THESIS

IMPORTANCE OF HETEROGENEITY CORRECTION FOR PROSTATE THERAPY PLANNING AS IT RELATES TO PROSTATE MOTION

Submitted by

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In partial fulfillment of the requirements

For the Degree of Master of Science

Colorado State University

Fort Collins, Colorado

Fall 2012

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ABSTRACT

IMPORTANCE OF HETEROGENEITY CORRECTION FOR PROSTATE THERAPY PLANNING AS IT RELATES TO PROSTATE MOTION

Prostate adenocarcinoma is the most common cancer among men and second leading cause of mortality of men in the United States. External beam radiotherapy (RT) is often used for local prostate tumor control as part of multimodality therapy. Dosimetric treatment planning for RT is based on complex calculations made by computerized planning software, which are designed to achieve a target prescribed dose to the prostate while not exceeding normal tissue constraints. Those RT planning calculations are made from an initial pre-treatment computed tomographic (CT) scan, which provides the location, volume and density of the prostate and critical normal tissues. The calculation step applies Heterogeneity Correction (HC) during RT planning, which adjusts the delivered radiation fields according to regional tissue densities such as the presence of bone in the anatomic region of interest.

Inter-fraction and intra-fraction prostate movement are both known to occur during the course of radiotherapy. Current standards of practice utilize ways to track and account for prostatic movement in order to maintain accurate delivery to that organ. However, those methods do not adjust for the HC that was already applied during the original treatment plan calculations. The use of HC for prostate cancer RT is therefore of particular importance because prostate movement relative to the pelvic skeleton might result in dosimetric inaccuracies, since the HC used in initial RT planning is based on the original prostate position.

This project was part of a larger research study in which intact normal male dogs received hypofractionated stereotactic radiation to the prostate, as a translational animal model for human prostate cancer. In this study, inter-fraction prostate motion was evaluated and then those data were used to examine the impact of this movement on the use of heterogeneity correction (HC) on stereotactic body radiation therapy (SBRT) of the prostate, by evaluating the dose received by the planned target volume (PTV) and surrounding tissue during prostate RT planning.

In Aim 1, cone beam CT (CBCT) images from ten dogs were evaluated retrospectively to estimate typical inter-fraction prostate movement. Organs of interest were contoured on each daily treatment CBCT data set, and those images were registered (fused) to the original planning CT. Prostate motion was quantified by determining the displacement of each isocenter relative to the original radiotherapy planning CT.

For Aim 2, CT scans acquired during the course of SBRT were used to prospectively calculate new treatment plans that incorporated prostate displacement from four dogs, with and without HC. Organs of interest were contoured on each CT data set, and images were registered (fused) to the original planning CT. As above, prostate motion was quantified by measuring the isocenter movement in three axes relative to original RT planning CT. An optimal original planning CT was run twice for each CT, with and without HC, while adjusting the prostatic isocenter. Dosimetric data for organs of interest were evaluated using dose volume histograms (DVH) and comparing doses to previously defined constraint values.

Results indicated a wide range of inter-fraction prostate displacement in both Aims 1 and 2, slightly greater in magnitude than similar human prostate movement data. The greatest prostate displacement was in the y axis (anteroposterior). No statistically significant differences were seen in target or normal tissue doses, with or without HC,

suggesting that even in the presence of marked prostate motion, potential inaccuracies caused by HC may not have a great impact on the prostate RT planning. As expected, without HC there was a trend for the dose to the most organs of interest to increase slightly.

In terms of how displacement affected tissue doses, maximum displacement of prostate was associated with adjacent tissues exceeding the known normal tissue tolerance. In particular, caudal and left displacement led to large doses exceeding the constraint limits for the posterior rectal wall. Those data indicate the importance of continued tracking or other methods to counteract prostate motion.

The results provide a more informed approach for using HC relative to prostate motion during treatment of prostate cancer, as well as providing data relevant to tumor control, acute and late toxicities associated with inter-fraction movement of prostate RT.

ACKNOWLEDGMENTS

First of all, Thanks to God who has helped me through my life in State, lighted my way with all decision that I made, and blessed my time to complete the project. I owe major gratitude to many people who helped and supported me in completing this project. I want to thank my parents, who believe in me and endured the burden of the long distance away and the overseas move. Their love and encouragement helped me to be what I am today. I hope I can make them proud of me one day.

I would like to show my greatest appreciation to my co-advisors Drs. Susan Kraft and Susan LaRue for their support, care and help. You kept track of my work to finish the project within my time line. Also, I would like to thank my committee who were always very involved in every process of my project. Without their guidance this project would not have materialized.

To Dr. LaRue, whose project funded my work and thank you for your contributions in the decisions which were vital in this project.

To Dr.Custis, thank you for your tireless efforts in making this project perfect and I'll be forever proud of it.

To Dr.Zhang, thank you for helping me and for being kind when I spent time in physics lab.

Also, thank you to Mike Nolan and Lynn Griffin for helping me to understand treatment planning, answering my questions in RTX field, and getting the images that supported my project. Thank you to the VTH staff of technologists and anesthetists who participated in getting the work done.

To Dr. Annette Bachand, thank you for doing the statistical analysis of my project.

To Alaa, thank you for being my sister and best friend. You are sharing my happiness and sadness. You are such a joy in my life.

To Mouath, my little boy and brother, thank you for your prayers for me.

To Abdullah, thank you for your greatest and constant support, optimistism, encouragement and love you have always provided. You inspire me with power through my struggling. I can't say thanks enough to you.

To the Saudi Cultural Mission, thank you for paying my tuition, without your funds I wouldn't be here and getting my degree.

And last but not least, Thank you to my Fort Collins friends.

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INTRODUCTION

Prostate cancer:

Prostate cancer is the most common cancer among men and the second highest cause of male mortality. It is initially an asymptomatic disease, therefore by the time patients come to a clinic complaining from the symptoms, the cancer is often in an advanced stage. Adenocarcinoma, a malignant type of gland cancer, is the most common tumor type of prostate gland cancer. The prostate is located in the pelvic area between the rectum and bladder. The average size of the human male prostate is between 30-40 grams and it is usually enlarged in patients over 40 years of age. The prostate contains glands, ducts, muscular tissues, and is enclosed by fibrous tissue. The prostate is divided into four regions: the transitional, the central, the anterior, and the peripheral zones. The peripheral zone is the posterior part of the prostate and the most common and predominant location for tumor to grow.[1,2] One third of the prostate is made of muscle and the rest is comprised of glandular tissue. Therefore, the most common tumor has a glandular origin such as adenocarcinoma. However, transitional cell carcinoma (TCC), a rare form of prostatic cancer, is often associated with bladder cancer and originates from this cell which lines the urethra and bladder, and can secondarily invade the prostate. Another type of prostate cancer is sarcoma, which is also an extremely rare tumor and originates from the muscular and connective tissue of the prostate itself. In this project, the term of prostate cancer refers to adenocarcinoma.[3]

There are many risk factors that are associated with prostate cancer including age, race, family history, and obesity.[4] Of the patients with prostate cancer, 70% are over 65 years of age while 30% of these patients are in the age range of 50 - 65. Moreover, although prostate

enlargement is associated with the elderly due to benign prostatic hyperplasia, it is not always a risk factor.[3] The second risk factor is race; African Americans are at high risk of developing prostate cancer in older age, followed by Caucasian Americans. Additionally, prostate cancer is more likely to occur in men with a family history of any other type of cancer. The increased incidence of prostate cancer associated with family history is 13%, and this also increases if there have been other family members who have had prostate cancer. Lastly, obesity may play a role in the incidence of prostate cancer but there is no study that shows the relationship between the cause of obesity and prostate cancer.[3,4]

Prostate Cancer Treatment:

Staging plays an important role in determining treatment options for cancer given patient. Treatment of prostate cancer is based on tumor, node, and metastasis (TNM) stage and Gleason score of the prostate-specific antigen (PSA) level. High TNM stage and PSA levels are more likely to be found in patient with an aggressive or malignant tumor, while the opposite is true for a benign tumor. In addition, the age and physical health of the patient can modify the treatment plan.[5]

Watchful waiting is an active surveillance for early stage, slow growing tumors, and very elderly patients. However, follow up imaging and the PSA test are highly recommended to determine whether a tumor may require further therapy.[6] Radical prostatectomy, most recommended treatment, is performed either by surgery or laparoscopy.[5] Laparoscopic prostatectomy is associated with fewer complications and reduces the morbidity of surgery, and allows for rapid recovery, but it has high risk of residual disease especially with high tumor stage ≥ T3 and/ or high PSA level.[6] It is recommended for younger patients with early stage and poorly differentiated tumors. [5]

The alternative to surgery is radiotherapy, which is optional for a variety of patients,

either singly or in combination with other therapies in all stages of tumor. In general, surgical options will be considered for prostate cancer that has a lower tumor stage and is more localized. On the other hand, external beam radiation therapy is more often recommended for higher stage tumors which may have a larger primary tumor and/or regional metastases.[5-7] External beam radiotherapy can be effective for tumor control and has low side effects, however this is not recommended for a patient who has obstructive urinary disease which is most appropriately relieved surgically.[8-10] There are many types of radiation therapy which will be covered later.

Finally, there is hormonal therapy to inhibit the production of testosterone and androgen either temporarily or permanently. These two hormones are normally produced but can nourish prostate cancer to grow. Hormonal therapy is usually used in aggressive and late stage tumors. Moreover, the combination of these therapies is widely used in practical treatment especially with more aggressive tumors, those that have a high PSA score and/ or high tumor stage. For example, the gross part of the tumor can be removed by radical prostatectomy, and then followed by radiation to ensure there is no residual tumor at the surgical bed.[5] Any residual tumor increases the risk of tumor recurrence which is an unfavorable event.

