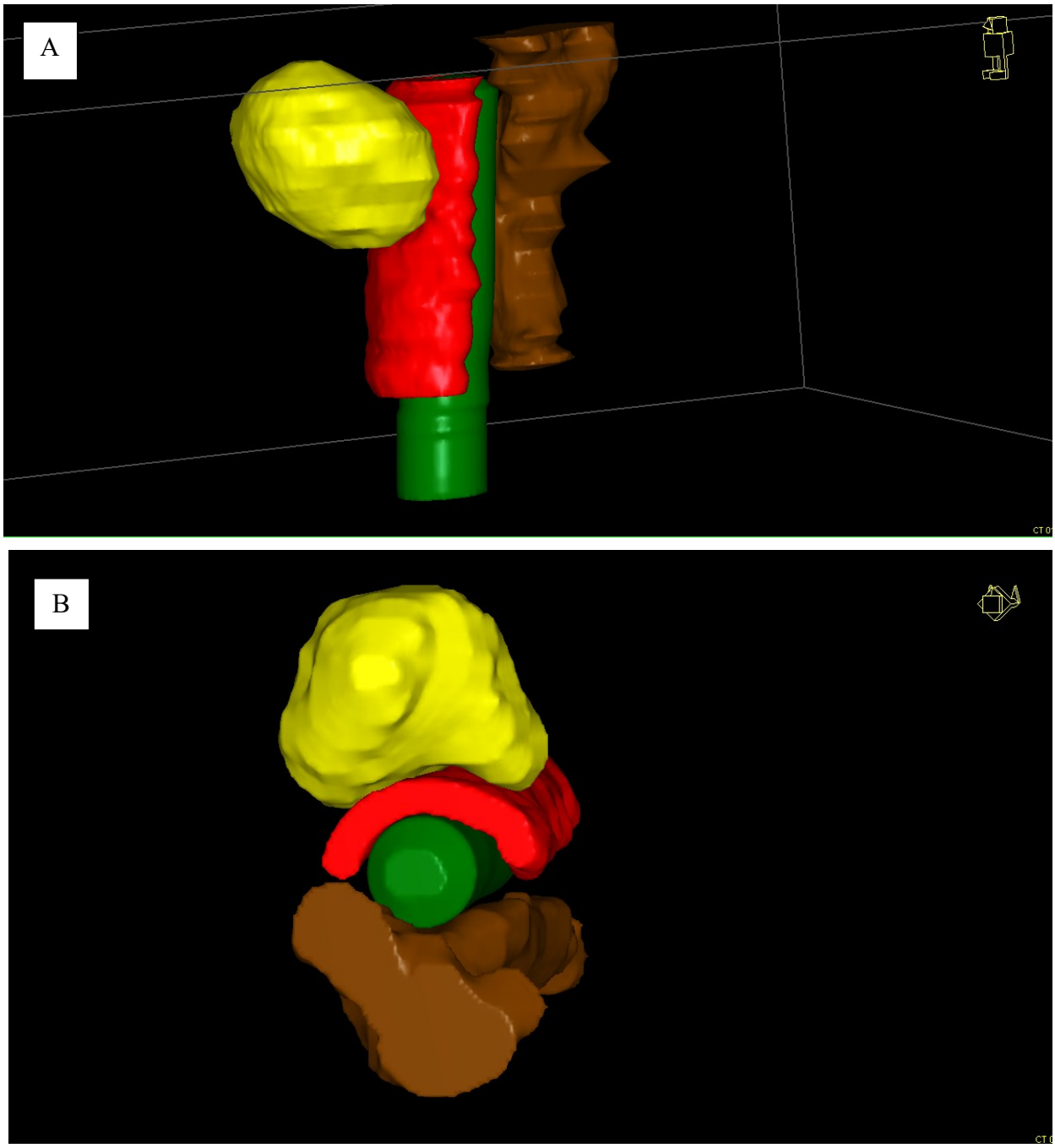


Figure 3.8 3D representation of Patient 5. The applicator is shown in green, CTV in red, bladder in yellow and the rectum in brown. A) shows the anatomy in the sagittal plane while B) is in the transverse plane

When observing the patient's images, air gaps are present between the applicator and the CTV. The air gaps can be seen in Figure 3.9, indicated with an arrow.

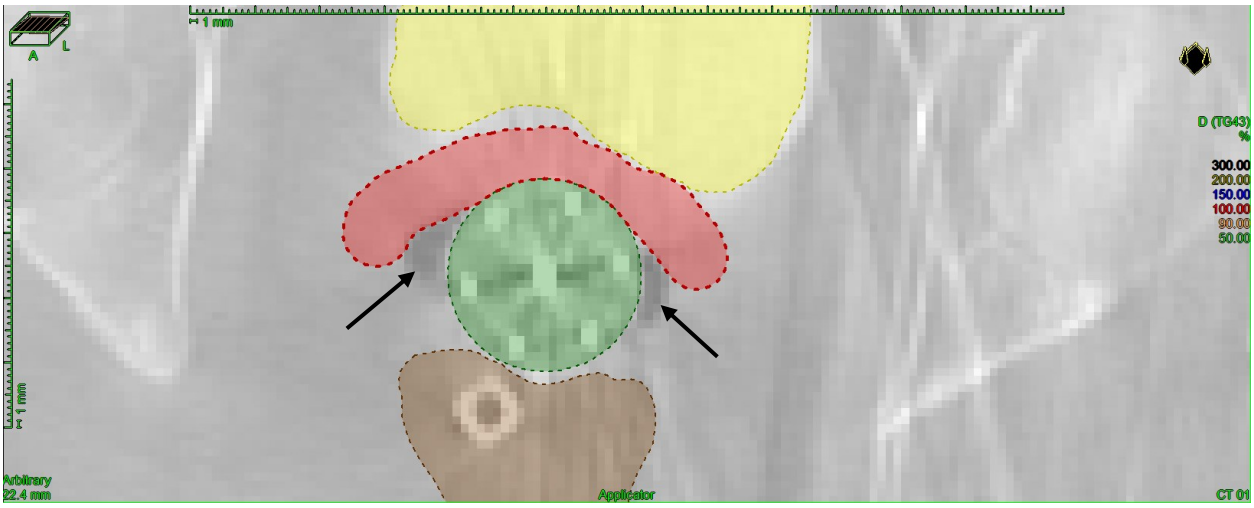


Figure 3.9 A slice of Patient 5 with air gaps indicated by arrows. The applicator is shown in green, rectum in brown, bladder in yellow and CTV in red.

Due to the air gaps present, it shown to be difficult to create a treatment plan that will satisfy the desired objectives, described in Section 3.2, so an additional interstitial/intracavitary hybrid applicator plan was also made. For the hybrid applicator plan, the catheters were within the applicator, then exited into the CTV. A 3D representation of the catheter positions can be seen in Figure 3.10.

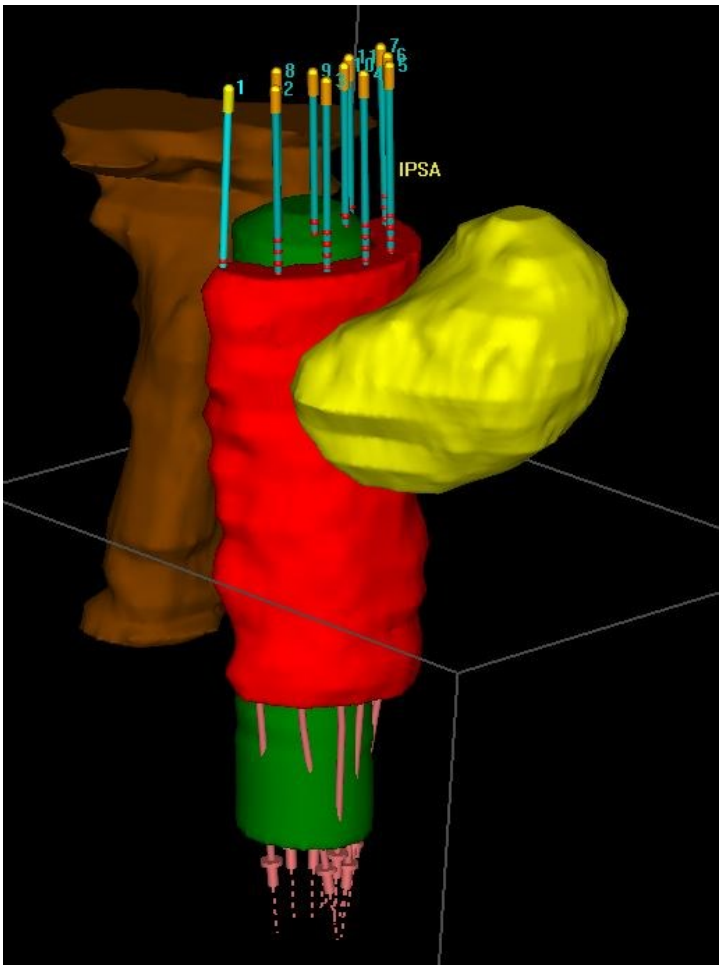


Figure 3.10 Patient 5 with a hybrid applicator. 4 catheters remain within the applicator and 7 catheters exit the applicator and enter the CTV. The applicator is shown in green, CTV in red, bladder in yellow and the rectum in brown. Note that in a real treatment plan created to treat the patient, the catheters would not extend a large distance beyond the target, to avoid physical injury to normal tissues.

The three plans were optimized using IPSA and graphical optimization, with the dose distribution for all plans in Figure 3.11.

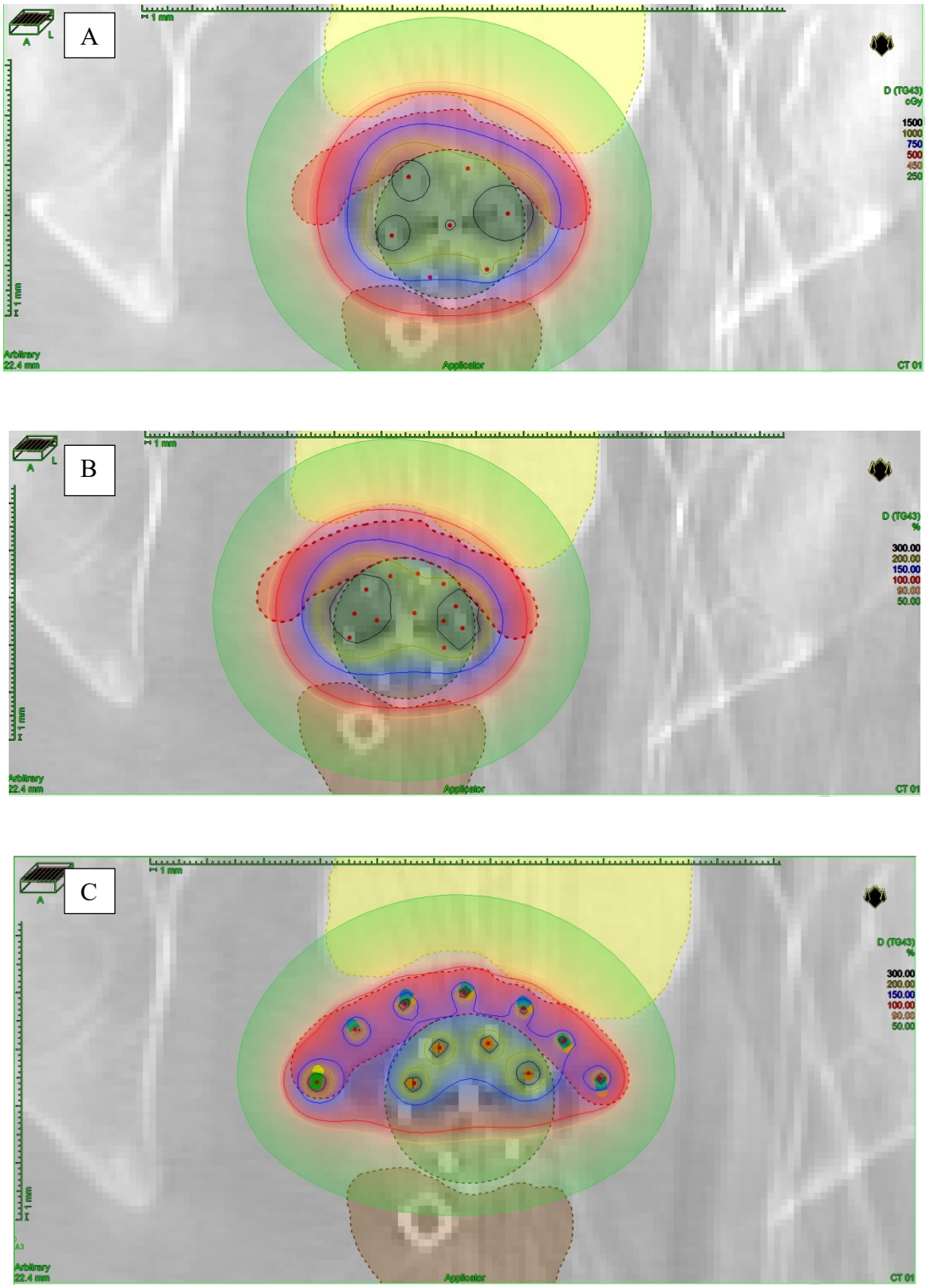


Figure 3.11 Dose Distribution for Patient 5. A) shows the original treatment plan, B) shows the patient-specific treatment plan, and C) shows the interstitial/intracavitary hybrid applicator treatment plan.

The original applicator plan has 7 catheters activated, the patient-specific intracavitary applicator treatment plan has 12 catheters activated, and the hybrid applicator plan has 7 catheters activated within the CTV and 4 catheters that remained inside the applicator activated. Ideally, the 100% isodose line, shown in red, should be encompassing most of the CTV, while avoiding the nearby tissues and organs at risk. In Figure 3.11 A & B, the red isodose line is overlapping with the bladder, rectum, and surrounding tissues. This is due to the distance between the applicator, and the lateral edge of the CTV. For the hybrid applicator plan, Figure 3.11 C, the 100% isodose line is encompassing the CTV and is delivering less dose to the surrounding tissues. The 100% dose being delivered to the rectum and bladder volumes are also visibly less for this case.

The 150% and 200% isodose lines, blue and yellow respectively, for all cases are partially within the CTV. For the hybrid applicator, this is unavoidable as the catheters are placed within the CTV, causing the dose fall off, discussed in Section 1.3.3, to occur within the CTV. For the patient-specific applicator and the original intracavitary plans, a larger amount of 150% and 200% dose are being delivered to the CTV, as the distance between the target and the catheter is large. This causes the dwell positions to have long dwell times to ensure dose coverage of the CTV. The volumetric dose data for these three plans was analyzed and is shown in Table 3.5.