Radiation therapy for treating prostate cancer:

Radiation therapy can be delivered by an external beam, or using brachytherapy (via locally implanted radioactive seeds) and this choice depends upon on clinical, biological, and technological factors. Indeed, evolving technology has markedly changed the way that prostate cancer patients are treated. The goal of therapy is to kill the prostate cancer cells while minimizing the risk of toxicity to the rectum and bladder. Also, the doses experienced by those critical normal tissues have to be within their tolerance constraints.[11]

External beam radiation therapy (EBRT) has evolved markedly over the last few decades to increasingly more advanced forms of conformal therapy, meaning that the radiation dose is shaped as closely as possible to the target with an appropriate surrounding margin. This advancement has been made possible by the development and increased availability of more sophisticated imaging technology, which has enabled more sophisticated treatment planning as well as on-board imaging for patient verification during treatment. One of the first advancements was the ability to perform 3D computerized imaging of CT scans to create RT treatment plans (3DCRT), which then progressed to intensity modulated radiation therapy (IMRT).[12] Multileaf collimation (MLC) has been used to shape the therapy field to the target, creating a uniform target dose which meeting strict tolerance constraints to the surrounding tissue. IMRT also varies the incident beam by modulating the intensity of the fields, while the radiation dose is delivered.[6,13] IMRT is conventionally administered in multiple small daily fractions over a 2-6 week time period, depending upon the protocol.[14]

Stereotactic body radiation therapy (SBRT) has developed from conventional radiation therapy as an even more targeted way of delivering radiation to a tumor. Delivering high dose per fraction over a short treatment period is a major feature of SBRT, and a departure from IMRT and conventionally fractionated RT. High biologically equivalent dose (BED) and good tumor control probability (TCP) are expected from this modality. SBRT uses a steep dose drop-off at the tumor edges to spare normal tissues from the high dose intensity being delivered to the tumor, which results in less normal tissue toxicity. In SBRT, accuracy in delineating the tumor helps to minimize the volume of normal tissue within the planned target volume. Also, tracking the motion of displacement is important to deliver such a high dose with confidence while minimizing normal tissue toxicity. SBRT is undergoing use for prostate cancer but needs further investigation in terms of maximum dose

to target, tumor control, and normal tissue toxicity.[6,11,15]

SBRT targets have to be well defined, with a small planning treatment volume (PTV) and no added margin for the clinical treatment volume (CTV). Dose delivered to the target is heterogeneous, with a few fractions (1-5) given over a shorter period of time. This is appropriate for smaller tumors that can be well localized with image guidance, and requires exact localization of the target in order to avoid over-treating surrounding normal structures. Recently, studies suggest a low α / β ratio for prostate cancer, indicating this may respond best to large doses in a few fractions or a hypofractionation regimen such as that delivered by SBRT. With this small α / β ratio (1.5 for prostate)[16,17] hypofractionated radiation could damage and kill tumor which is desirable for tumor control. As evidence, there is correlation between the biochemical control of PSA level and the use of hypofractionated SBRT.[11,15]

The most recent advance in radiation therapy for prostate tumors is the use of image guided radiation therapy (IGRT) to improve targeted delivery for either IMRT or SBRT. IGRT leads to increased ability to verify tumor/ target location, decrease the planned target margins, and possibly resulting in less toxicity to the organs in the treatment field. With IGRT, on-board imaging detects the location of the target and allows the treatment to be adjusted according to its movement relative to the original treatment plan. This adjustment is made via precise patient table movements which overcome inter and intra- fractional organ motion without modifying the original plan.[6,18,19] Therefore, IGRT can reduce geometric errors, and provides precise management of organ motion. Also, IGRT allows for an escalation of dose and a better outcome than IMRT alone.[12] Adequate patient immobilization, prostate immobilization, and accurate target volume delineation are essential for successful EBRT, particularly for SBRT planning and delivery.[18,19]

Inter-fraction prostate movement:

Because the prostate has a transient movement and its size can change during the radiation therapy, recently, there are many studies that have attempted to manage the movement of the prostate during the daily setup of fractional delivery, diagnostic imaging, and biopsy. Methods for prostate tracking can provide valuable information to overcome uncertainties in the geometry. The major sources of geometric error during RT course are target delineation, patient position, and organ motion. The delineation of tumors varies depending on many factors like site, size and stage of the tumor, and patient age and size. Also, the experience and the knowledge of the oncologist and consulting radiologists play a major role in target delineation. The shape and size of the bladder and rectum can affect prostate displacement during the course of radiation treatment.[19-22]

Intra-fraction and inter-fraction movement of the prostate gland has been studied extensively. Intra-fraction displacement decreased when the time between the CBCT and delivering the treatment course was minimized. In a study of 20 patients receiving IMRT, table adjustments were required for 10% of the irradiations so as to compensate for intrafraction movement documented by fiducial markers.[23] Furthermore, from day to day with more time between the fractions, inter-fraction displacement of prostate will also increase. In addition, bladder and rectal filling are changing too. New modalities like IGRT allow for verification of the organ position before treatment is delivered, making a shift of the patient position to account for the inter-fraction motion of the prostate. Accurate patient position setup and localizing the target volume of prostate have also been improved throughout the course of RT by the use of IGRT. In a study of inter- and intra-observer variation during prostate definition, it was found that significant systematic error occurred compared to a standard prostate volume.[24] In this study, the volume of the prostates that were contoured were larger than the true volume of prostate, most likely related to conservative prostate definition in order to spare rectal tissues. In fact, none of the observers

in this study included the entire prostate in their treatment plan. The posterior part was missed by 2.8 mm while normal tissue from the anterior part was included by 5.8 mm.[24] In a separate study on the effect of time between CBCT and delivery of radiation therapy, dose uncertainty increased with increased intrafraction time.[9] Therefore, the intrafraction movement would be expected to further worsen any existing systematic error in target definition.

There are many ways to overcome, minimize, and track prostate displacement. One of them is fiducial markers. Urethral catheter and rectal balloon also contribute to prostate immobilization and deal partially with prostate inter-fraction motion. However, even with fix immobilization and good tracking there are uncontrolled prostatic movements.[18,25-31]

Implanted fiducial markers have been used for over than 10 years to measure prostate inter-fraction, isocenter and setup accuracy, however, the associated drawbacks can limit the usage of fiducial markers. First, the implantation of fiducial has to be done under the guidance of an imaging modality like US or x-ray to ensure its proper placement, and this sometimes requires general anesthesia. Second, the implant procedure should be done at least a week before the stimulation CT is acquired, to allow swelling from implantation to resolve. Therefore, there is more work, cost and time associated with the use of fiducial markers. Also, there is a chance of marker migration and furthermore, there can be prostate trauma or infection associated with the implantation.[32-35] According to Emile et al, when studying 53 patients receiving fiducial markers, less than 10 patients encountered transient hematuria and hematospermia, less than 30 patients had mild rectal bleeding at the day of procedure, and just 2 patients had marker migration.[32] Instead of fiducial markers, placement of a urethral catheter and rectal balloon can immobilize the prostate and deal partially with prostate intra-fraction motion. However, even with fixed immobilization and good tracking there are uncontrolled prostate movements,[18,19] but the use of imaging

tracking is faster, easier, less invasive and associated with less patient morbidity than these other methods.[18,19,32,35] Considering the movement of the organ is an important factor in successful radiation therapy. Systematic and random set up errors were lower when using prostate fiducial markers than using bony registration, for all directions of displacement (anterior- posterior (AP), cranial-caudal (CC), and right-left (RL)). The highest rate of both systematic and random error for inter-fraction prostate motion was in AP coordinate followed by CC coordinates, and then less remarkably in LR coordinate.[35] Bladder and rectal filling played a role during prostate shifts.[32,35] IGRT can reduce the uncertainty from geometric error and localize the displaced organ instead of fiducial markers.

Also, to detect intra-fraction motion, the table position adjustment can be used during IMRT and lead to a reduction in treatment margins.[23] Real time monitoring with fluoroscopy and US helps in some cases. Inter-fraction prostate movement has been shown to cause shifts in the isodose line for the prostate on dose volume histograms (DVH). This could lead to clinically significant changes in delivered dose if the clinical treatment volume (CTV) is large enough that the prostate isocenter moves outside of the planned treatment volume (PTV, which is CTV plus a 5 mm margin).[14]

Two main causes of inaccuracy with EBRT are patient structure misalignment and uncertainty in treatment delivery.[36] There are different methods to verify daily setup error associated with IGRT, including the use of both kilovoltage radiographic imaging (KV) and CBCT.[33] KV radiographic images are used for matching bony structures to digitally reconstructed radiographic images (DRR) that have been derived from the original treatment planning CT scan. On the other hand, CBCTs are used to match soft tissue anatomy to the original CT scan, however CBCT images are lower in resolution. In this fashion, the IGRT images match the planning conditions. Also, megavoltage (MV) radiography is available but using the high energy beam for imaging lacks structural anatomy, poor image quality due

to image scatter. US and fluoroscopy can be used for real time tracking. The accuracy of imaging varies with technique, image quality, interpretation, availability, and how quickly the match and re-alignment can be done by the radiation therapy system like a linear accelerator. All these factors should be taken into consideration. Matching the CBCT images with the original radiation therapy plan does increase the time of the radiation therapy session, which must be considered given the fact that the prostate's intrafraction motion also increases with session time.[6,32,33,35-38]

Many studies have investigated a way to image the prostate prior to delivering the dose with better efficiency so as to correct for prostate movement and improve sparing of normal tissues in the field. In an investigation of inter-fraction motion based on bony structures as assessed by daily CBCT imaging, it was found that the largest movement was on the anterioposterior (z) direction and the smallest was on the lateral (x). [39,40] Automatic registration of CBCT to CT images is usually based on bony anatomy and/or soft tissue with skin markers. In a study of 14 patients receiving IMRT, setup error was largest when based on three-point skin markers, and alignment based on implanted fiducials was more effective in improving the accuracy of setup errors as well as being a major predictor on the need to shift margins to a new prostate position. Because the prostate is not connected to bony anatomy directly, the shift based on bony anatomy is small but did not improve the target position over the use of three-point skin markers. Therefore, depending upon bony structures alone should be regarded carefully because the largest prostate motion was in the AP direction.[21] Without treatment verification or tracking, prostate margins for the PTV as high as 6-8 mm are required. The result might be changed on other study with same goal, and that could be because of the difference of delineation of target volume.[21,39,40]

Inter-fraction prostate motion differs with the method of immobilization. When an endorectal balloon (ERB) was used, prostate displacement was reduced by 1.3-1.8 mm.

Random changes in prostate location can be caused by daily changes in rectal contents. Although this displacement was considered low, the biggest displacement was still in the AP direction.[21,32] The displacement range was between 1.5- 4.5 mm (1 SD), 0.9-3.9 mm, and 0.7-1.9 mm for AP, CC, and RL respectively. In this case the advised CTV-PTV margins should be between 8 -15 mm toward the rectum. By precise controlling the margins, the degree of rectal irradiation will be precisely controlled too, thereby reducing toxicity which is a limiting factor. Pushing the rectum away from the field to protect it from toxicity is quite challenging. Using an ERB is advantageous because it is possible to displace the prostate to the pubic bone and the posterior rectal wall is moved away from the high radiation beam delivered to the target. Also, the inflated balloon adds a small amount of attenuation by itself which in turn reduces the delivered dose to critical tissues.[19,21,35]

Prostate shift and movement has been detected in x, y, z directions but the direction and degree of motion is not consistent between studies. In some studies, prostate motion was largest in the z direction while lowest in x direction. In contrast, with other studies, displacement was largest in the y direction and least in the x direction. Rectal filling is the main factor for inter-fraction motion,[24] in addition to the correlation between the organ at risk (OAR) and organ motion.[21,23] CBCT allows for accurate identification and localization of the soft tissue during the treatment course which is not possible with other tools. 6- 8 mm PTV margins are recommended if CBCT is not applied because there are bony misalignment and prostate transient motion. Mainly, prostate movement in the AP direction is significant relative to the pelvic bony anatomy.[39]

Therefore, to minimize and evaluate prostate displacement, first, it is recommended to immobilize the patient in a reasonable manner and use the same form of immobilization for every treatment throughout the course of radiotherapy. Second, control and minimize the transient movement of the organ especially the target. Finally, PTV margins should be

accurately covered and surrounding tissue excluded for better tumor control and free toxicity. Increasing both the prescribed radiation dose and PTV margins yields the risk of increasing treatment-related toxicity. Small changes in delineation and set up might have a big effect on dose escalation.[18,21,41]

Diet can impact rectal and bladder filling and therefore prostate position. Some institutes utilize food constraints and medicine like laxatives before planning and therapy. The purpose of special diets is first to reduce intestinal gas and to improve image quality. Moreover, reducing changes in rectal volume through the course of radiation reduces inter-fraction motion. Also, the standard protocol is to instruct the patient to empty his bladder and rectum, and drink 250 ml before the simulation scan and therapy. Usually, the special diet is started a week before CT simulation planning and adhered to until the end of treatment course. Mild laxative can be taken 2 days before scanning. After the registration of images based on bony structure and prostate, prostate motion was calculated for groups of patients who were following a special diet or not. It has been found that diet has an effect in reducing rectal mobility due to gas and feces significantly, and as a consequence prostate motion is reduced too. However, the non-diet group showed small prostate motion, and there was no correlation between the size of the rectum and the degree of inter-fraction and intra-fraction motion.[30,42,43]

Patient position can also be used to reduce inter-fraction motion and improve rectal sparing with IMRT. Increasing the distance between the target and organ at risk is favorable in order to target the tumor and avoid organ at risk. This principle can be employed either invasively or noninvasively. Invasive methods are interaoperative and limited to certain organs such as the ovary, and to certain kinds of patients. Noninvasive methods are widely used, especially for treating regions like the abdomen or thorax that are associated with much involuntary movement. Supine positioning is more comfortable for

the patient and better stabilizes the thorax or abdomen during radiotherapy. In contrast, prone positioning might increase the dose to organs at risk. In the situation with treating prostate cancer, the rectum and bladder are organs at risk, and the prone position has been found to have an impact on toxicity because this position increases the distance between the anterior rectum wall and prostate.[19,23,44-46] It is therefore more favorable over the supine position and the beam arrangement when it comes to rectal sparing, at least for 3D-CRT. No study has shown this same effect of prone vs. supine position for IMRT and SBRT. As we know, IMRT and SBRT have more stringent requirements for accurate delivering of radiation comparing to 3D_CRT.[12,42,47]

As for volume, the only remarkable change was in the bladder volume with prone position and when taking into account the time it takes a patient to change position from supine to prone (which increases bladder filling). Prone 3DCRT was superior than supine 3DCRT in terms of homogeneity of dose, but inferior to supine IMRT in term of sparing of organs at risk. Prone positioning caused more mobility of internal organs and displacement of prostate anteriorly although the rectal wall is restricted by muscles, ligaments and abdominal contents. Indeed, those factors lead to uncertainties of dose and introduce organs to potential toxicity. However, the table top does put some pressure against the abdomen, sparing the normal tissue with external beam therapy is correlated with accurate delineation of target (prostate) based on CBCT as an effective way to match the target with the planning and reduce the delivered dose.[23,42,45,48-50]

Evaluation of the treatment plan by dose volume histograms (DVH) is a widely accepted method to evaluate the efficiency of treatment planning. DVH provides the 3D conformational distribution of the radiation dose displayed on a 2D graph. The dose level, uniformity and homogeneity of distribution of the region of interest (ROI) are provided and evaluated by this graph.[14,51] Heterogeneity correction is routinely applied during the

planning of RT. HC accounts for the different densities of anatomic structures such as bone, air, and soft tissue, which allows the calculation of beam attenuation. In dense structures like bone, the radiation beam is more attenuated and tissues beyond that will receive less dose. In contrast, air-filled structures (such as the lungs), the radiation beam is not attenuated as much and the structures beyond that will receive more dose. Thus, calculation error might be a concern if electron density was not calculated based on different tissue densities.[52,53]

There are a few studies on the impact of planning with and without HC. This has been evaluated for brain, lung, and prostate planning RT. No difference was found for planning with or without HC in the brain and prostate, however, it is important to consider HC in areas with low density like lung. Moreover, the effect of Mega voltage cone beam computed tomography (MV_CBCT) may effects imaging and may need for reoptimization. However, MV -CBCT has a higher dose to the patient than conventional CBCT. With a small monitor unit (MU), the dose to critical organs in the field, like the bladder and rectum, is smaller than CBCT while the reoptimization is not necessarily. However, with high MU the reoptimization is important. (Use of MV-CBCT is infrequent).[42,54]

Over the course of therapy, the volume, shape, and location of tumor and surrounded tissue change from day to day due to tumor shrinkage, loss of weight, rectal and bladder contents, and organ displacement.[55] As a result, uncertainty of daily positioning is unavoidable as structures changed during the course of therapy, potentially leading to poor tumor control, and more toxicity.[56-58]

In summary, SBRT is newly being used for human prostate cancer, but the radiation therapy planning may be impacted by prostate movement relative to the pelvic anatomy. The influence of prostate movement on the relevance of heterogeneity correction applied to the planning is not known yet, and yet may affect the dose delivered to the prostate and

normal tissue.

The radiation dose to the prostate and critical normal tissue may change using heterogeneity correction due to influence of the prostate movement. The objective of this project was first to evaluate the inter-fraction prostate motion on daily basis CBCT. Second, determine whether heterogeneity correction makes difference on the calculated planning or not regarding the target and critical organ.

Hypothesis and Aims:

This Masters project was part of a larger IACUC-approved research study in which intact normal male dogs received prostatic stereotactic hypofractionated radiation, as a translational animal model for human prostate cancer. In this study, inter-fraction prostate motion was evaluated and then those data were used to examine the impact of this movement on the use of heterogeneity correction (HC) on EBRT of the prostate, by evaluating the dose received by the target volume and surrounding tissue during prostate RT planning.

In Aim 1, cone beam CT (CBCT) images from ten dogs were evaluated retrospectively to estimate typical inter-fraction prostate movement. Organs of interest were contoured on each daily treatment CBCT data set, and those images were registered (fused) to the original planning CT. Prostate motion was quantified by measuring isocenter movement in three axes relative to original RT planning CT.

For Aim 2, CT scans acquired during the course of SBRT were used to prospectively calculate new treatment plans that incorporated prostate displacement from four dogs, with and without HC. Organs of interest were contoured on each CT data set, and images were registered (fused) to the original planning CT. As above, prostate motion was quantified by determining the displacement of each isocenter relative to the original radiotherapy planning CT. An optimal original planning CT was run twice for each CT, with and without HC,

while adjusting the prostatic isocenter. Dosimetric data for organs of interest were evaluated using dose volume histograms (DVH) and comparing doses to previously defined constraint values.

MATERIALS AND METHODS

Animal subjects and patient preparation for CT simulation scan. This project was done as part of a larger study in which dogs received 5 fractions of SBRT radiation to the prostate, in order to investigate normal tissue toxicity. Prostate movement and its effect on HC during the treatment planning process was studied in this dog group, using the CT scans that were obtained during the process of treatment planning and radiation.

The dogs in the study were purpose-bred young adult male Walker hounds. Initially dogs in this project received a standard diet of dry food, but later in the course of the project (after approximately Dog 5) the dogs' diets were altered to a low residue canine food in an attempt to standardize rectal sizes on a daily basis. All dogs were fasted for 12 hours prior to RT and an enema (soapy water) was administered four hours prior to RT. In addition, the treatment was delivered at approximately the same time each day.

The steps taken to prepare and position each animal for CT and radiation fractions are shown below in Figures 1-5. To minimize the prostate intra-fraction movement, a Foley catheter was placed rectally first; using a 55cm long and 8 French catheter. Then, the balloon was insufflated with air for the CT simulation scan, but with sterile saline for RT using a volume of ~35 cc. A urinary catheter was also placed in the urethra to better allow that anatomy to be visualized on the CT scan.

In order to maintain the same exact position for imaging and each radiation fraction, animals were positioned in a trough with a vacuum cushion molded to each animal with the dogs positioned in dorsal recumbency. That same cushion was used for each radiation fraction so that the treatment couch could be indexed identically for each radiation fraction. The rear limbs were then extended and secured caudally, and the animal taped securely into

position.

Diagnostic CT scans: The original planning CT scans (simulation scans) were performed using a PET/CT hybrid instrument (Gemini TF Big Bore, Philips Healthcare, Andover, Mass., USA). This instrument has a sixteen slice, helical CT x-ray tube and detector configuration and a lutetium: yttrium orthosilicate PET detector ring. CT helical scanner images were acquired using 16 X 0.75 detector rows, 08.17 pitch, 1.0 second tube rotation time, 120 KV, 250 mAs/ slice and reconstructed at 2.0 mm thickness with 2.0 mm increment, 512 matrix, with a standard filter (algorithm), then transferred to the Eclipse® (Varian, Las Vegas, NV, USA) planning system.

Non-contrast images were obtained of the pelvis from mid-lumbar vertebrae 2 through the ischial tuberosities to include the most caudal extent of the male urethra. A post-contrast series was obtained to be fused with the last non-contrast data set for radiation planning after IV infusion with Omnipaque ™ 350 (GE Healthcare, Princeton, NJ, USA).