	Original Applicator Plan (Intracavitary)	Patient-specific Applicator Plan (Intracavitary)	Interstitial Hybrid Applicator
V_{95} (%)	96.51	96.92	97.30
V_{150} (%)	44.69	42.54	46.00
V_{200} (%)	16.22	15.10	19.04
D_{98} (%)	88.93	89.93	93.08
EQD2 D_{2cc} Bladder (Gy)	59.35	58.18	56.08
EQD2 D_{2cc} Rectum (Gy)	60.80	58.28	51.05

Table 3.5 Patient 5 dosimetric data

Both patient-specific applicator plans show better target coverage, with a reduction to the high dose regions, when compared to the original applicator plan. The volume of dose covering 95% of the volume is greater for the interstitial hybrid applicator, showing the highest volume of dose coverage of the CTV. The V_{150} and V_{200} are increased for the hybrid applicator because the catheters are within the volume itself, therefore, the dose fall off, discussed in Section 1.3.3, will occur within the target volume. The intracavitary plans show large, contiguous volumes of high dose delivered to the CTV, as demonstrated in Figure 3.11. Considerable adjoined volumes of high dose regions are not clinically desirable in brachytherapy plans and can lead to areas of necrosis, inflammation, fibrosis, or fistula, for example.[46] The goal for V_{150} is less than 50%, and V_{200} is less than 20%. For all three plans, the values satisfy these goals.

D_{98} for the intracavitary plans are low. This decrease could be due to the air gap and large distance between the CTV and the catheter positions. When the catheters are placed within the CTV, for the hybrid applicator, D_{98} increases to 93.21%.

Based on the ABS recommendations, the goal for the rectum was a cumulative dose of ≤ 65 Gy and ≤ 80 Gy to the bladder. The D_{2cc} for the bladder and rectum are decreased for the patient-specific plan, and even less for the interstitial hybrid applicator. All three plans satisfy the dose constraints for the bladder. Overall, due to the air gap in this patient, a hybrid applicator provides a better treatment plan with increased dose delivered to CTV while also limiting dose to the OARs.

3.1.3 Patient 7

Patient 7 had 2 CTVs that were planned. As shown in the 3D representation in Figure 3.12, CTV1 is the upper target, with a target width of 5.4 mm, and which is in proximity to the rectum and bladder. CTV2 is the lower target, not near OARs, but by surrounding normal tissue, with a width of 6.9 mm.

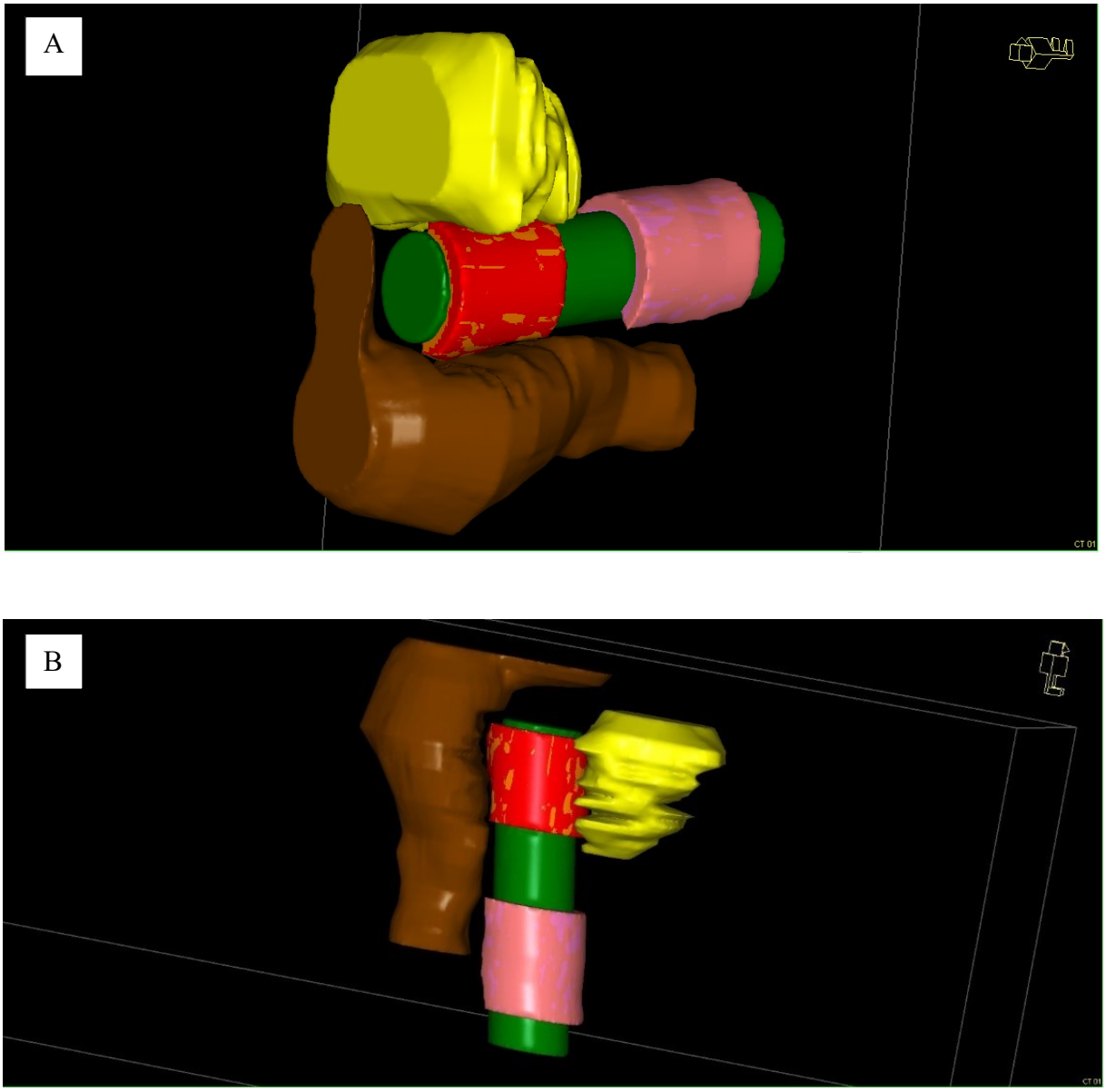


Figure 3.12 3D representation of Patient 7. The applicator is shown in green, CTV1 in red, CTV2 in pink, bladder in yellow and the rectum in brown. A) shows the anatomy in the transverse plane while B) is in the sagittal plane.

To ensure entire coverage of both target volumes, two rows of catheters were placed. 10 catheters were digitized within the applicator and can be seen in Figure 3.13.

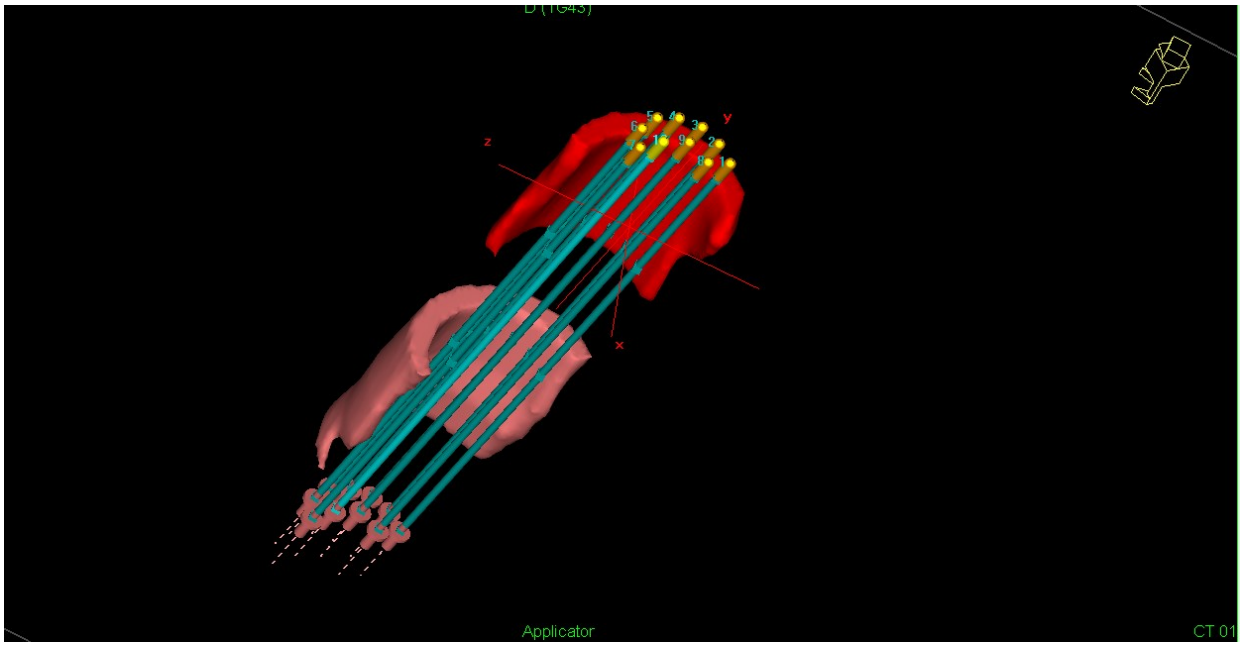


Figure 3.13 A 3D representation of the patient-specific applicator plan with custom catheter positions. The CTV1 is shown in red and CTV2 is shown in pink.

For CTV1, the dose distribution can be seen for the original applicator plan and the patient-specific applicator plan in Figure 3.14.

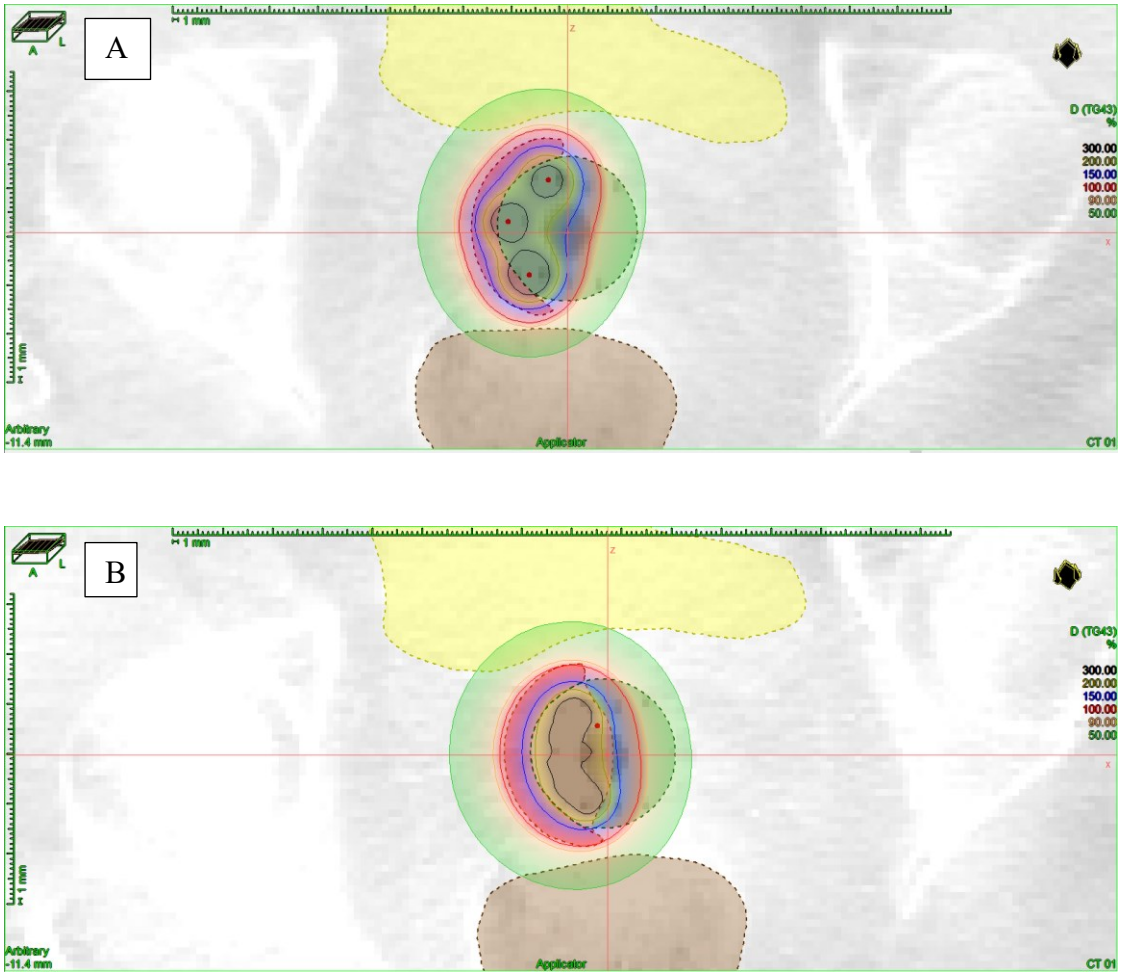


Figure 3.14 Dose distribution for Patient 7 CTV1. A) shows the original applicator plan and B) shows the patient-specific applicator plan

The 100% isodose line is completely encompassing CTV1 in both plans. For the optimized original applicator plan, the 100% line is "overcovering" the target (ie., the 100% isodose line extends beyond CTV1). The overcoverage of CTV1 in the original applicator plan was tried to be reduced using GO, however, this decreased the dose to the CTV2. The 150% and 200% lines treat a large volume of the CTV1 for the original applicator plan, while both are decreased for the patient-specific applicator plan. The green 50% isodose line is also visibly less delivering dose to the OARs in the patient-specific applicator plan. The dose distributions for CTV2 can be seen in Figure 3.15.

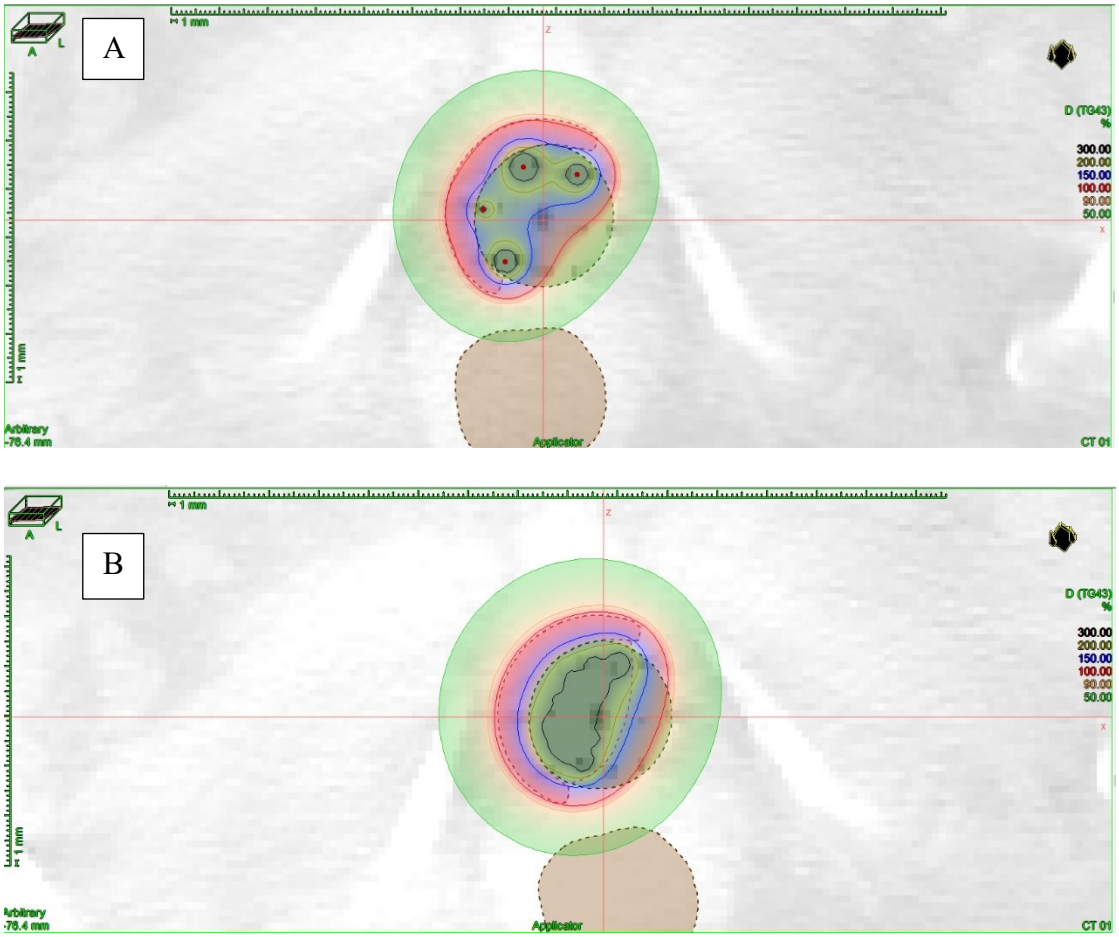


Figure 3.15 Dose distribution for Patient 7 CTV2. A) shows the original applicator plan and B) shows the patient-specific applicator plan

For both plans, the 100% isodose line is encompassing the CTV2. There are no large differences between these two plans with respect to target coverage for CTV2, but there is a visible difference in the volume of 200% being delivered to CTV2. The dosimetric data for these two plans are compared in Table 3.6.