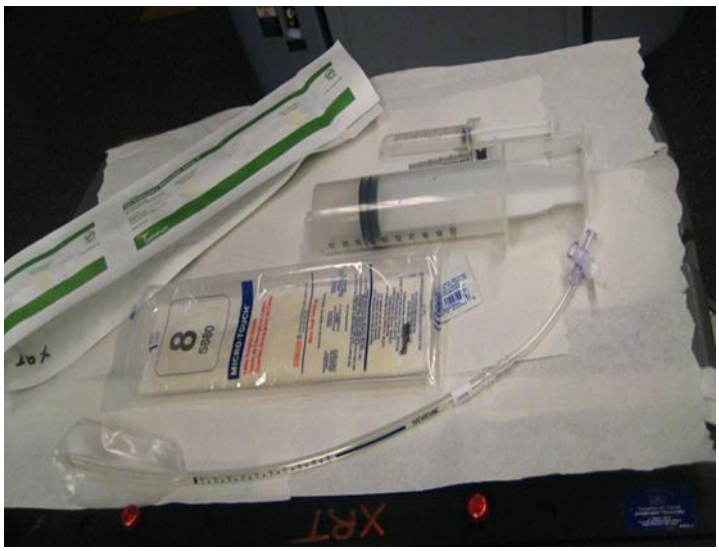


Figure 1: Foley catheter with balloon to be placed rectally.

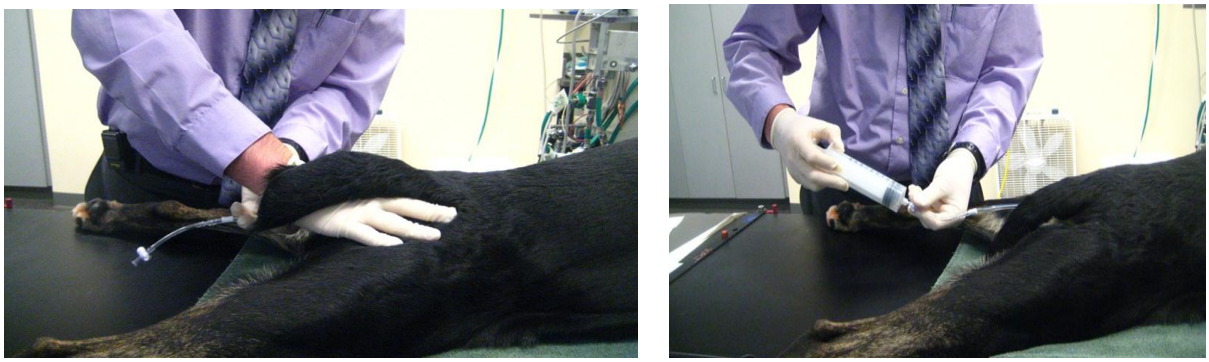


Figure 2: Placement and insufflation of the rectal balloon catheter with the animal anesthetized.

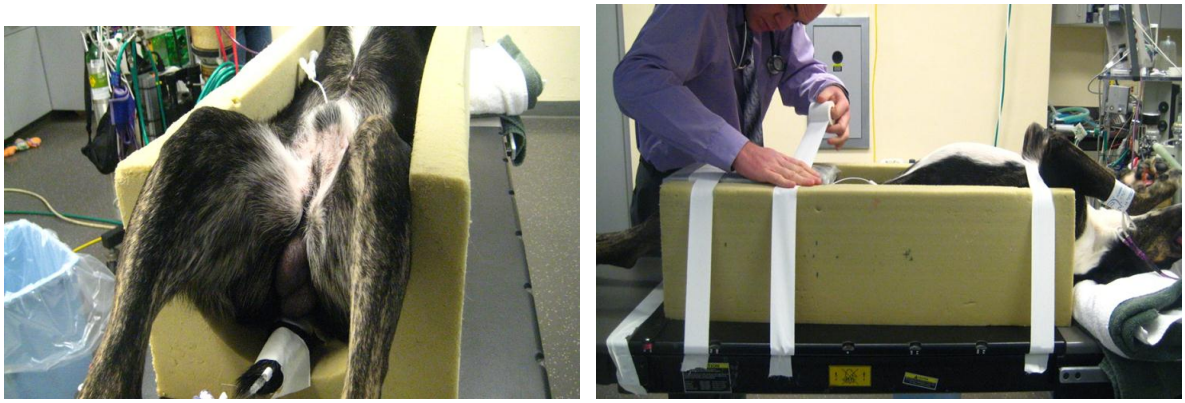


Figure 3: The rectal and urinary catheters are now in place (left) and the anesthetized animal is taped into place to minimize movement.

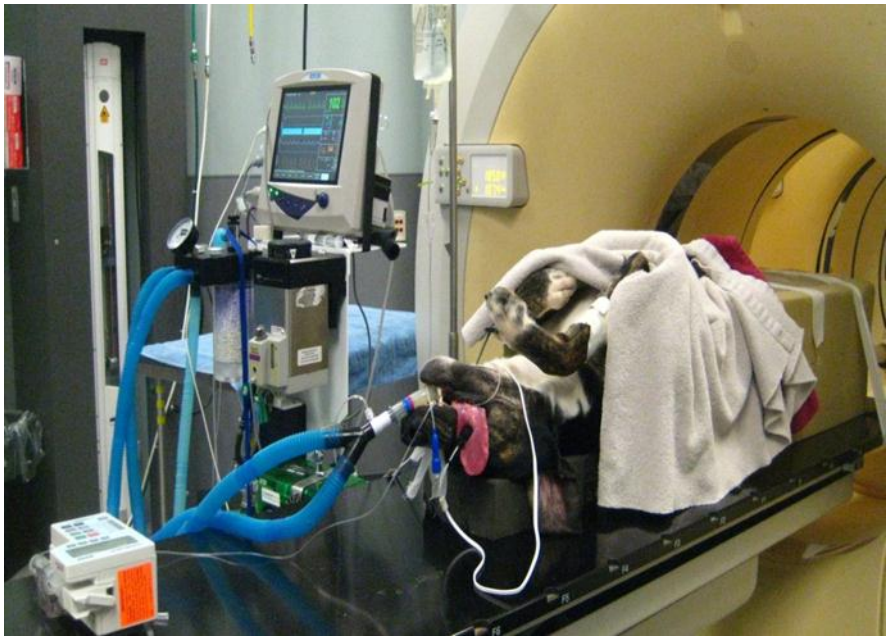


Figure 4: Final animal position during CT simulation scan after proper immobilization.

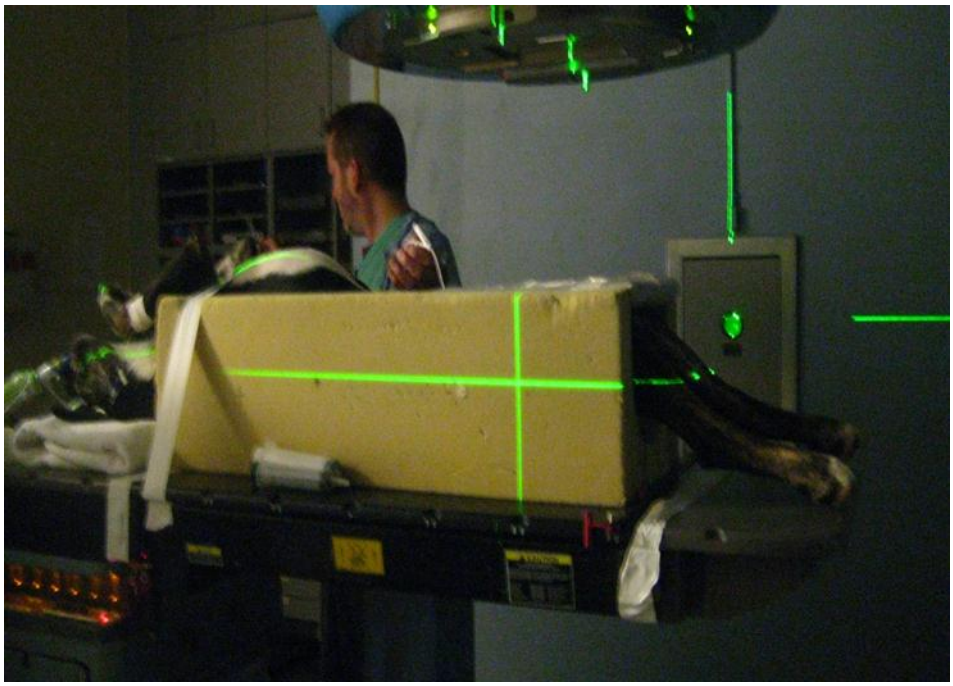


Figure 5: Landmark for alignment with the isocenter laser line on the patient table of the linear accelerator for SRT delivery.

Cone beam CT scans for Aim 1: In order to perform image guided RT (IGRT) during SBRT, cone beam CT images were acquired of each animal immediately prior to each daily radiation fraction, using the Varian Trilogy on- board imaging devices (Varian Medical Systems, Palo Alto, CA, USA). The CBCT makes one complete 360-degree rotation around the patient using 125kVp and 80 Ma. The scans are reconstructed using 2 mm slices and a 512 × 512 matrix size.

Stereotactic radiation administration: A typical 7-field IMRT technique (0, 51, 102, 153, 204, 255, and 306 degree of gantry angles) (Figure 6) was used using dynamic multileaf collimators (dMLC) to modulate the beam field intensity by sliding leaves during SRT. The treatment dose typically combined 6 and 10MV photons to administer a prescription for these dogs of 50 Gy in 5 fractions.

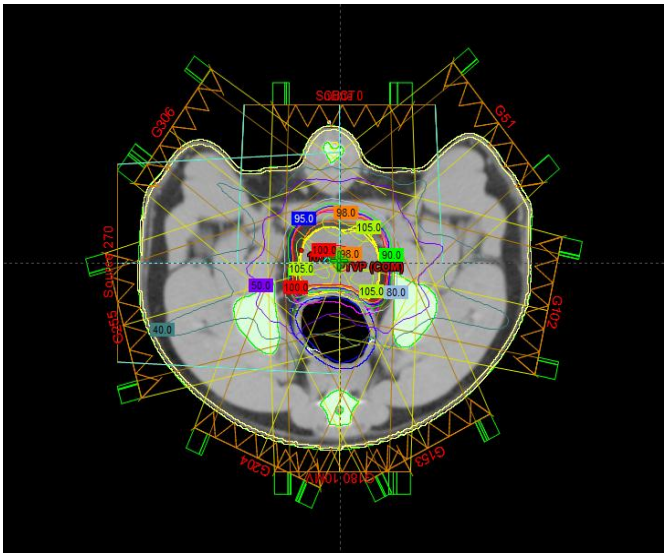


Figure 6: A screen capture from planning computer showing the beam geometry and dose distribution for 7 beams SRT.