	Original Applicator Plan	Patient-specific Applicator Plan
CTV1 V_{95} (%)	97.03	97.64
CTV1 V_{150} (%)	41.15	27.78
CTV1 V_{200} (%)	14.47	2.10
CTV1 D_{98} (%)	91.43	94.04
CTV2 V_{95} (%)	98.57	98.58
CTV2 V_{150} (%)	25.84	25.09
CTV2 V_{200} (%)	4.95	0.38
CTV2 D_{98} (%)	96.4	97.05
EQD2 D_{2cc} Bladder (Gy)	60.48	58.08
EQD2 D_{2cc} Rectum (Gy)	57.74	57.59

Table 3.6 Patient 7 Data

For CTV1, the patient-specific plan shows a slight increase in V_{95}, from 97.03% to 97.64%. When analyzing V_{150} and V_{200}, the patient-specific plan shows a great decrease, V_{150} decreases 13.37%, and V_{200} decreases 12.37%. The original applicator plan still satisfies the conditions of V_{150} of less than 50%, and V_{200} less than 20%.

For CTV2, the patient-specific applicator plan does not show a difference in the volume receiving 95% of the dose. The V_{150} and V_{200} are also decreased for CTV2, and both plans still satisfy the dose conditions for the high doses laid out in the Methods.

Based on the ABS recommendations, the goal for the rectum was a cumulative EQD2 dose of less than or equal to 65 Gy and 80 Gy to the bladder. The D_{2cc} for the bladder and rectum are slightly decreased for the patient-specific plan. Both plans are still consistent with the dose

goals. Overall, this plan showed a patient-specific applicator can reduce high volume doses within the CTV.

3.1.4 Discussion

An ideal intracavitary cylindrical applicator should provide coverage of the target volume, while avoiding overdose to the OARs and surrounding normal tissues.

Yan *et al.* was the first to perform dosimetric comparison between MCC applicators and 3D printed applicators for vaginal brachytherapy, although it was to treat the vaginal cuff post-hysterectomy.[15] By comparing the two applicators, they found that the 3D-printed applicator delivered a higher dose to a larger volume of the target volume while also showing a more homogenous dose and better target coverage. For the CTV, they achieved a D_{98} value of 85.82%. For our intracavitary patients, we achieved a D_{98} average of 95.16% ($p<0.0007$). This is a 9.34% increase in the dose covering the CTV. The catheter positions for this case were 5 mm away from the applicator edge, with a 10 mm space between catheters. [15] For our study, the minimum distance was set to 5 mm between catheters. They also evaluated the four quality indices, CI, DHI, DNR and OI. They achieved an average CI of 0.939, DHI of 0.366, DNR of 0.594 and OI of 0.343.[15] We achieved average values of CI of 0.984 ($p<0.0009$), DHI of 0.733 ($p<0.0007$), DNR of 0.226 ($p<0.0007$) and OI of 0.037 ($p<0.0004$). The conformity index is closer to the ideal value of 1 for our patient-specific applicator plans, as opposed to Yan *et al*.'s equally distributed MCC applicators. The DHI and DNR difference shows a more homogeneous dose distribution in the CTVs and a smaller volume of non-homogeneous dose within the CTVs. A smaller OI for our patient-specific applicator plans show a smaller region of high dose within the target volumes.

Gebhardt *et al.* analyzed the use of multichannel vaginal cylinders for the treatment of gynecologic malignancies to the vagina. [47] These cylinders were not patient specific; they used a Miami applicator. For V_{150}, they received an average of 56.1% and a V_{200} average of 37.0%, while we achieved a V_{150} average of 22.0% ($p<0.0002$) and an average V_{200} of 3.3%($p<0.0001$) for our patient-specific applicator plans. For our patient-specific applicator plans, we achieved a smaller high dose region being delivered to the CTV. The EQD2 D_{2cc} to the rectum was 58.4 Gy, and 59.0 Gy to the bladder for their plans. We achieved an average of 52.2 Gy ($p<0.001$) for the bladder and 56.3 Gy ($p<0.001$) to the rectum for our patient-specific applicator plans. This shows patient-specific plans can greatly decrease the high dose regions within the CTV, while also limiting dose to the organs at risk.

The intracavitary patient-specific applicator plans achieved in this study provided a statistically significant improvement in terms of dose coverage to the CTV and limiting dose to OARs when comparing to the original applicator plan. An intracavitary patient-specific applicator can provide good results for patients that have a unique vaginal cavity shape. All patients with targets less than 5 mm showed an improvement in dose coverage and hot spots with a patient-specific applicator, but when the target size increased to greater than 5 mm, some patients did not. For example, Patient 11 had a tumour that was encompassing the entire CTV, with a width of 4.6 mm. The patient-specific plan achieved a V_{200} of 0% within the CTV. Patient 5, discussed in Section 3.1.2, had a width of 12.4 mm, and a length of 95.2 mm. The patient-specific intracavitary applicator did not provide a plan that met constraints, due to the extensive airgap and large tumour volume. For this patient, an interstitial approach showed a better plan, with higher coverage of the CTV and less dose to the OARs. These examples reiterate the clinical knowledge that targets greater than 5 mm should be treated interstitially.[32]

3.2 Interstitial Patients

Patients 13 to 25 were originally treated with a MUPIT applicator at the QEII Cancer Centre for gynecological brachytherapy. The patient-specific treatment plan created for each patient was a hybrid interstitial-intracavitary applicator that consisted of catheter positions that remained within the applicator, as well as catheters entered the CTV through the applicator. All these patients had a CTV diameter of more than 5 mm, which is why the patients were treated with an interstitial applicator in clinic.

3.2.1 Interstitial Patient Summary

To assess dose coverage and within the CTV for Patients 13 to 25, V_{95}, $V_{150,}$ and V_{200} were analyzed. The results for each patient can be seen in Table 3.9.

	V_{95} (p=0.002)		V_{150} (p=0.0002)		V_{200} (p=0.0001)	
Patient	Original Applicator Plan (%)	Patient-Specific Applicator Plan (%)	Original Applicator Plan (%)	Patient-Specific Applicator Plan (%)	Original Applicator Plan (%)	Patient-Specific Applicator Plan (%)
13	97.05	97.74	34.48	33.92	10.71	13.89
14	97.50	97.50	49.98	47.34	18.90	17.34
15	97.31	97.80	37.25	31.42	12.52	10.26
16	97.05	97.76	27.85	19.34	5.74	11.51
17	96.51	96.92	44.88	33.23	16.84	12.56
18	96.43	97.62	40.05	35.84	11.32	12.74
19	97.41	97.24	46.11	31.18	20.86	11.99
20	96.53	96.86	66.20	45.83	32.43	16.35
21	96.46	97.49	27.58	23.99	8.81	10.17
22	97.96	97.94	30.40	20.51	11.85	8.21
23	97.73	97.57	34.5	42.41	15.19	18.10
24	97.46	97.37	47.62	45.17	26.39	20.67
25	97.35	97.30	15.32	31.83	6.10	12.69

Table 3.7 Interstitial dosimetric patient data for Patient 13 to 25.

Table 3.9 shows a statistically significant difference for V_{95}, V_{150} and V_{200} for the patient-specific plans compared to the original applicator plans. The volume covering 95% prescription dose to the CTV is slightly larger for the patient-specific applicator plans, a difference of 0.4% with a p-value of 0.002.

V_{150} and V_{200} describe the high dose regions within the CTV. For the patient-specific plans, the amount of V_{150} shows a median decrease of 4.6% (p=0.0002). The V_{200} has less of a change with patient-specific applicators, with a median volume reduction of 1.6% (p=0.0001).

3.2.1.1 V_{95}

V_{95} represents the relative CTV volume that receives at least 95% of the prescription dose. Every patient that was treated with the patient-specific interstitial applicator achieved a V_{95} greater than 95%. Figure 3.16 shows a box and whisker plot of the original applicator plans and the patient-specific applicator plans.

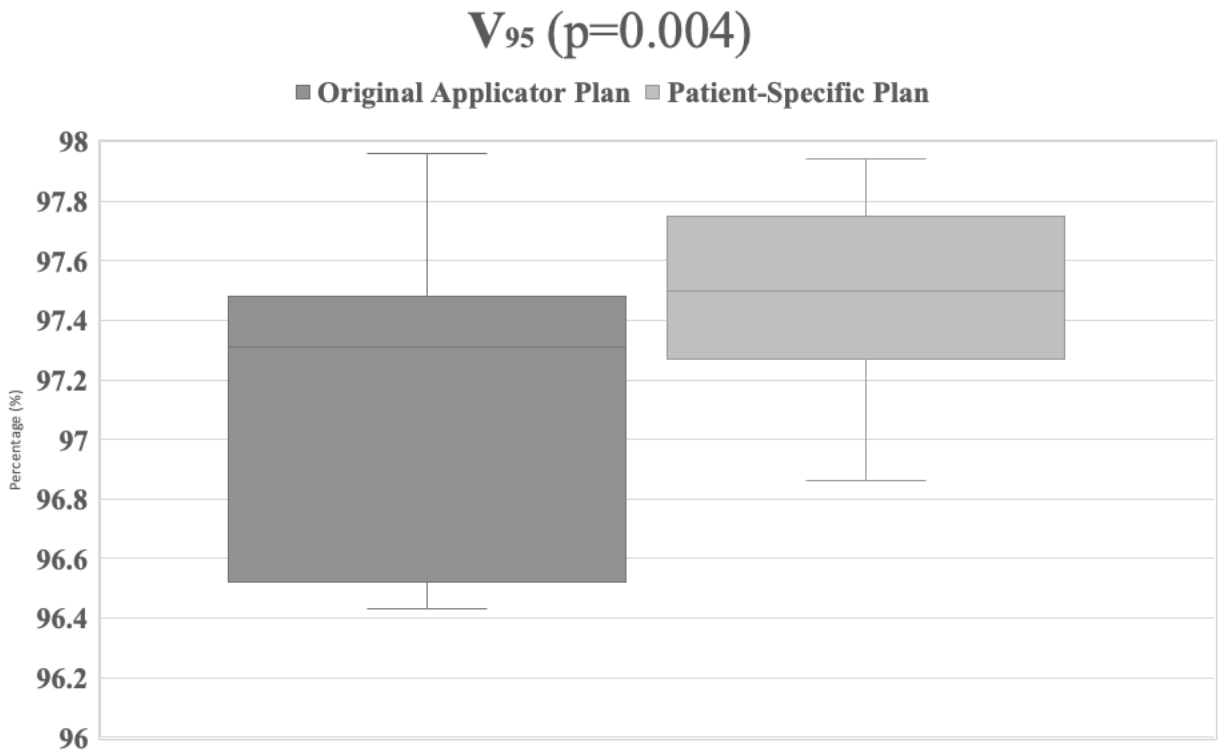


Figure 3.16 Box plot of V_{95} for interstitial original applicator plans and the patient-specific applicator plans.

Figure 3.16 represents the median V_{95} value by the horizontal line within the box. For the original applicator plans, the median V_{95} value is 97.1%. The patient-specific applicator plans show a statistically significant increase of 0.4%, with a median of 97.5% ($p=0.004$).

The box for the original applicator plans indicates a skew, meaning a larger number of patients achieved a V_{95} less than the median. The box for the patient-specific applicator plans is smaller, indicating values that closer to the median value, and less dispersed data set. For V_{95}, the patient-specific applicator plans show a statistically significant higher volume receiving 95% of the dose.

3.2.1.2 V_{150} and V_{150}

V_{150} and V_{200} assess the high dose regions within the CTV. The dose goal for V_{150} is less than 50% of the prescription dose, and 20% for V_{200}. To limit patient toxicity, these values should be as low as possible.

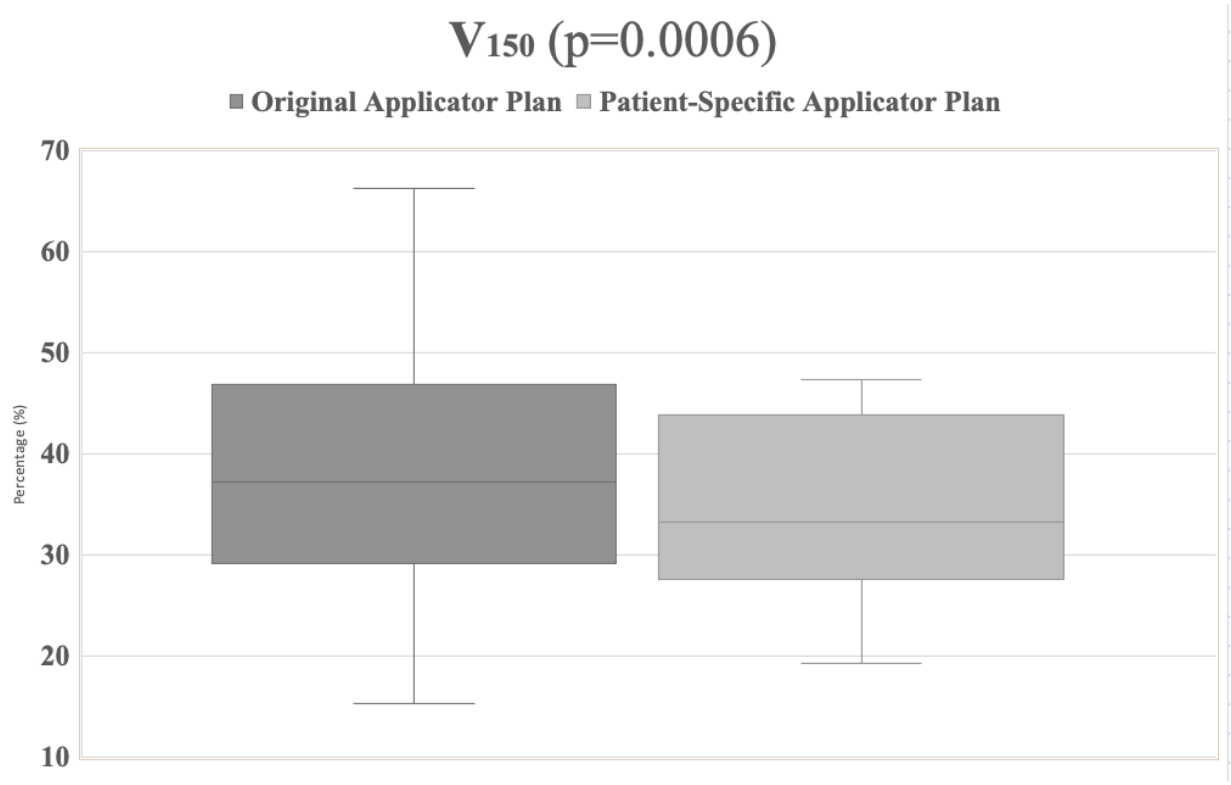


Figure 3.17 Box plot of V_{150} for interstitial original applicator plans and the patient-specific applicator plans.