Project's Experimental design: For Aim 1 of this study, the prostate movement data was collected retrospectively from cone beam CT scans (CBCT) that were performed just prior to the delivery of each of their 5 different fractions of stereotactic radiation therapy, totaling 50 CBCT scans from these 10 normal dogs.

Image analysis for Aim 1: All planning CT scans and CBCT images were transferred to the Varian Eclipse Treatment Planning System (TPS), software version 8.6.15. The prostate was contoured on each slice of the daily CBCT scans to include its entire volume for the first 10 study dogs (Aim 1). All organs contours were drawn on each slice by hand by the same investigator (AB) to ensure consistency.

The original planning CT was copied, and a new 3D image was created from the CBCT for registration. The CBCT data sets were registered to the corresponding original planning CT images using bony anatomy such as the spine, femoral heads, and pelvis as landmarks using the Varian rigid registration algorithm. The algorithm uses CT pixel values and provides the option for manual or automatic adjustment as needed for the bony anatomy

registration (Figure 7). The purpose of the bony anatomy registration was to match the skeleton, so that variations in each daily prostate position could be measured with respect to the original prostate's contour and isocenter as defined on the planning CT. After registration, the CBCT prostate contours from the daily CBCT scans were then copied onto the original planning CT.

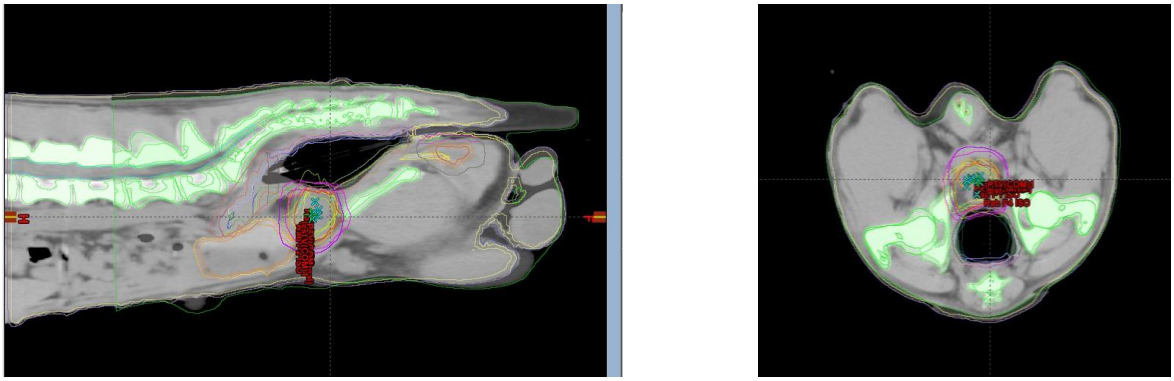


Figure 7a and 7b: Bony registration in sagittal image (left) and transverse views (right); the green lines represent the skeletal contours.

Prostate displacement was measured in three axes x, y, and z. Each axis represents the direction of movement, as follows: right-left (RL) (x axis), anterior-posterior (AP) (y axis), and cranial-caudal (CC) (z axis) respectively. Each coordinate could be represented as positive (+ve) or negative (-ve) values according to the direction of the CBCT prostate isocenter shift compared to the original planning CT isocenter (center of the mass, or COM) location (Figure 8). Positive (+) values were used for the right, posterior and caudal shifts while the other directions were negative (-) for all three axes (Figure 9). Once a point was defined for each patient on the original planning CT, the intersection of the x, y, and z axes were moved to designate this isocenter as the point of user origin, as 0, 0, 0. This point from the original planning CT remained constant for all subsequent measurements of prostate position for that patient. The prostate contours for each CBCT were named as Prostate 1 and so on for the second, third, fourth and fifth CBCT. Reference points for each CBCT

copied prostate contours were assigned and then x, y, and z displacement were measured relative to the 0,0,0 original planning CT isocenter, because they now all shared the same bony anatomy reference point due to the bony registration.

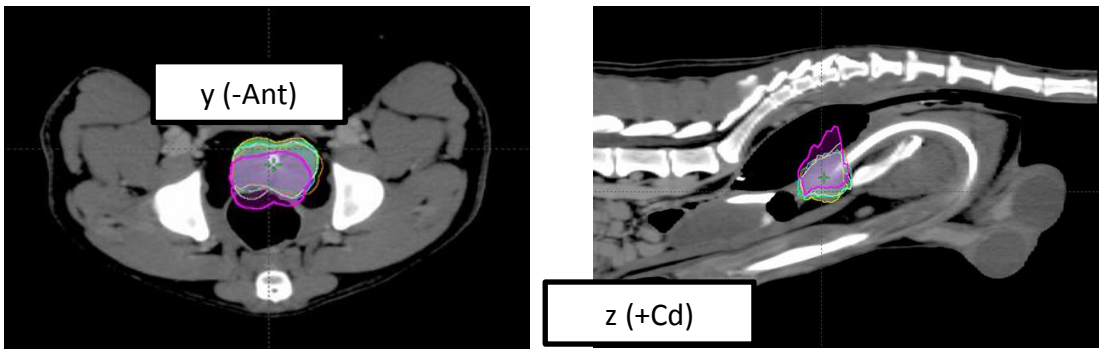


Figure 8a and 8b: This image shows two different prostate contours that were copied onto the original planning CT as an example of the variations in prostate position in the left-right imaging plane (x axis), the anterior-posterior axis (AP plane) and cranial caudal plane (z axis); transverse view in 8a (left) and sagittal view in 8b (right).

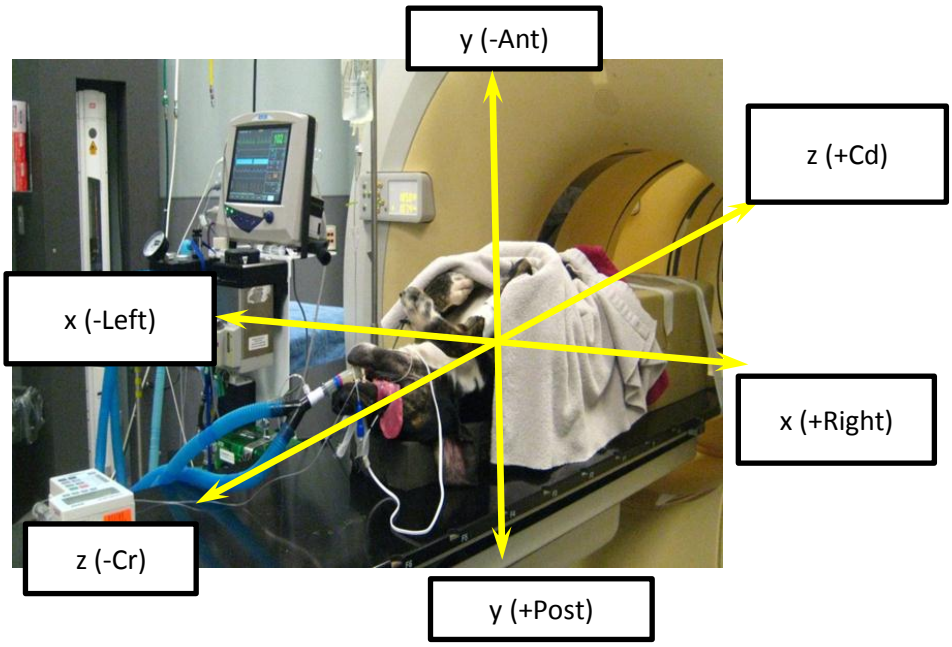


Figure 9: x, y, z axes shown relative to an animal positioned for CT scanning or RT; + ve values indicates caudal, dorsal, and right displacement.

Animal protocol for Aim 2: The goal of this aim was to calculate new RT plans based on multiple prostate positions per animal, and determine whether HC led to significantly altered target and normal tissue doses. Four dogs were studied in this aim, in which multiple diagnostic quality CT scans were obtained with new prostate positions in conjunction with their radiation fractions. This was necessary because the CBCT scan data was not of sufficient quality for calculating new comparison treatment plans. This was done by two different methods. Dogs 13 and 14 were transported back to the CT scanner on 4/5 days after receiving their RT fraction, to obtain a repeat CT scan for measuring the new prostate position and calculating the new RT plan. For Dogs 15 and 16, the original treatment planning scan was repeated 3 new times after slight adjustments of position of the rectal catheter to simulate prostate movement while manipulating the pelvis as little as possible. This was all done on the first day and under the same anesthetic episode when the RT CT simulation scan was done.

Image Analysis for Aim 2:

First, a new plan had to be created from the original treatment plan to modify the plan to target the prostate only, because the original treatment plans from these dogs also included radiation targeted to some of the other pelvic organs. In that plan, the grouped fields had to be realigned to only the prostate, before optimizing. Then, the prostate volume was calculated and normalized to the planning treatment volume prostate (center of mass), or PTVP (COM). The PTVP (COM) was a point within prostate, and care was taken to keep it away from the edge of prostate or on urethra.