A box and whisker plot for V_{150} is shown in Figure 3.17. The patient-specific applicator plans show a statistically significant smaller V_{150} value. For the original applicator plans, the median V_{150} is 38.6%. For the patient-specific applicator plan, the median V_{150} is 34.0%, showing a 4.6% decrease for the patient-specific plan (p=0.0006). The lower median shows a smaller volume of the CTV receiving 150% of the prescription dose.

The whiskers for the original applicator treatment plans are long compared to the patient-specific applicator plans. The long whiskers indicate a larger range of V_{150} values for the original applicator plan. The upper whisker of the original treatment plans is 66.2% and 47.62% for the patient-specific treatment plans. The V_{150} for the patient-specific applicator plans show a less dispersed range of values. Figure 3.18 shows the plot for V_{200} values for the original applicator plans and the patient-specific applicator plans.

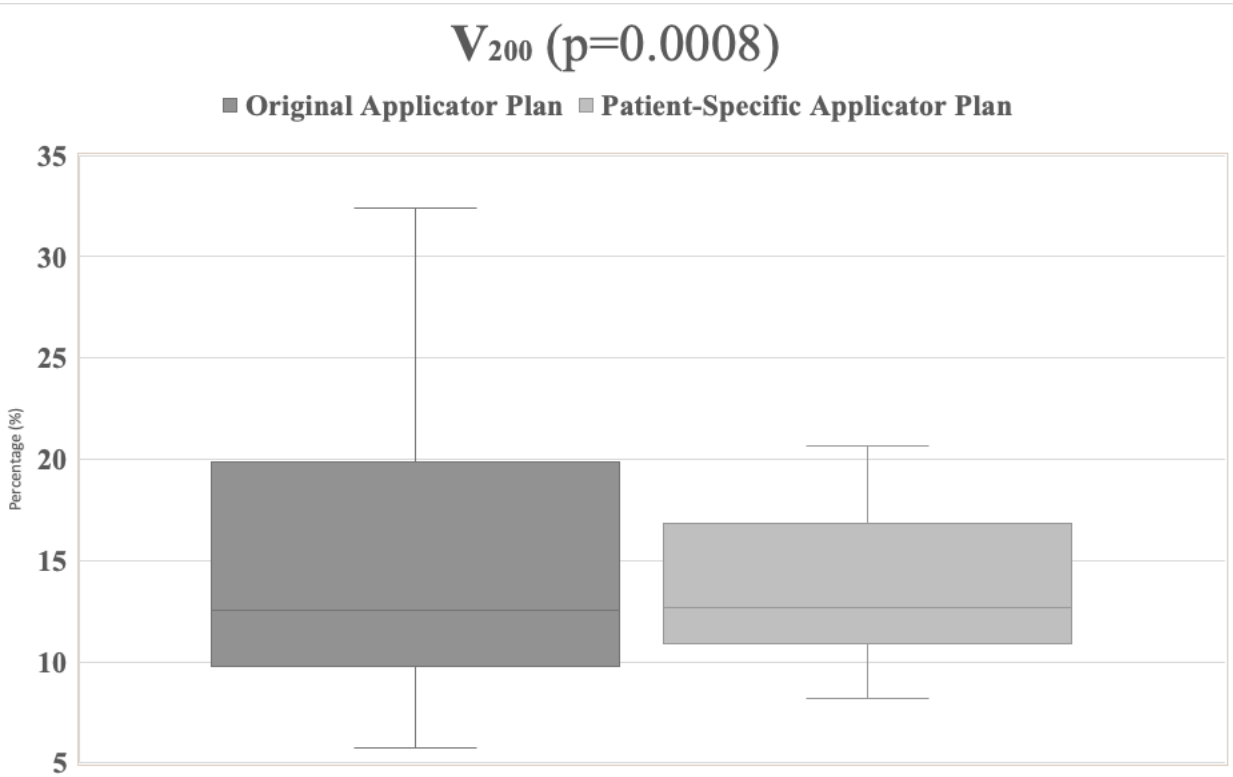


Figure 3.17 Box plot of V_{200} for interstitial original applicator plans and the patient-specific applicator plans.

Figure 3.18 shows the differences for both plans in terms of V_{200}. The median V_{200} for the original treatment plans is 12.69% and 12.52% for the patient-specific applicator plans. The V_{200} shows a statistically significant decrease for the patient-specific applicator plans, p=0.0008.

The patient-specific plans have a smaller box, indicating a less dispersed range of data around the median value. The original treatment plans have a larger box, showing that more patients receive a V_{200} greater than the median. The upper whisker for the original applicator plans indicates that the highest value is much larger than that for the patient-specific applicator plans. Overall, the dose is slightly less for V_{200} when using patient-specific applicator plans.

3.2.1.3 D_{98}

The dose delivered to 98% of the CTV is analyzed in Figure 3.19.

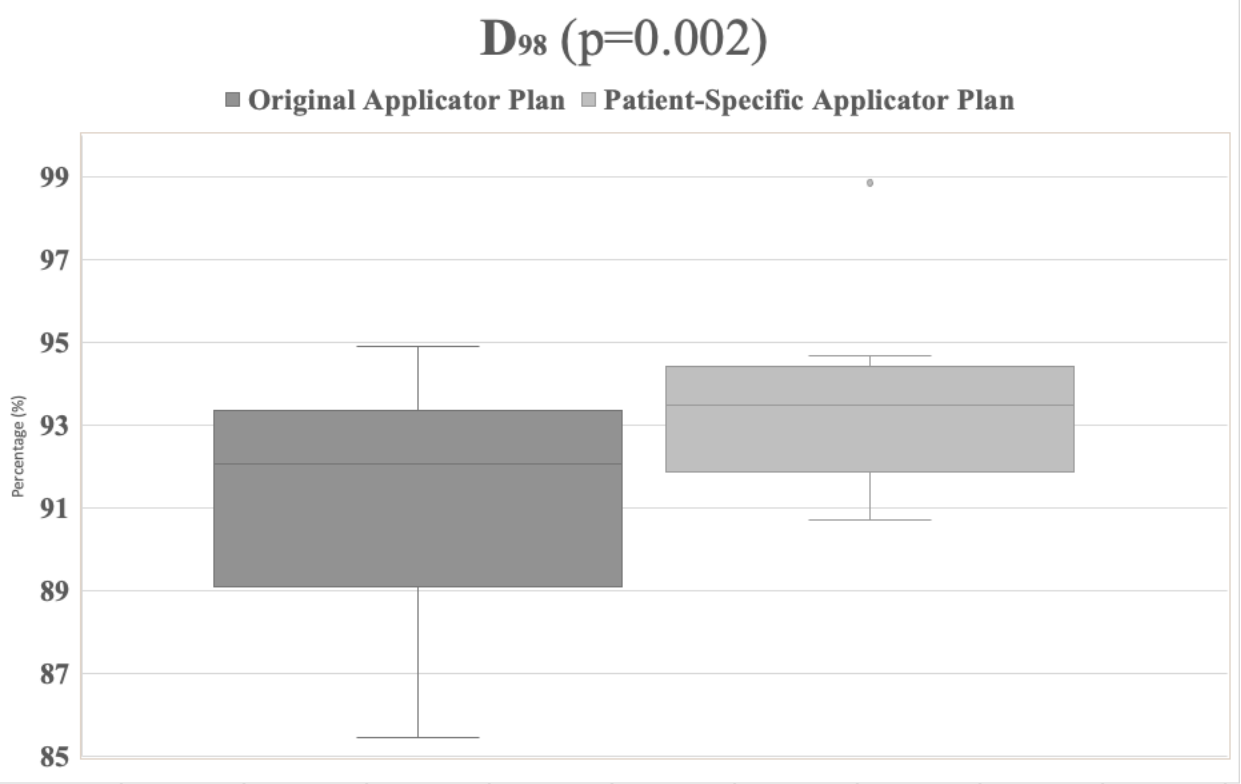


Figure 3.19 Box plot of D_{98} for interstitial original applicator plans and the patient-specific applicator plans.

In Figure 3.19, the patient-specific applciator plans have a median of 93.5%, a statistically significant increase from the original applicator plans that have a median of 91.3% (p=0.002). This shows that the median dose delivered to 98% of the CTV is statistically larger for the patient-specific applciator plans.

Both plans show a negative skew, meaning a larger number of patients have a D_{98} value of less than the median. The median of the patient-specific plan is larger than the upper range of the box for the original applicator plan. This shows the patient-specific plans achieve a higher D_{98}.

The outlier for the patient-specific plan is Patient 22. This patient has a CTV volume that extends on both sides of the cylindrical applicator. The right side has a maximum thickness of 12.3 mm and 11.4 mm on the left side. The patient specific applicator has catheter positions

within the CTV to ensure coverage of both sides. Both plans have 13 catheters. The placement of the patient-specific catheters increases D_{98} from 94.9% to 98.9% for the patient-specific plan.

3.2.1.4 EQD2 for OARs

The dose delivered to the bladder and rectum, directly from the TPS, can be seen in Table 3.8.

	Bladder (p=0.001)		Rectum (p=0.001)	
Patient	Original Applicator Plan (Gy)	Patient-Specific Applicator Plan (Gy)	Original Applicator Plan (Gy)	Patient-Specific Applicator Plan (Gy)
13 5 Gy x 3 fx	1.42	1.16	2.21	1.28
14 4.5 Gy x 3 fx	1.32	0.97	2.03	1.23
15 5.5 Gy x 3 fx	4.22	2.87	3.64	3.25
16 6 Gy x 1 fx	4.54	4.08	4.49	3.83
17 4 Gy x 3 fx	0.65	0.59	2.53	1.96
18 5 Gy x 3 fx	2.66	1.62	3.44	2.77
19 5 Gy x 3 fx	3.37	2.75	2.81	1.91
20 7 Gy x 2 fx	2.02	2.01	5.13	5.01
21 5.5 Gy x 3 fx	1.41	1.10	3.36	2.71
22 6 Gy x 3 fx	4.47	4.06	5.67	4.40
23 5.5 Gy x 3 fx	1.84	1.59	1.61	0.93
24 5 Gy x 3 fx	1.03	0.79	3.51	2.91
25 5 Gy x 3 fx	1.76	1.36	2.84	2.06

Table 3.8 Interstitial Patient Data for D_{2cc} for the OARs.

The dose delivered to the bladder and rectum was assessed using the EQD2 calculations, discussed in Section 1.6.6. The cumulative EQD2 D_{2cc} dose constraint to the bladder of less than or equal to 80 Gy, and less than or equal to 65 Gy to the rectum. Table 3.9 shows the data for each patient for EQD2 D_{2cc} for both OARs.

	Bladder (p=0.001)		Rectum (p=0.0004)	
Patient	Original Applicator Plan (Gy)	Patient-Specific Applicator Plan (Gy)	Original Applicator Plan (Gy)	Patient-Specific Applicator Plan (Gy)
13	46.96	46.11	49.15	46.49
14	46.61	45.5	49.31	46.31
15	61.50	53.31	57.71	55.36
16	50.06	48.97	49.92	48.44
17	44.63	44.47	51.6	49.03
18	52.25	47.69	56.50	52.77
19	56.09	52.73	53.00	48.86
20	47.25	47.13	59.89	58.76
21	46.94	45.91	56.02	52.47
22	63.20	60.37	71.83	62.70
23	48.53	47.58	47.46	45.40
24	45.68	44.99	56.90	53.54

Table 3.9 Interstitial Patient Data for the OARs. D_{2cc} was converted to EQD2 for comparison.

In the patient-specific applicator plans, less dose is being delivered to the bladder and rectum. The average dose delivered to the bladder for the original applicator plans are 50.6 Gy, this decreased to 48.6 Gy for the patient-specific applicator plans (p=0.001). For the original treatment plans, the median dose to the rectum is 54.9 Gy. This decreased to 51.5 Gy for the patient-specific applicator plans (p=0.0004). Both sets of plans for the interstitial patients achieved a dose less than the cumulative dose restriction. Figure 3.26 shows a plot to compare the original applicator plans and patient-specific applicator plans for EQD2 D_{2cc} to the bladder.

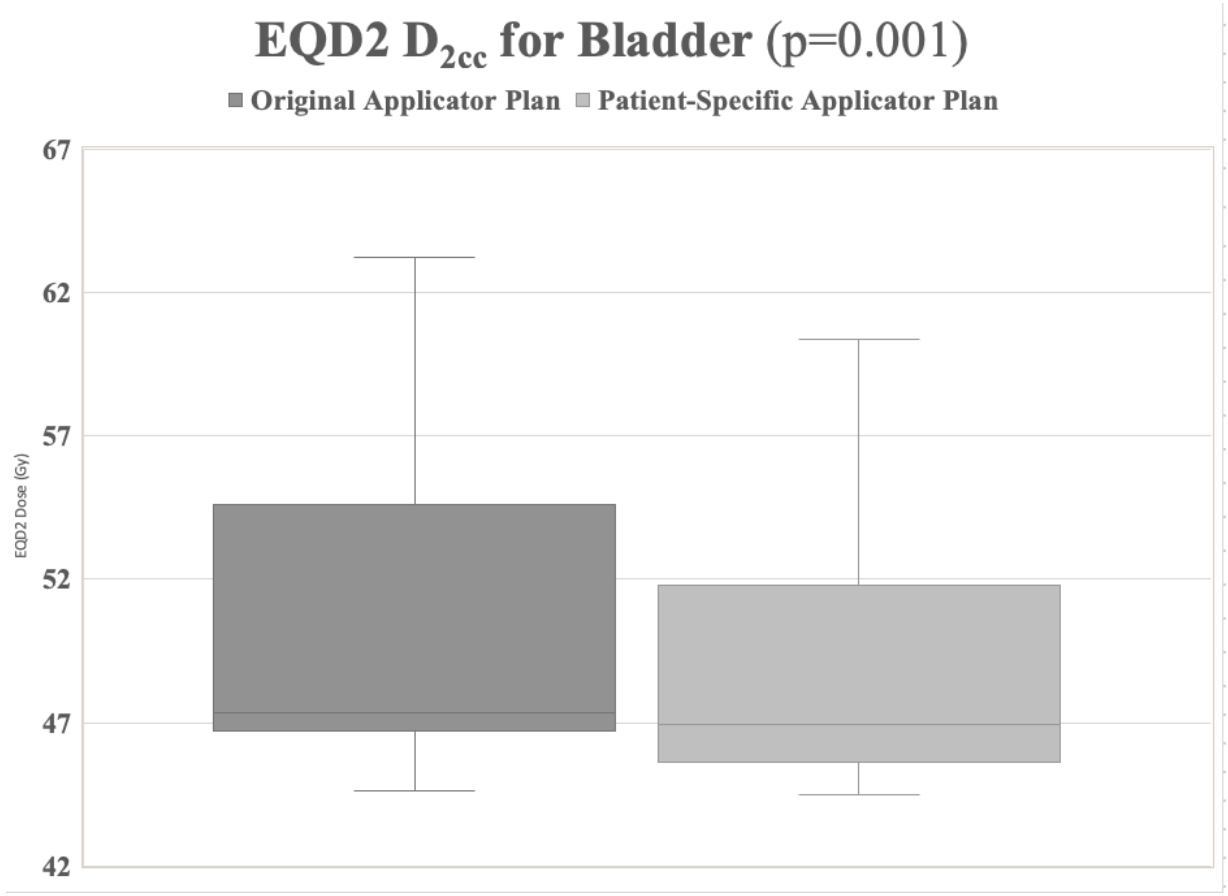


Figure 3.20 Box plot of EQD2 D_{2cc} to the bladder for interstitial original applicator plans and the patient-specific applicator plans.

In Figure 3.20, the median value dose received by the bladder is lower for the patient-specific plans. The original applicator plans have a median of 50.6 Gy. This value decreases to 48.6 Gy for the patient-specific applicator plans (p=0.001).

The box for the patient-specific plans is smaller, showing a less dispersed data set for the dose being delivered to the bladder. Both plans show a positively skewed data set; more patients receive a dose to the bladder that is higher than the median. Both plans for each patient receive a dose to the bladder less than the dose restriction of less than or equal to 80 Gy. Overall, the patient specific applicator plans show a statically lower dose to the bladder. Figure 3.21 shows the data for EQD2 D_{2cc} to the rectum.

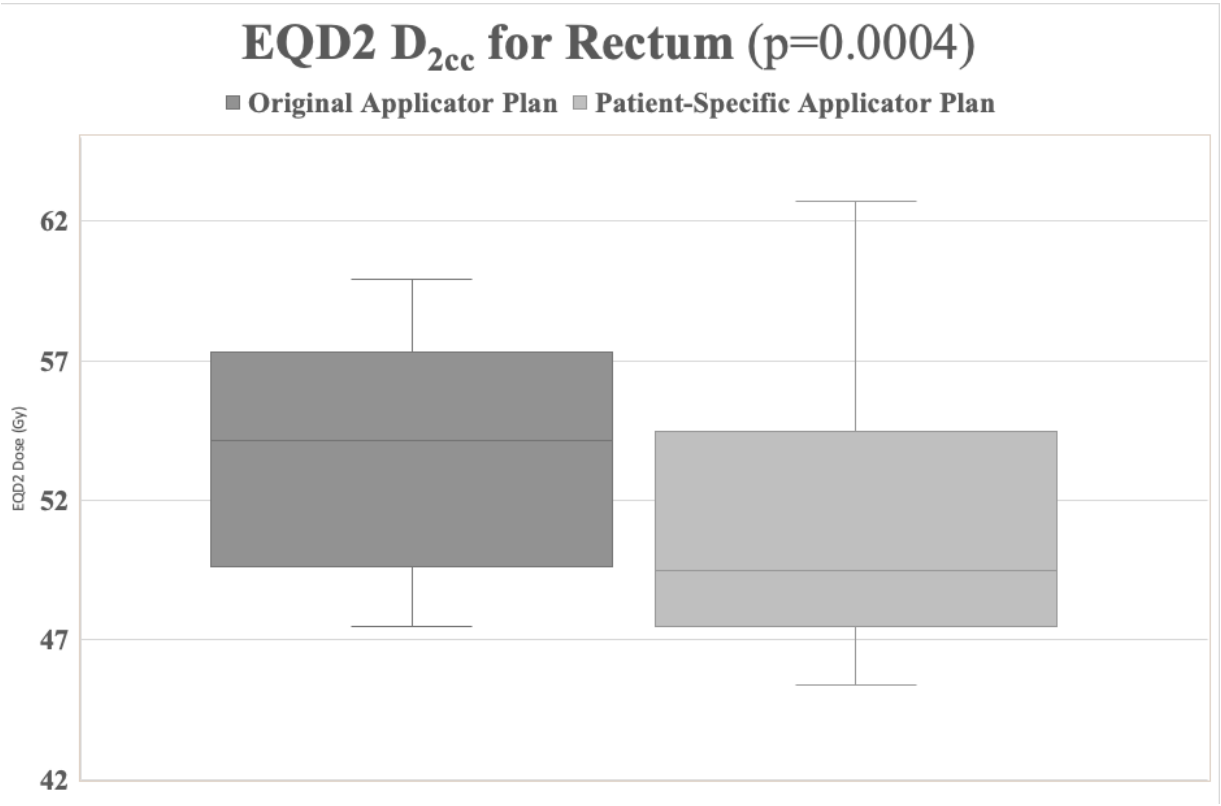


Figure 3.21 Box plot of EQD2 D_{2cc} to the rectum for interstitial original applicator plans and the patient-specific applicator plans.

The patient-specific applicator plans display a statistically significant lower median rectal D_{2cc} (EQD2). The median for the patient-specific plans is 51.5 Gy. The original applicator plans have a median of 54.9 Gy (p=0.0004). For the original applicator plans, the median is almost equivalent to the highest point of the box for the patient-specific plans. This shows that the patient-specific applicator plans have a lower dose applied to the rectum.

3.2.1.5 Quality Indices

As described in Section 1.6.5, quality indices were used to assess the dose within the CTV.

Index	Optimized Original Plan	Customized Plan	p-value
CI	0.971	0.975	0.004
DHI	0.564	0.610	0.002
DNR	0.407	0.358	0.0006
OI	0.160	0.143	0.0008

Table 3.10 Quality Indices for interstitial patients

Table 3.10 shows that all quality indices are statistically superior for the patient-specific plans. Conformity index shows a higher statistically significant value for the patient-specific plans, indicating a more conformal dose within the targets. The dose homogeneity index is also statistically higher for the patient-specific plans, showing a more homogeneous dose within the CTV. The dose non-uniformity index is lower for the patient-specific plans, indicating a lower region of non-uniform dose within the CTV. Overdose index is also statistically lower for the patient-specific plans, describing a smaller region of overdose within the CTV.

3.2.2 Patient 17

For Patient 17, the CTV had a maximum target thickness of 12.9 mm. The rectum is adjacent to the CTV. The prescription dose is 4 Gy times 3 fractions. A 3D representation of this patient can be seen in Figure 3.22. The applicator is shown in green, the CTV in red, the bladder in yellow and the rectum in brown.

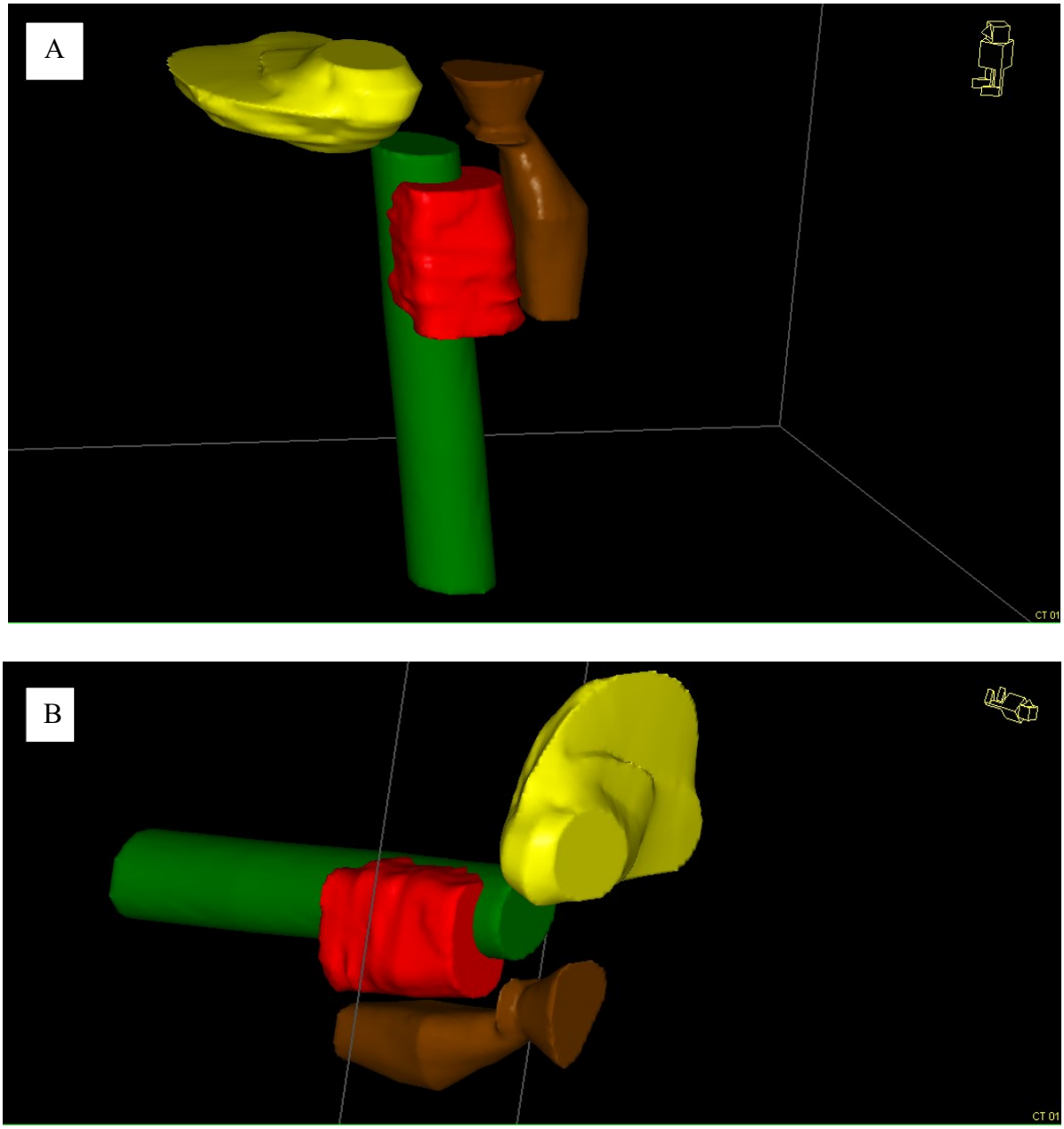


Figure 3.22 3D representation of Patient 17. The applicator is shown in green, the CTV in red, the bladder in yellow and the rectum in brown.

For the patient-specific applicator plan, 4 catheters remained within the applicator and 5 catheters were implanted into the CTV through the applicator. The placement of the catheters is shown in Figure 3.23. Note that catheter 5 has a kink in the superior end, beyond the target. The

catheters are straight within the tumour volume so even changing this catheter to remove the bend will not affect the dose distribution of the overall plan.

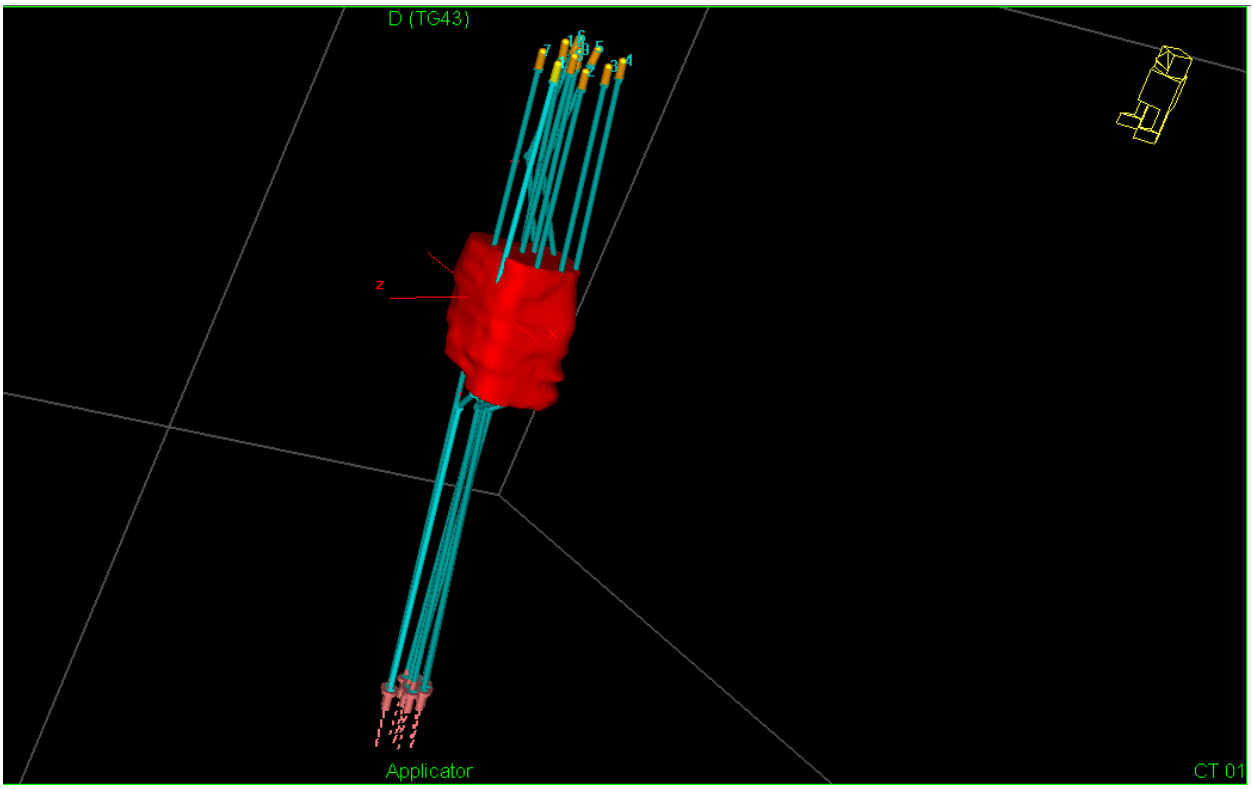


Figure 3.23 Patient 17 with a patient-specific hybrid applicator. 4 catheters remain within the applicator and 5 catheters exit the applicator and enter the CTV. The applicator is shown in green, CTV in red, bladder in yellow and the rectum in brown. Note that in a real treatment plan created to treat the patient, the catheters would not extend a large distance beyond the target, to avoid physical injury to normal tissues.

The plans were optimized using IPSA and graphical optimization. The dose distribution for both plans is shown in Figure 3.24.