The dose volume histogram (DVH) was evaluated and the dose per fraction adjusted slightly so that 95% of PTV (less rectum) would get as close to 50 Gy as possible, and then the plan was renormalized. The DVH shows the dose distribution to the organs based on tissue dose tolerance limit and this, along with a dose color wash map, was used to decide whether the treatment plan was acceptable or not (Figures 10 and 11). This was determined by comparing to standardized tissue constraints as well as keeping in mind that the overall goal of RT was to ensure precise and adequate dose coverage to the target, while keeping the dose to the critical structures as low as possible.[51,59]

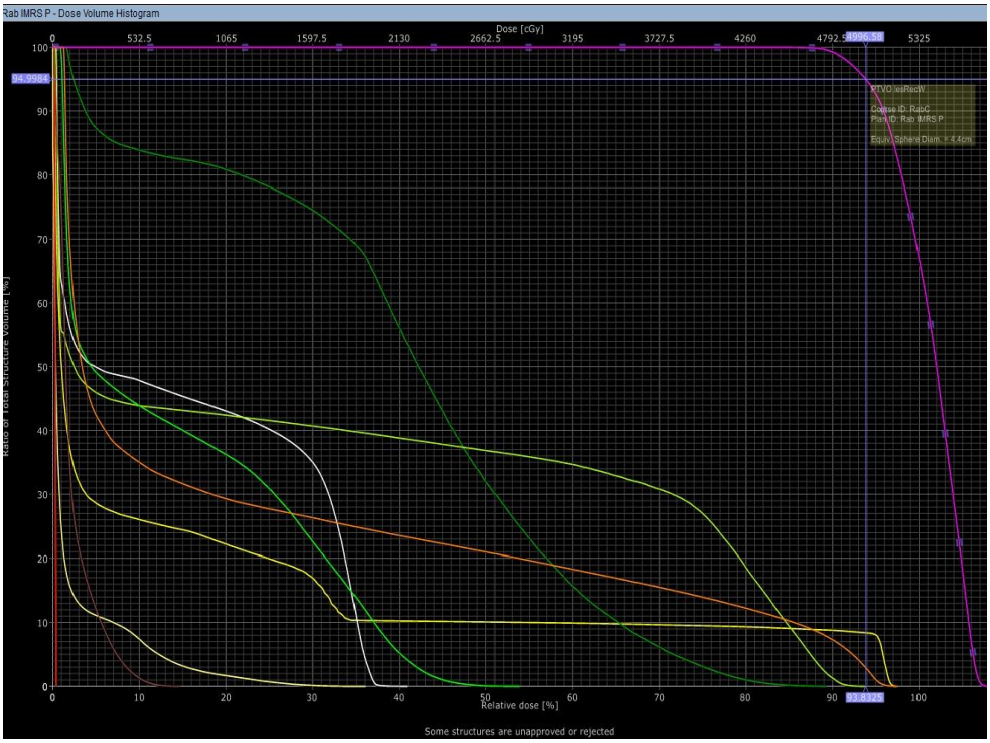


Figure 10: DVH showing an example of dose distribution for an SRT plan.

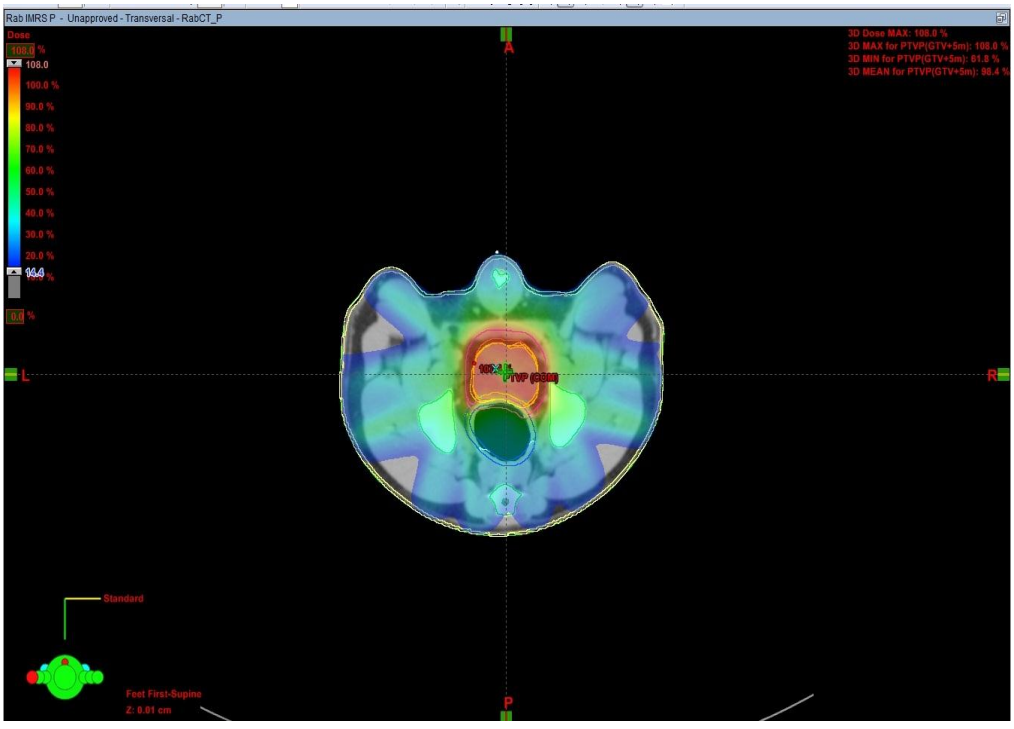


Figure 11: Color wash image showing dose distribution for an SBRT plan; the orange color indicates the highest relative dose and the grey the lowest (see color scale on left of image).

Once the desired tissue constraints were achieved, this plan was applied to the other CT scans in which the prostate was in a new location. This was done by first registering the new scan to the original, this time using soft tissue registration to match the prostate location, and then adjusting the body for the best overall match possible (Figure 12).

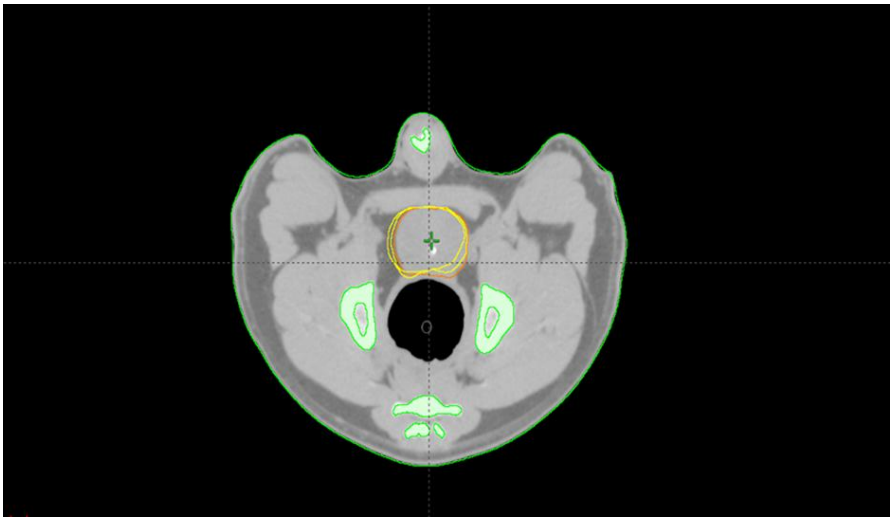


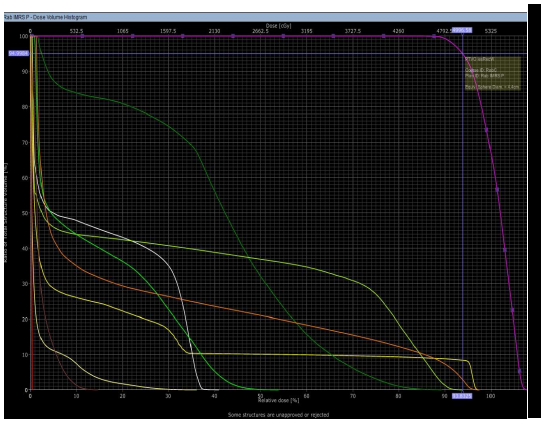
Figure12: Example of registration of the new CT to the original planning CT based on prostate location.

Then, other selected regions of interest were contoured on the new CT scans and the new treatment plan was calculated using the planning treatment volume (PTV), defined as being the gross tumor volume (GTV) with a symmetrical expansion of 5 mm. For CTs with prostate displacement, the group field of fluence was aligned to the prostate isocenter and then the volume was calculated.

For the purpose of this study, two sets of DVH were created for each CT with manual prostate displacement, one with heterogeneity correction (HC) and the other one without HC, to compare the difference on the planning with and without HC. After evaluation of the DVH of the original planning CT with the organ constraints, the plan was copied and pasted,

and the volume was calculated without HC. For the other CTs, the plan for the original CT was copied and pasted, and then the CT image with prostate displacement was opened in the planning window. After that, the structure set was assigned to the copied plan on the new CT with prostate displacement. Furthermore, the volume needed to be calculated with the same MU. Thus, for each new CT with prostate displacement there were two plans, one with HC and the other one without the HC.

Two sets of DVHs and color wash dose images were created for each new CT treatment plan associated with prostate manual displacement, one with HC turned on and the other with HC turned off, for comparison. This was done by copying and pasting the plan again and repeating the calculation with the preset value after the HC was turned off. The plan had to be calculated using the same preset value each time it was copied or when then HC was turned on or off (Figure 13 through 16).



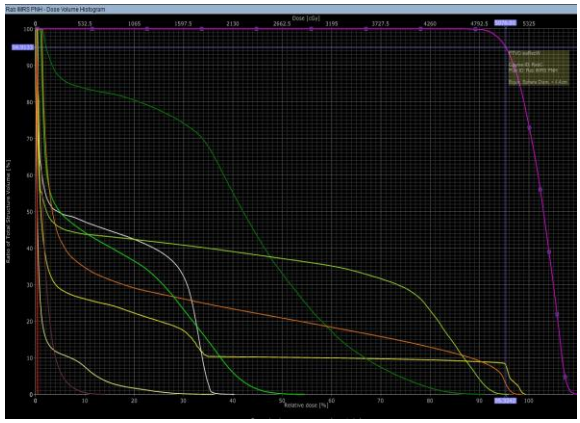
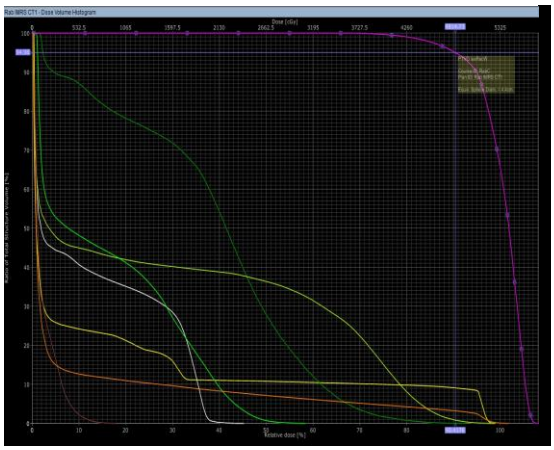


Figure13a (left) and 13b (right): Example of DVH of Dog 16 with and without HC for the original planning CT (with HC, left and without HC, right). Note the differences in the DVH curves generated for this dog on the subsequent CT scans, below, due to different prostate positions.