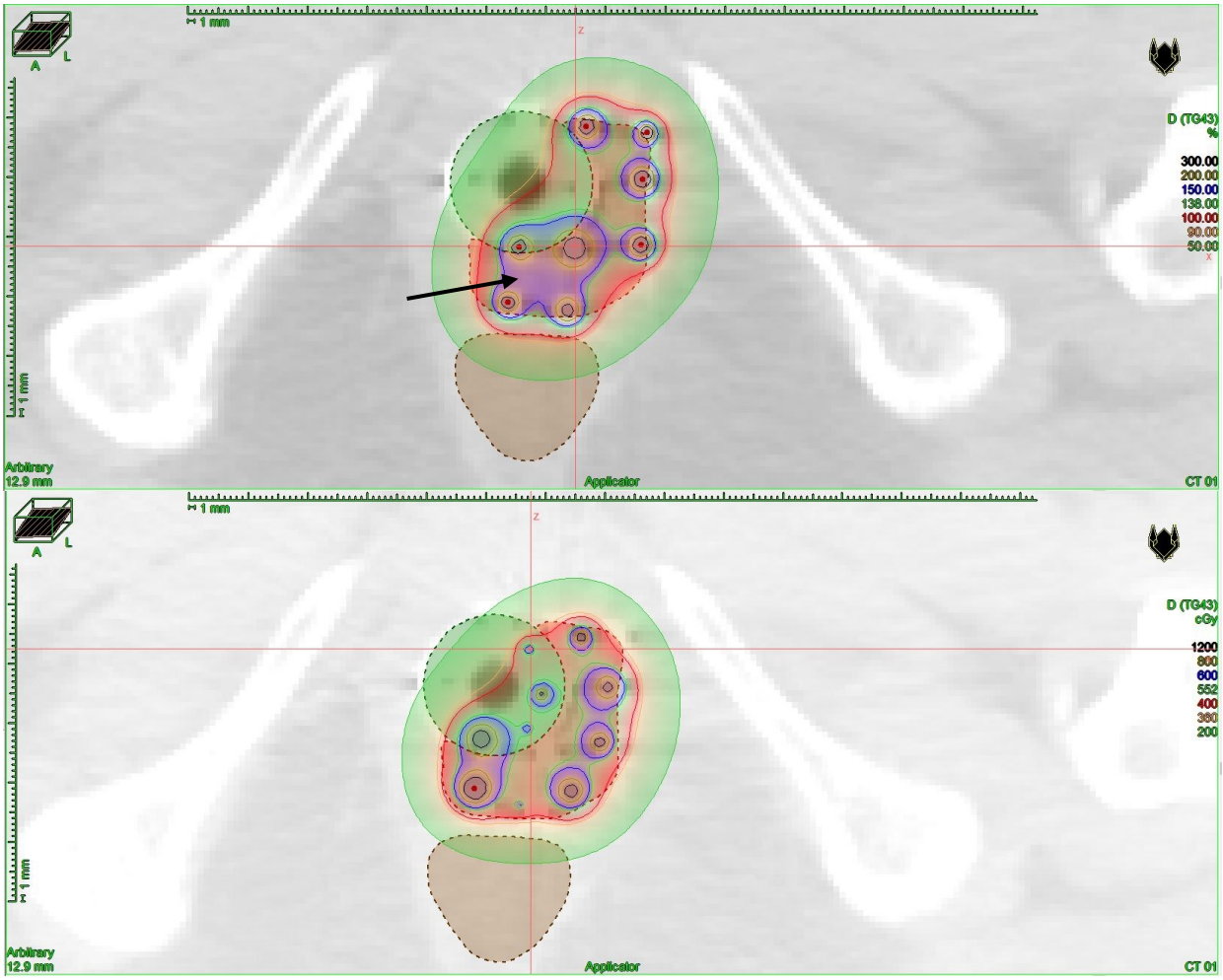


Figure 3.24 Dose distribution for Patient 17 A) shows the original applicator plan and B) shows the patient-specific applicator plan.

Figure 3.24 A shows the dose distribution for the original applicator plan. The 100% isodose line, shown in red, is "overcovering" the CTV and is delivering dose to nearby tissues. This is not ideal, the 100% isodose line should be confined to the CTV to decrease the risk of patient toxicity. The dose distribution for the original treatment plan shows the 100% prescription dose line overlapping with the superior end of the rectum. For Figure 3.24 B, the patient-specific applicator plan shows a confined 100% isodose line to the CTV, visibly limiting the 100% prescription dose applied to the surrounding tissues and rectum.

The hot dose regions are analyzed using the 150% and 200% isodose lines, blue and yellow respectively. Figure 3.24 A shows a hot spot region within the CTV, indicated by the arrow. Volumes of high dose regions within the CTV are not clinically desirable and can lead to patient toxicity. In Figure 3.24 B, the hot dose region within the CTV is decreased.

When catheters are placed within the target volume for interstitial plans, the high dose regions are increased. The dose fall-off of the source will occur within the target volume, described in Section 1.3.3. This results in a larger V_{150} and V_{200} for the interstitial applicator plans versus the V_{150} and V_{200} values for the intracavitary applicator plans. The volumetric dose data for the two plans were analyzed and shown in Table 3.11.

	Original Applicator Plan	Patient-Specific Applicator Plan
V_{95} (%)	96.51	96.92
V_{150} (%)	44.88	33.23
V_{200} (%)	16.84	12.56
D_{98} (%)	88.95	90.72
EQD2 D_{2cc} Bladder (Gy)	65.39	58.93
EQD2 D_{2cc} Rectum (Gy)	52.18	50.11

Table 3.11 Patient 17 dosimetric data

The patient-specific applicator treatment plan results in a higher coverage of dose delivered to the CTV, with a reduction of dose delivered to the OARs. The volume of dose covering 95% of the volume, V_{95}, is slightly greater for the patient-specific applicator plan by

0.41%. The dose covering 98% of the CTV, D_{98}, also shows an increase for the patient-specific plan of 1.77%.

The volume of high dose regions within the CTV are decreased for the patient-specific applicator plan. V_{150} decreased from 44.88% for the original applicator plan, to 33.23% for the patient-specific plan. V_{200} showed a decrease for the patient-specific applicator plan by 4.28%. The dose goal for the high dose regions were V_{150} of less than 50% and a V_{200} of less than 20%. Both the original applicator plan and the patient-specific applicator plan satisfy these dose goals.

Based on the ABS recommendations, the dose constraint for the rectum is a EQD2 D_{2cc} cumulative dose of less than 65 Gy and less than 80 Gy to the bladder. Both plans for this patient satisfy the dose constraints for the OARs. For the patient-specific applicator, the dose to the rectum and bladder decreased by 2.07 Gy and 6.46 Gy, respectively. Overall, the patient-specific applicator showed a more homogeneous dose delivered to the CTV, while also reducing dose to the OARs.

3.2.3 Patient 23

For Patient 23, the CTV had a maximum target thickness of 11.2 mm. The bladder is adjacent to the CTV. The prescription dose is 5.5 Gy times 3 fractions. A 3D representation of this patient can be seen in Figure 3.25. The applicator is shown in green, the CTV in red, the bladder in yellow and the rectum in brown.

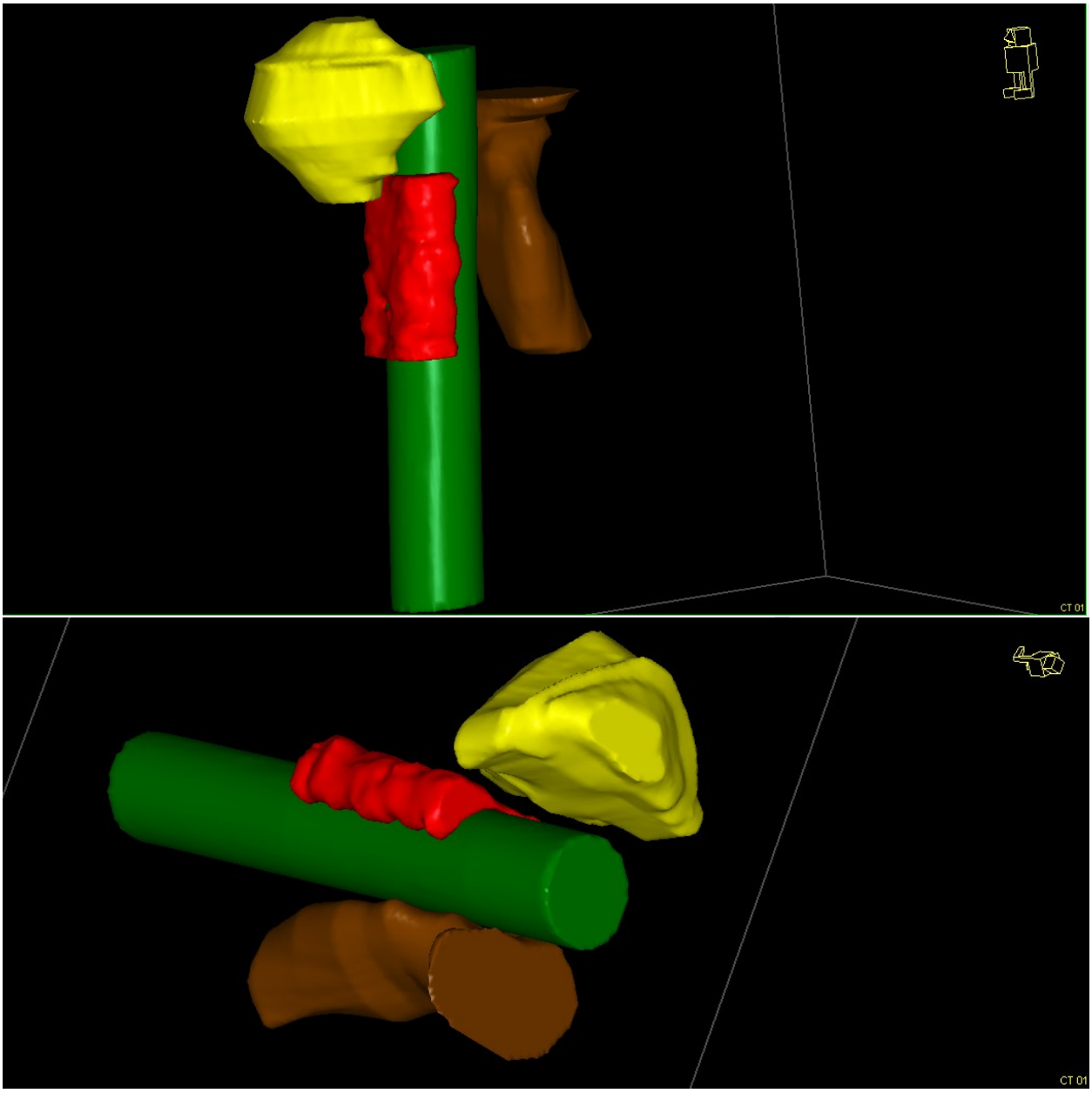


Figure 3.25 3D representation of Patient 23. The applicator is shown in green, the CTV in red, the bladder in yellow and the rectum in brown.

For the patient-specific plan, 8 catheters entered the CTV to ensure complete coverage. 2 catheters remained in the applicator to cover the thinner portion of the CTV. A 3D representation of the catheters can be seen in Figure 3.26.

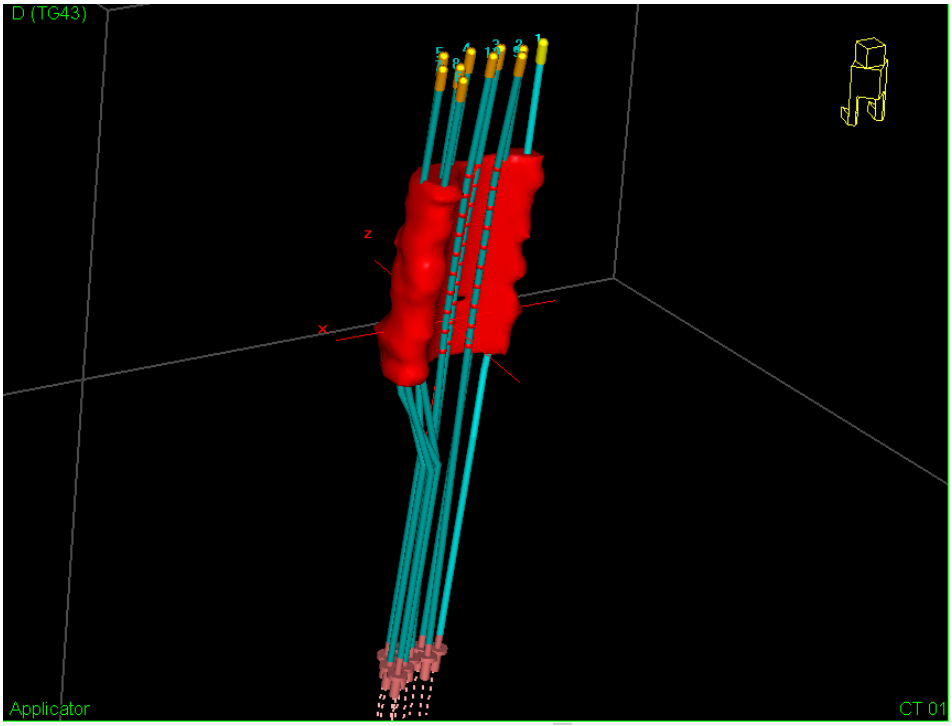


Figure 3.26 Patient 17 with a patient-specific hybrid applicator. The applicator is shown in green, CTV in red, bladder in yellow and the rectum in brown. Note that in a real treatment plan created to treat the patient, the catheters would not extend a large distance beyond the target, to avoid physical injury to normal tissues.

The dose distributions for the original applicator plan and the patient-specific applicator plan can be seen in Figure 3.27.

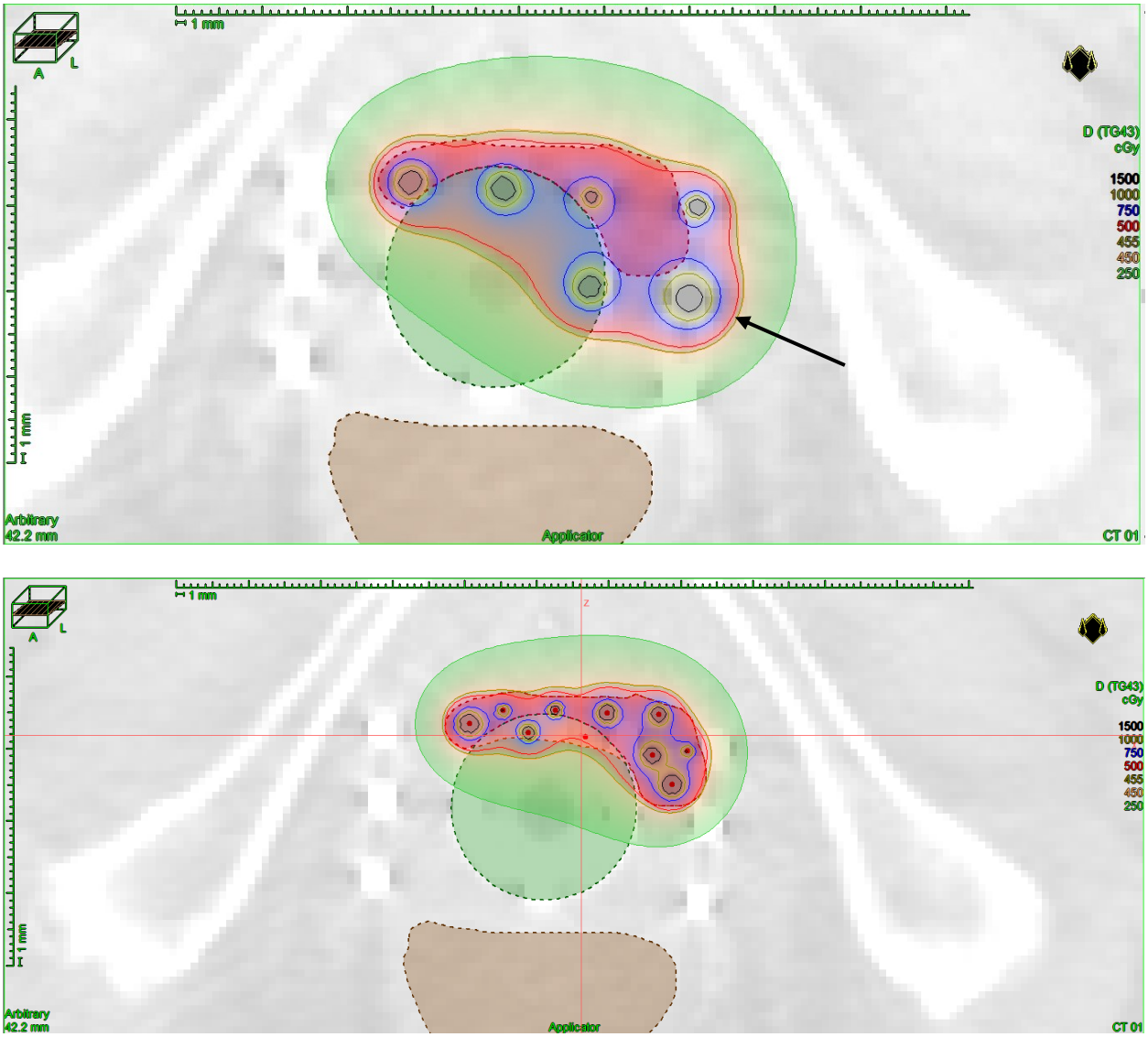


Figure 3.27 Dose distribution for Patient 23. A) shows the original applicator plan and B) shows the patient-specific applicator plan.

Figure 3.27 A shows the dose distribution for the original applicator plan. The 100% isodose line is "overcovering" the CTV and delivering unwanted dose to nearby tissues. The overcoverage can be seen by the arrow. This distribution was optimized using GO, however, the coverage of the CTV declined. In the dose distribution for the patient-specific applicator, the 100% isodose line is confined to the CTV. The patient-specific applicator plan visibly shows a reduction of dose delivered to surrounding tissues.

The 150% and 200% isodose lines, blue and yellow respectively, represent the high dose regions. The regions of high dose occur around the catheter, because of the steep dose fall off, described in Section 1.3.3. For Patient 23, the template that was used for the original applicator plan has needle placements outside of the target volume, therefore, the high dose regions in the original applicator plan occur outside of the target volume, shown by the arrow in Figure 3.27 A. In the patient-specific plan, the catheters were placed inside the target volume, causing the high dose regions to occur within the CTV. This is a trade-off scenario, between high dose regions being delivered to the CTV or to the surrounding normal tissues. The dosimetric data for these two plans are compared in Table 3.12.

	Original Applicator Plan	Patient-specific Applicator Plan
V_{95} (%)	96.51	97.23
V_{150} (%)	34.75	42.41
V_{200} (%)	15.45	18.10
D_{98} (%)	94.35	93.63
EQD2 D_{2cc} Bladder (Gy)	49.70	48.90
EQD2 D_{2cc} Rectum (Gy)	48.90	46.80

Table 3.12 Dosimetric data for Patient 23

The patient-specific applicator plan shows an increase in V_{95} by 0.72%. As expected from viewing the dose distribution, V_{150} and V_{200} are larger for the patient-specific applicator plan. V_{150} increased from 34.75% for the original applicator plan to 42.42% for the patient-specific applicator plan. V_{200} also increased from 15.45% for the original applicator plan to 18.10% for the patient-specific plan. The goal for V_{150} is less than 50%, and V_{200} of less than

20%. Even with the increased hot regions in the CTV of the patient-specific applicator plan, V_{150} and V_{200} are still within acceptable range.

Based on the ABS recommendations, the dose constraint to the rectum is a cumulative EQD2 D_{2cc} of less than or equal to 65 Gy and less than or equal to 80 Gy to the bladder. The D_{2cc} for the bladder and rectum are slightly decreased for the patient-specific plan. The bladder is decreased by 0.8 Gy, with a reduction of and 2.1 Gy for the rectum in the patient-specific applicator plan. The original applicator plan and the patient-specific applicator plan are consistent with the dose goals.

For this patient, the original applicator showed a smaller high dose volume within the CTV, but there was a high dose region delivered to the nearby surrounding tissues. The patient-specific applicator plan delivered slightly less dose to the OARs. For this patient, the results show that for the metrics chosen to evaluate this study, there is little between the plans.

3.2.4 Discussion

Our study showed statistically superior results when creating a treatment plan with patient-specific interstitial and intracavitary catheter positions. Qin *et al.* investigated the effectiveness of 3D printed, customizable applicators for patients with central pelvic-recurrent cervical cancer after hysterectomy.[48] The applicator had optimized arrangement catheters that can be straight or curved according to the position of the vaginal cavity. They compared the plans for the SCC applicator and the 3D printed applicator for 9 patients. One of the metrics they analyzed was D_{98}, they achieved 89.26%.[48]

For our patient-specific applicator with intracavitary and interstitial needles, our average D_{98} for 13 patients was 93.5%. For Qin *et al.*'s study, straight and curved catheters were placed

according to a template that was 3D printed for the specific patient anatomy, allowing the needles to be curved or straight according to the patients vaginal cavity and lesion position. They also analyzed V_{100}, and recieived an average of 93.0%.[48] Each of our patients in this study had a V_{100} of 95.0% after optimization. In our study, we placed intracavitary and interstitial catheters within the target volume based on the patients anatomy. Qin *et al*. showed that using a hybrid interstitial/intracavitary applicator, can increase the dose covering 98% of the CTV.[48]

Lindegaard *et al.* analyzed the use of 3D printed vaginal templates that were founded on a ring and tandem applicator for vaginal cancer.[49] The treatment plan consisted of EBRT of 45 Gy in 25 fractions, followed by the specific brachytherapy dose prescription for each patient. The 3D printed template was planned in Oncentra Brachy, and the catheter positions were selected based on the location of the CTV and the applicator.[49] They achieved a EQD2 D_{2cc} to the bladder of 85 Gy and a EQD2 D_{2cc} of 61 Gy to the rectum. For our patient-specific interstitial applicator plans, we achieved an EQD2 D_{2cc} to the bladder of 48.5 Gy and to the rectum 51.5 Gy. For vaginal cancers, a customized, patient-specific cylindrical applicator with interstitial capabilities and no template, can limit dose to the OARs.

Kudla *et al.* created patient-specific cylinder applicators for hybrid interstitial brachytherapy plans for primary vaginal cancers and recurring tumours in the vagina.[41] They created a 3D printed patient-specific cylindrical template that included flexible intracavitary and interstitial needles for 10 patients. These patients were chosen to represent a range of vaginal tumour locations and geometries. The catheter placement was manually chosen based on the CTV location. Initial needle spacing was less than 1 cm. If the CTV wasn't adjacent to an OAR, needles were placed within 5 mm of the CTV. Needle location and geometries were refined after analyzing the dose, and dwell times were adjusted until an acceptable plan was created.[41] They

achieved an average V_{100} of 96.84%. For our study, we achieved V_{100} of 95% in all plans. For V_{150}, they had an average of 41.89%, and for V_{200}, an average of 15.08%. For our study, we have an average for V_{150} of 34.0% and V_{200} of 13.58%. Since our V_{100} values differ by 1.84%, it is expected that our values for V_{150} and V_{200} will also be less. The difference in V_{150} for our study and Kudla *et al.* is 7.89%. This study and our study are similar, we both achieved a patient-specific interstitial applicator that successfully increased dose to the tumour volume and lowered dose to the OARs.

For the interstitial/intracavitary applicator patients studied in this research, those with large target volumes encompassing nearly the entire circumference of the vagina showed improved dose coverage and smaller hot spots when planned with a patient specific applicator. Patient 23 had a smaller width of 11.4 mm, but still benefitted from a patient specific applicator due to the location of available needle positions in the original applicator template. Although there were no patients with superior tumours in this patient cohort, the patient-specific interstitial applicator will also enhance treatment options for tumours located in areas that are difficult for traditional applicators to reach. The interstitial/intracavitary patient-specific applicators achieved the best results when the target volume had a long length, with larger width.

A limitation of this study is that it represents an idealized situation where the targets are known, and the catheters can be designed using that knowledge. In this work, the planner has the ability to place catheters within the patient nearly anywhere to achieve the dose objectives. Inherent to the study design, this work was not subject to the real-world scenarios where the catheters are inserted into the patient in the operating room and are not in the exact location as planned. This limitation is especially evident for the interstitial cases, where large targets to be treated will result in catheter positions that are difficult to place.

3D printing has the capability to create customized, patient-specific, gynecological brachytherapy applicators with patient-specific catheters positions, as demonstrated by this work as well as others. Yan *et al.* compared a MCC and a 3D-printed applicator for vaginal cuff brachytherapy[15] while Qin *et al.* formed high-quality intracavitary and/or interstitial brachytherapy 3D printed applicator.[48] Recently, Kudla *et al.* published a study the dosimetric differences between a patient-specific cylindrical template with flexible intracavitary and interstitial catheter positions and compared to the applicator used in clinic.[41] Overall, the patient-specific applicators in this work showed a statistically significant increase to the dose coverage for the target volume, while also decreasing dose to OARs.

CHAPTER 4 CONCLUSION

In this study, we investigated the dosimetric differences between the applicator used for treatment and a customized, patient-specific applicator with catheter positions placed strategically throughout the applicator for asymmetrical vaginal cancers. Current vaginal brachytherapy patients at the QEII Cancer Center are treated with vendor supplied interstitial or intracavitary applicators. These applicators have pre-set catheter positions. For asymmetric targets, a 3D printed patient-specific applicator with catheter positions based on the patient's anatomy could create a better treatment plan by increasing dose coverage to the CTV and reducing dose to the OARS.

It was our hypothesis that a customized, patient-specific applicator will improve the dose distribution and metrics when compared to the plan with the original applicator that was used for the clinical treatment. The treatment plans for the patient-specific intracavitary and interstitial applicator plans showed statistically significant higher dose coverage to the CTV, while limiting dose to the OARs. Patient-specific applicators provide the best result for patients that have a unique vaginal cavity shape, as well as an asymmetric target volume.

For patient-specific intracavitary applicators, when the target volume was greater than 5 mm, the high dose regions entering the CTV volume were increased for all patients, but the high dose volume for the patient-specific applicator was reduced. For the interstitial/intracavitary applicator patients, those with large target volumes, demonstrated an improvement with respect to target dose coverage and reduced hot spots when planned with a patient specific applicator. The patient-specific interstitial applicator will also enhance treatment options for tumours located in areas that are difficult for traditional applicators to reach.

4.1 Future work

The applicators in this work were cylindrical in shape because that was the patient data available within the clinic for retrospective study. If designing the study prospectively, the applicator itself can be created in a way so that it conforms to the patient's internal anatomy, which would be a benefit to patients where there was an air gap between the cylinder and the target. A CT scan with a standard applicator can be taken prior to treatment, or for a true patient-specific applicator, the patient could have radiopaque gauze inserted into the vagina so that the shape of the cavity is captured. The gauze or standard applicator can be contoured based on the patient's specific anatomy, and the catheters can be pre-planned within the planning system. Yan *et al.* used vaginal packing with gauze soaked in diluted diatrizoate meglumine, a radio-opaque medium that is visible on CT, then imaged with CT. After scanning, the gauze was extracted, and the catheter positions were placed based on the CT images.[15] MR imaging can also be used to create an applicator, this can be done similarly, using a gel that is MR-safe.

Another way to provide a custom applicator, a vaginal impression can be taking to accurately show the anatomy of the vagina and cervix, as well as the location of the tumour. Based on the impression, an applicator can be designed, and catheter positions can be placed throughout using the TPS.[50] This can be done similarly to Yan *et al.*, with a radio-opaque gauze that is suitable for imaging. Ideally, the pre-planned catheter positions could be exported with rest of the contours to create the 3D model of the applicator as it's sent to the 3D printer, if not possible, the catheter positions would need to be designed in a secondary software that prepares the TPS-created applicator for printing.

There are various open-source applications that have been used to create the computer-designed models. Yan *et al.* used a 3D Slice software that allows the catheter positions to be placed within the applicator.[15] Sekii *et al.* used Autodesk to design the template used for personalised template-guided interstitial applicators.[51] 3D Brachy, available from Adaptiiv Medical Systems (Halifax, Nova Scotia, Canada), is a vendor solution to 3D printing in brachytherapy. This software is able to import datasets from planning systems, including contours. The catheter positions can be modeled in the software, which incorporates the safety feature of alerting the user if the bend in the catheter trajectory exceeds the sources bend radius. This software allows the user to create a 3D model of the applicator with tunnels where the actual catheters would be inserted. At this time, the software is only available for surface brachytherapy applicators, but perhaps an intracavitary module will be available. In the case of a 3D Brachy created model, the 3D printed-applicator can even be printed "on-demand" with Adaptiiv's off-site printing service. Otherwise, the model can be sent to an in-house 3D printer. The flexible catheters from the brachytherapy vendor would be inserted into the applicator, with buttons fastening them in place inferiorly so that there will be no motion. For interstitial catheters, plastic needles could be inserted through the tunnels and into the target. Of course, with any interstitial catheters being used, the patient would be under anaesthetic during the implant.

In order for the applicator to be used clinically, it must be biocompatible, sterilizable, and free of imaging artifacts. The choice of printing materials is important as only a few have been proven to possess these qualities. Yan *et al.* used a biocompatible OBJET MED610 polymer.[15] Kudla *et al.* printed their patient-specific applicators in Polymether Ether Ketone, a bio-compatible thermoplastic that is commonly used for brachytherapy devices.[41] Cunha *et al.*

analyzed the use of PC-ISO for the printing of brachytherapy devices. PC-ISO is a readily available material that is FDA-approved for temporary implants in the body.[42] When sterilizing the applicators, the material of the applicator must withstand sterilization.

Once the applicator is printed, quality assurance testing is required to ensure a proper fit and treatment. This includes making sure each catheter can travel through its respective tunnel with no kinks or additional force required, ensuring that the surface of the applicator is smooth for patient comfort, and carrying out sterilization testing to guarantee that the sterilization does not affect the physical properties or geometry of the applicator. This would include verifying the dimensions of the applicator, as well as the positions of the tunnels made for the catheters. A CT scan of the applicator can be acquired, verifying the geometry of the applicator by creating an image fusion of the original scan with the designed applicator to compare to the CT of the 3D printed applicator. The patient would also undergo a CT simulation with the applicator and catheters in place, so that the treatment plan can be created. Ideally, MRI would be available to delineate the target but the use of MR for brachytherapy planning is not readily available in our clinic. A workflow table can be found below in Figure 4.1. This workflow could be adapted for cervical brachytherapy treatment as well if a patient-specific applicator was determined to be of benefit to patients.