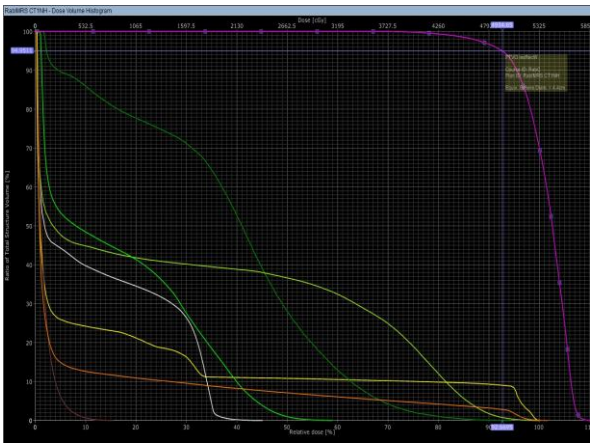
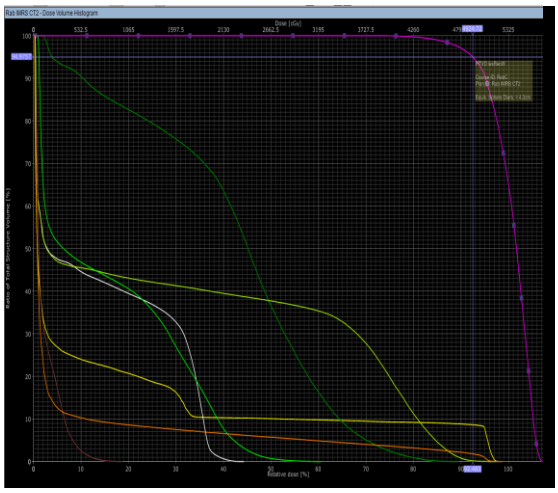


Figure 14a (left) and 14b (right): Example of DVH of Dog 16 with and without HC for CT1 (with HC, left and without HC, right).



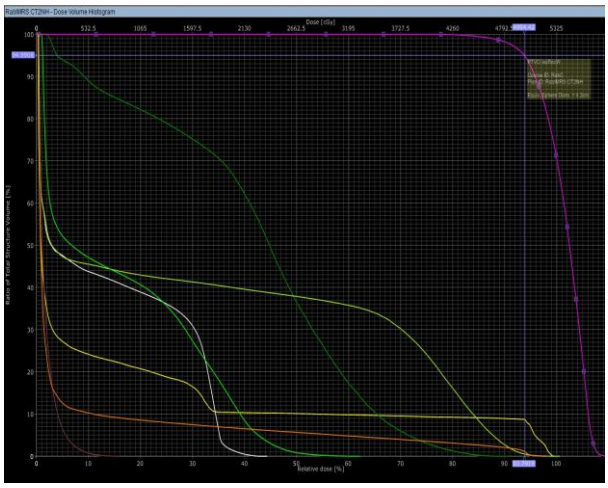


Figure 15a (left) and 15b (right): Example of DVH of Dog 16 with and without HC for CT2 (with HC, left and without HC, right).

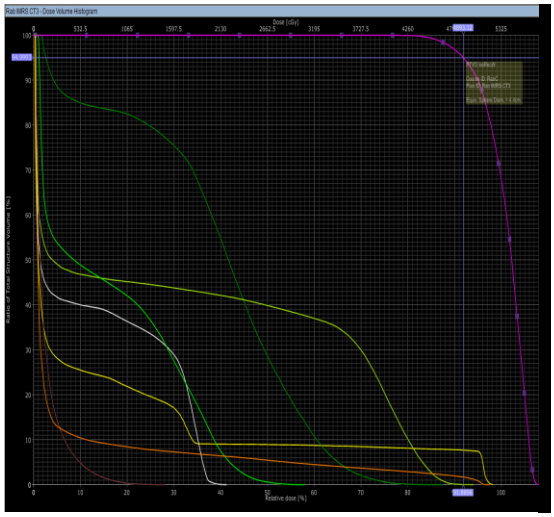
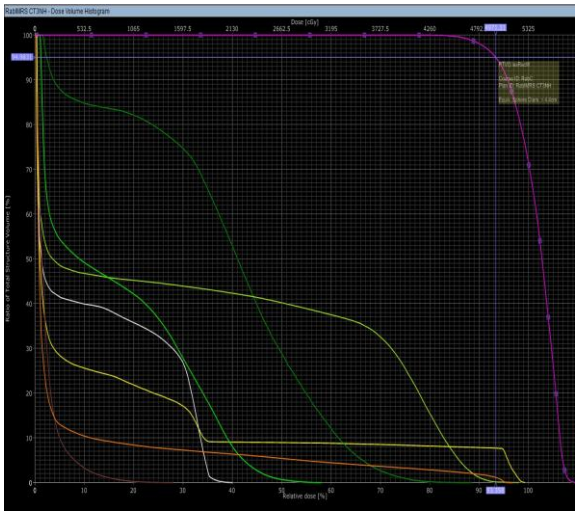



Figure 16a (left) and 16b (right): Example of DVH of Dog 16 with and without HC for CT3 (with HC, left and without HC, right).

The dose was then evaluated for the following regions: prostate (prostate volume less rectum or PVOLR), femoral heads, various regions of the rectal wall, proximal rectum, urethra and urinary bladder, using recommended tissue constraints established by the Radiation Therapy Oncology Group (RTOG) (Table 1). The percentage of PTVO less rectum volume receiving 95% of prescribed dose was obtained from DVH to evaluate the plans. The volume (cc) of different part of rectum, receiving different percentage of the prescribed dose was obtained to evaluate rectal irradiation. In these guidelines, some organs have constraints based on a maximum dose percentage, whereas other tissue constraints are described as a certain tissue volume (cc) receiving no more than a certain dose specified in Gy. Some tissue constraints are described using both methods (Table 1).

Table 1: Tissue's dose constraints for evaluating DVH

Organ	Volume	Dose(Gy)
PTVOLess Rectal Wall	95% of PTVO less Rectum	50Gy
Anterior Rectal Wall	Maximum point dose	No more than 105% of the prescribed dose
Lateral Rectal Wall	Maximum point dose	No more than 100% of the prescribed dose
	< 3 cc	No more than 90% of the prescribed dose
Posterior Rectal Wall	Maximum point dose	No more than 45% of the prescribed dose
Proximal Rectal Wall	Maximum point dose	30 Gy
	<10 cc	25 Gy
Urethra	Maximum point dose	No more than 105% of the prescribed dose
Urinary Bladder Wall	Maximum point dose	No more than 105% of the prescribed dose
Femoral Heads	< 10 cc	30 Gy
Skin	Maximum point dose	27 Gy

Statistical analysis: Prostate displacement was measured in 3 coordinates and the amount of displacement was evaluated on a daily basis of RT. Student's t test and Signed Rank test (more conservative and assumes non-normal data) were used to evaluate for differences in dose delivered to the following tissues, with and without HC: PTVOLR, anterior rectal wall (Ant. R W), lateral rectal wall (Lat. R.W), posterior rectal wall (Post. R.W), proximal rectum (Prox. R), urethra, bladder wall, and femoral heads (F.Hs). Statistical significance was assumed at $P < 0.05$. All statistical analysis was performed using SAS statistical software v. 9.3 (SAS, Chicago, IL, USA).

RESULTS

For the first aim, ten dogs were CT scanned, and a total of fifty CBCTs were obtained. For the second aim, four dogs were CT scanned, with a total of fourteen CTs performed. The scan dates and times are shown in the Appendix. For the purpose of descriptive analysis, the prostate displacement data was split into two sets based on scanning technique (CBCT versus CT).

Prostate movement documented on CBCTs:

The degree and direction of prostate displacement is shown in Figure 17 (10 ED dogs, n= 50), and the CBCT prostate movement data are summarized in Table 2. Overall the largest displacement was in the dorsoventral direction (y coordinate), with a range of average displacement of -6.3 to 9.60 with a mean of 1.92 mm and SD of 2.84 mm (Figure 19). The greatest average displacement in this direction was dorsally at 9.60 mm. In the left-right direction (x coordinate) the range of average displacement was -7.60 to 6.20 mm with a mean of 0.41 mm and SD of 2.55 mm. The greatest average displacement was toward the left at -7.60 mm (Figure 18). In the cranial caudal direction (z coordinate), the range of average displacement was -2.60 to 5.30, with a mean of 0.57 mm and SD of 1.53 mm (Figure 20). The greatest average displacement in this direction was 5.30 mm toward caudal.