The limitations of this study is it is a retrospective study with a relatively small sample size also only represents a fraction of patients that are treated using brachytherapy, therefore, a larger data set can provide less deviation in the results. The catheters were also placed based on where I thought they should be placed. If this study was repeated, the catheter positions may be completely different.

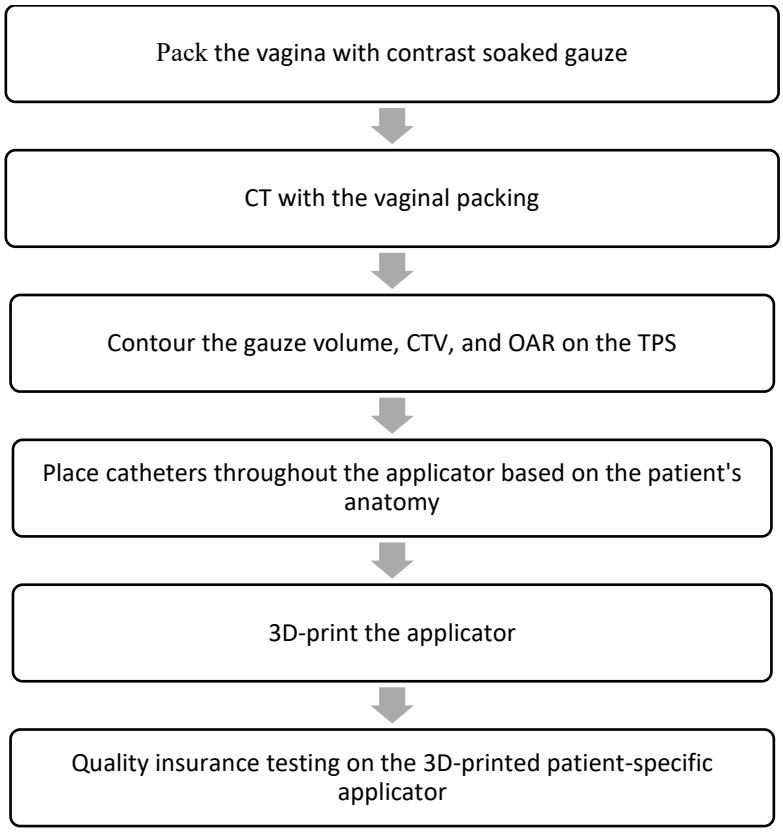


Figure 4.1 Workflow of study to create anatomical 3D printed applicators.

Another interesting avenue to continue the work started by this study is to focus on an algorithm that would optimize the location of each catheter. This optimization would ideally incorporate target dose coverage and OAR sparing in it design of the catheters and their locations. This will help ensure that each catheter is placed in a useful location, with a minimal number of catheters, to further increase the dose coverage to the CTV and limiting the dose to the OARs.

Further work could also examine the possibility of using a 3D-printed interstitial template for patients where insertion from a cylinder may be difficult. One patient to note for this method could be patient 5, who had a target that was nearly the length of the entire cylinder. This is a

way to increase the potential number of catheters used and provide a patient-specific location for them, while ensuring an easier insertion.

This study has demonstrated that opportunities for patient-specific applicator design can be incorporated into the preplanning phase for vaginal cancer and gynecological recurrences to create a better brachytherapy treatment plan for the patient. Technological gains in materials science, computation, and 3D additive manufacturing will contribute to furthering that cause.

BIBLIOGRAPHY

[1] Centres for Disease Control and Prevention, “What is Gynecologic Cancer?,” 2021.

[2] Canadian Cancer Society, “What Is Ovarian Cancer?,” 2023.

[3] E. B. Podgorsak, “Radiation Oncology Physics: A Handbook for Teachers and Students.”

[4] M. Stasenko, O. Fillipova, and W. P. Tew, “Fallopian Tube Carcinoma,” 2019. [Online]. Available: https://doi.org/10.

[5] E. C. Fields, W. P. McGuire, L. Lin, and S. M. Temkin, “Radiation treatment in women with ovarian cancer: Past, present, and future,” *Frontiers in Oncology*, vol. 7, no. AUG. Frontiers Media S.A., Aug. 21, 2017. doi: 10.3389/fonc.2017.00177.

[6] S. Pecorelli, H. Y. Ngan, N. F. Hacker, and L. W. Denny Howard Jones III John Kavanagh Henry Kitchener Ernest Kohorn Gillian Thomas, “Staging Classifications and Clinical Practice Guidelines for Gynaecological Cancers.”

[7] D. Brenner *et al.*, “Members of the Canadian Cancer Statistics Advisory Committee Project management,” 2022.

[8] A. Gerbaulet, R. Pötter, J.-J. Mazeron, H. Meertens, and E. Van Limbergen, Eds., *The GEC ESTRO Handbook of Brachytherapy*. ESTRO, 2002.

[9] Canadian Cancer Society, “Chemotherapy,” 2023.

[10] “Linear Accelerator,” 2023. [Online]. Available: https://www.radiologyinfo.org/en/info/igrt

[11] V. Strnard, *Practical Handbook of Brachytherapy*, 1st Edition. London, Boston: International Medical Publishers, 2014.

[12] “The Leeds Teaching Hospitals NHS Trust Prostate Brachytherapy using Low Dose Rate (LDR) Permanent Seeds Information for patients.”

[13] “Applicator Guide Brachytherapy Applicator Guide 2020 Brachytherapy Applicator and Accessory Guide 2017,” 2020.

[14] M. J. Rivard, L. Beaulieu, and B. R. Thomadsen, *Clinical Brachytherapy Physics*. Madison, Wisconsin: Medical Physics Publishing, Inc., 2017.

[15] J. Yan, X. Qin, F. Zhang, X. Hou, L. Yu, and J. Qiu, “Comparing multichannel cylinder and 3D-printed applicators for vaginal cuff brachytherapy with preliminary exploration of post-hysterectomy vaginal morphology,” *J Contemp Brachytherapy*, vol. 13, no. 6, pp. 641–648, 2021, doi: 10.5114/jcb.2021.112115.

[16] A. Hassouna, Y. A. Bahadur, and C. Constantinescu, “Assessment of air pockets in high-dose-rate vaginal cuff brachytherapy using cylindrical applicators,” *J Contemp Brachytherapy*, vol. 6, no. 3, pp. 271–275, Sep. 2014, doi: 10.5114/jcb.2014.45436.

[17] H. Westerveld *et al.*, “Definitive radiotherapy with image-guided adaptive brachytherapy for primary vaginal cancer,” 2020. [Online]. Available: www.thelancet.com/oncology

[18] M. Kamrava *et al.*, “GEC-ESTRO (ACROP)–ABS–CBG Consensus Brachytherapy Target Definition Guidelines for Recurrent Endometrial and Cervical Tumors in the Vagina,” *Int J Radiat Oncol Biol Phys*, vol. 115, no. 3, pp. 654–663, Mar. 2023, doi: 10.1016/j.ijrobp.2022.09.072.

[19] “Vaginal cancer-early detection and referral.” [Online]. Available: www.bpac.org.nz

[20] “Guidelines_Interstitial_Brachytherapy_for_Vaginal_Cancer”.

[21] S. Kirkpatrick, ; C D Gelatt, and ; M P Vecchi, “Optimization by Simulated Annealing,” 1983.

[22] E. Lessard and J. Pouliot, “Inverse planning anatomy-based dose optimization for HDR-brachytherapy of the prostate using fast simulated annealing algorithm and dedicated objective function,” *Med Phys*, vol. 28, no. 5, pp. 773–779, 2001, doi: 10.1118/1.1368127.

[23] M. G. Jameson, L. Ohanessian, V. Batumalai, V. Patel, and L. C. Holloway, “Comparison of Oncentra® Brachy IPSA and graphical optimisation techniques: A case study of HDR brachytherapy head and neck and prostate plans,” *J Med Radiat Sci*, vol. 62, no. 2, pp. 168–174, Jun. 2015, doi: 10.1002/jmrs.107.

[24] S. Roy, V. Subramani, K. Singh, and A. Rathi, “Dosimetric impact of dwell time deviation constraint on inverse brachytherapy treatment planning and comparison with conventional optimization method for interstitial brachytherapy implants,” *J Cancer Res Ther*, vol. 17, no. 2, pp. 463–470, Apr. 2021, doi: 10.4103/jcrt.JCRT_749_19.

[25] A. Cunha, T. Siauw, I. C. Hsu, and J. Pouliot, “A method for restricting intracatheter dwell time variance in high-dose-rate brachytherapy plan optimization,” *Brachytherapy*, vol. 15, no. 2, pp. 246–251, Mar. 2016, doi: 10.1016/j.brachy.2015.10.009.

[26] B. Tang *et al.*, “Dosimetric comparison of graphical optimization and inverse planning simulated annealing for brachytherapy of cervical cancer,” *J Contemp Brachytherapy*, vol. 11, no. 4, pp. 379–383, 2019, doi: 10.5114/jcb.2019.87145.

[27] Khan F, *The Physics of Radiation Therapy*, Fourth. 2010.

[28] J. C. Rosenwald, G. Gaboriaud, and D. Pontvert, “La radiothhrapie conformationnelle : principes et classification *,” 1999.

[29] F. M. Waterman, C. M. Mansfield, L. Komarnicky, P. Rani Anne, B. Corn, and N. Suntharalingam, “PI1 SO360-3016(%)00472-S l Physics Contribution A DOSIMETRY SYSTEM FOR 19’IR INTERSTITIAL BREAST IMPLANTS PERFORMED AT THE TIME OF LUMPECTOMY,” LI. I, 1997.

[30] C. B. Saw and N. Suntharalingam, “QUANTITATIVE ASSESSMENT OF INTERSTITIAL IMPLANTS,” 1991.

[31] H. Meertens, J. Borger, and M. Steggerda, “Evaluation and optimization of interstitial brachytherapy dose distribution,” *Brachytherapy from radium to optimization*, pp. 300–3006, 1994.

[32] Sushil. Beriwal, “American Brachytherapy Society consensus guidelines for interstital brachytherapy for vaginal cancer,” *Brachytherapy*, vol. 11, pp. 68–75, 2012.

[33] X. Hou, A. Liu, F. Zhang, J. Wong, and Y. J. Chen, “Dosimetric advantages of using multichannel balloons compared to single-channel cylinders for high-dose-rate vaginal cuff brachytherapy,” *Brachytherapy*, vol. 15, no. 4, pp. 471–476, Jul. 2016, doi: 10.1016/j.brachy.2016.03.002.

[34] W. Huo *et al.*, “Application of 3D printing in cervical cancer brachytherapy,” *J Radiat Res Appl Sci*, vol. 15, no. 2, pp. 18–24, Jun. 2022, doi: 10.1016/j.jrras.2022.04.004.

[35] S. Su, “DESIGN AND PRODUCTION OF 3D PRINTED BOLUS FOR ELECTRON RADIATION THERAPY,” 2014.

[36] S. A. Clarke, “3D Printed Surface Applicators for High Dose Rate Brachytherapy,” 2016.

[37] J. C. A. Dimopoulos *et al.*, “The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: Clinical feasibility and preliminary results,” *Int J Radiat Oncol Biol Phys*, vol. 66, no. 1, pp. 83–90, Sep. 2006, doi: 10.1016/j.ijrobp.2006.04.041.

[38] R. Sethi *et al.*, “Clinical applications of custom-made vaginal cylinders constructed using three-dimensional printing technology,” *J Contemp Brachytherapy*, vol. 8, no. 3, pp. 208–214, 2016, doi: 10.5114/jcb.2016.60679.

[39] O. Semeniuk, A. Cherpak, and J. Robar, “Design and evaluation of 3D printable patient-specific applicators for gynecologic HDR brachytherapy,” *Med Phys*, vol. 48, no. 7, pp. 4053–4063, Jul. 2021, doi: 10.1002/mp.14888.

[40] Z. Zhao, X. Tang, Z. Mao, and H. Zhao, “The design of an individualized cylindrical vaginal applicator with oblique guide holes using 3D modeling and printing technologies,” *J Contemp Brachytherapy*, vol. 11, no. 5, pp. 479–487, 2019, doi: 10.5114/jcb.2019.88441.

[41] M. Kudla, F. Bachand, J. Moore, and D. Batchelar, “Patient-specific cylinder templates for hybrid interstitial vaginal brachytherapy: Feasibility of automated 3-D design, 3D printing, and dosimetric outlook,” *Brachytherapy*, 2023, doi: 10.1016/j.brachy.2023.03.002.

[42] J. Adam *et al.*, “Evaluation of PC-ISO for customized, 3D printed, gynecologic 192 Ir HDR brachytherapy applicators.” [Online]. Available: www.stratasys.com/materials/fdm/pc-iso.

[43] S. M. Glaser and S. Beriwal, “Brachytherapy for malignancies of the vagina in the 3D era,” *Journal of Contemporary Brachytherapy*, vol. 7, no. 4. Termedia Publishing House Ltd., pp. 312–318, 2015. doi: 10.5114/jcb.2015.54053.

[44] Z. Liu *et al.*, “Comparison of graphical optimization or IPSA for improving brachytheraphy plans associated with inadequate target coverage for cervical cancer article,” *Sci Rep*, vol. 7, no. 1, Dec. 2017, doi: 10.1038/s41598-017-16756-w.

[45] “DVH Markers, Presets, and Tables.” [Online]. Available: http://www.nucletron.com

[46] R. Pötter *et al.*, “Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy - 3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology,” *Radiotherapy and Oncology*, vol. 78, no. 1, pp. 67–77, Jan. 2006, doi: 10.1016/j.radonc.2005.11.014.

[47] B. J. Gebhardt *et al.*, “Image-based multichannel vaginal cylinder brachytherapy for the definitive treatment of gynecologic malignancies in the vagina,” *Gynecol Oncol*, vol. 150, no. 2, pp. 293–299, Aug. 2018, doi: 10.1016/j.ygyno.2018.06.011.

[48] X. Qin *et al.*, “Efficacy and safety of a 3D-printed applicator for vaginal brachytherapy in patients with central pelvic-recurrent cervical cancer after primary hysterectomy,” *Brachytherapy*, vol. 21, no. 2, pp. 193–201, Mar. 2022, doi: 10.1016/j.brachy.2021.11.004.

[49] J. C. Lindegaard *et al.*, “Individualised 3D printed vaginal template for MRI guided brachytherapy in locally advanced cervical cancer,” *Radiotherapy and Oncology*, vol. 118, no. 1, pp. 173–175, Jan. 2016, doi: 10.1016/j.radonc.2015.12.012.

[50] N. Magné, C. Chargari, N. SanFilippo, T. Messai, A. Gerbaulet, and C. Haie-Meder Christine, “Technical aspects and perspectives of the vaginal mold applicator for brachytherapy of gynecologic malignancies,” *Brachytherapy*, vol. 9, no. 3, pp. 274–277, Jul. 2010, doi: 10.1016/j.brachy.2009.08.014.

[51] S. Sekii *et al.*, “Inversely designed, 3D-printed personalized template-guided interstitial brachytherapy for vaginal tumors,” *J Contemp Brachytherapy*, vol. 10, no. 5, pp. 470–477, 2018, doi: 10.5114/jcb.2018.78832.