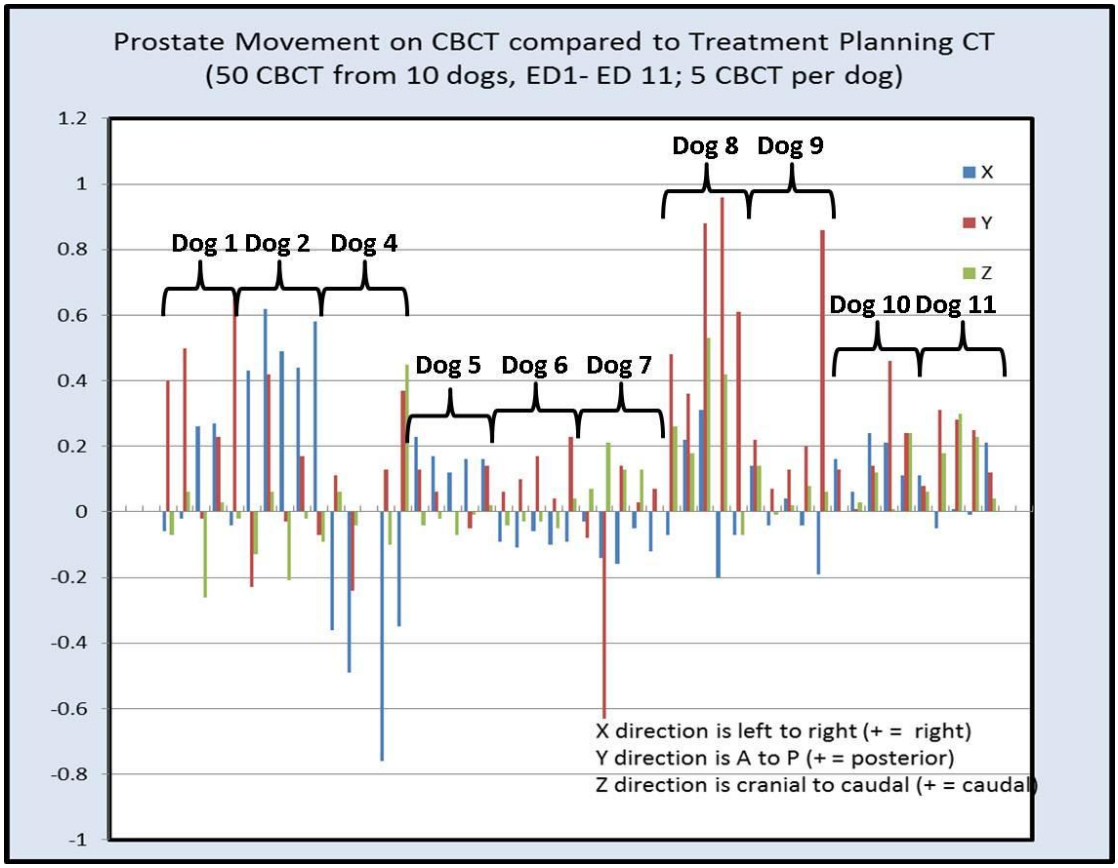


Figure 17: Aim 1: This bar graph shows the prostate movement for each dog in the 3 coordinate directions for the 10 dogs as measured from 5 consecutively shown CBCTs. Each column represents movement in one direction, and for each dog there are 5 sets of 3 columns.

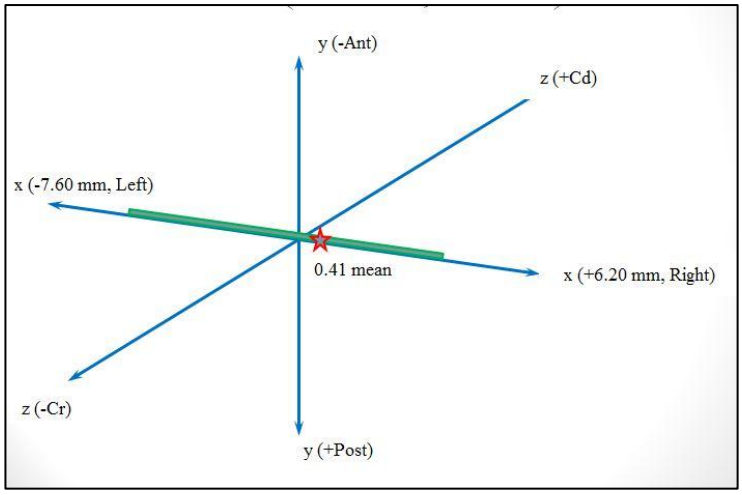


Figure 18: Average prostate movement in x axis for all dogs measured on CBCT.

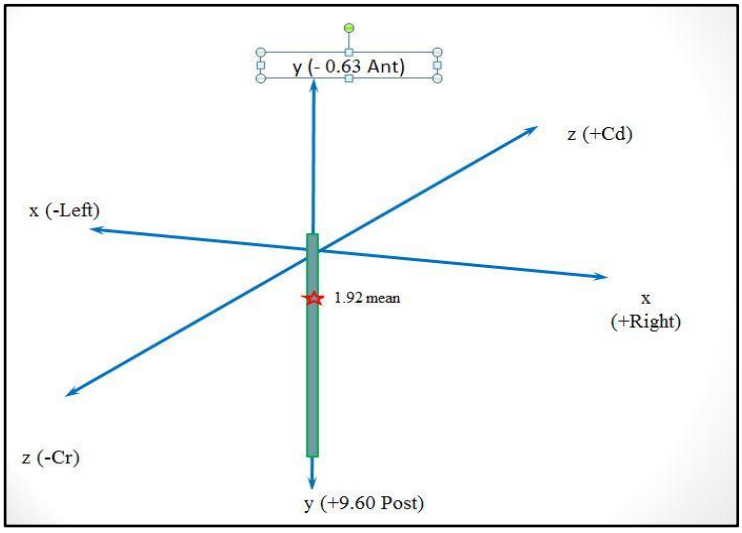


Figure 19: Average prostate movement in y axis for all dogs measured on CBCT.

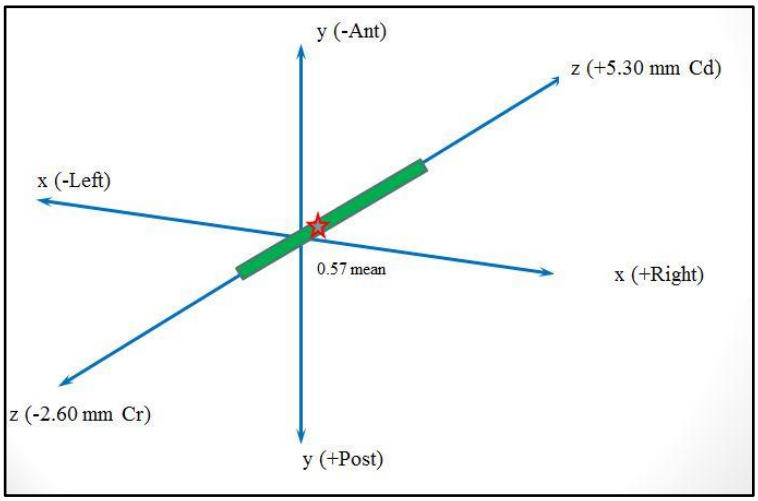


Figure 20: Average prostate movement in z axis for all dogs measured on CBCT.

Prostate movement documented on CTs:

The degree and direction of prostate displacement is shown in Figure 21 (5 ED dogs, n=16), and the data are summarized in Table 3. Overall the greatest displacement was in the ventrodorsal or y direction, with a range of average displacement of -1.20 to 8.10 mm with a mean of 2.08 mm and SD of 2.86 mm (Figure 23). The greatest displacement in this direction was 8.10 mm towards dorsal. In the left-right direction (x coordinate) the range of average of displacement was -7.80 to 1.60 mm with mean of -1.48 mm and SD of 2.54 mm (Figure 22). The greatest displacement was toward the left at -7.80 mm. In the cranial-caudal direction (z coordinate), the range of average displacement was between -1.90 to 5.00 mm with mean of 1.96 mm and SD of 1.97 mm (Figure 24). The greatest displacement in that direction was 5.00 mm toward the caudal.

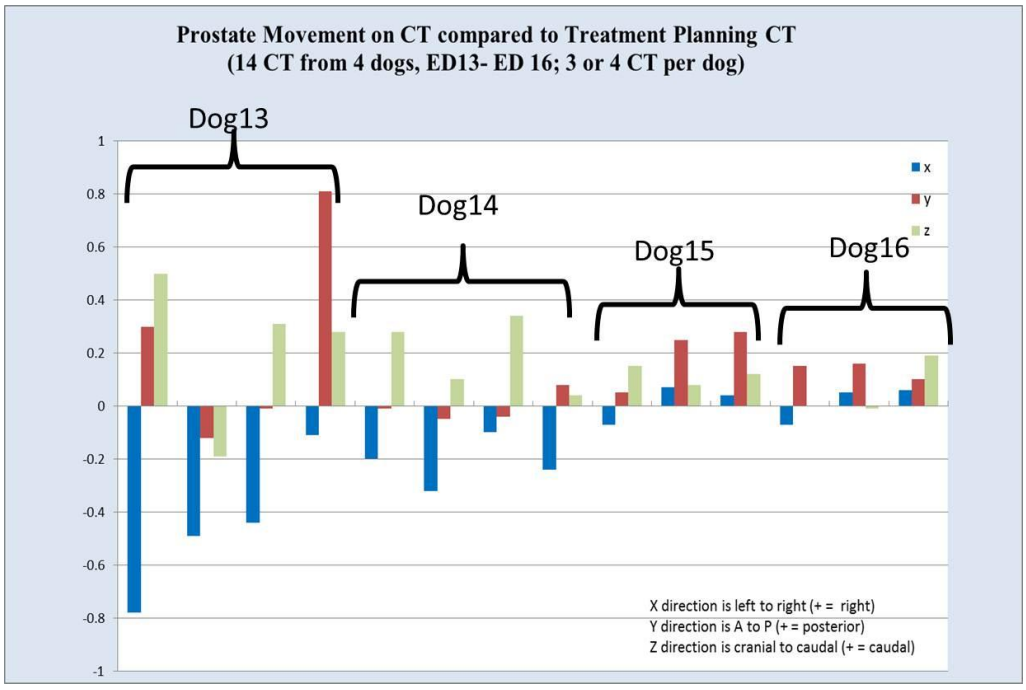


Figure 21: This bar graph shows the prostate movment for each of 4 dogs in the 3 coordinate directions measured from 3 or 4 consecutively shown CTs. Each column represents movement in one direction, and for each dog there are 3 or 4 sets of 3 columns.

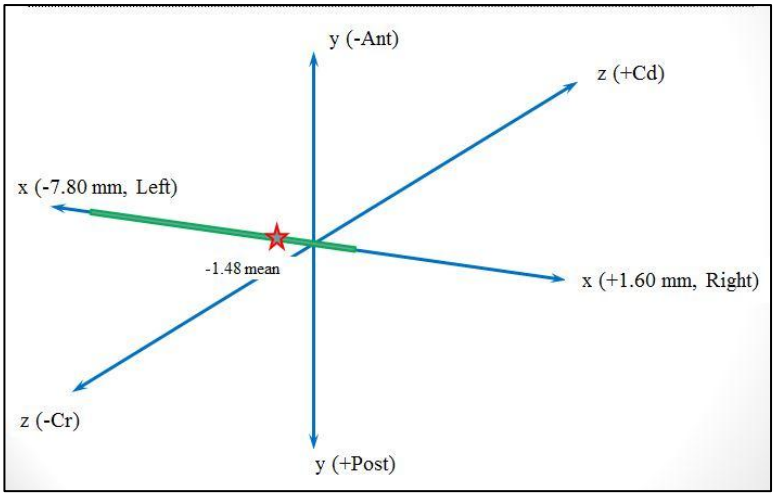


Figure 22: Average prostate movement in x axis for all dogs measured on CT.

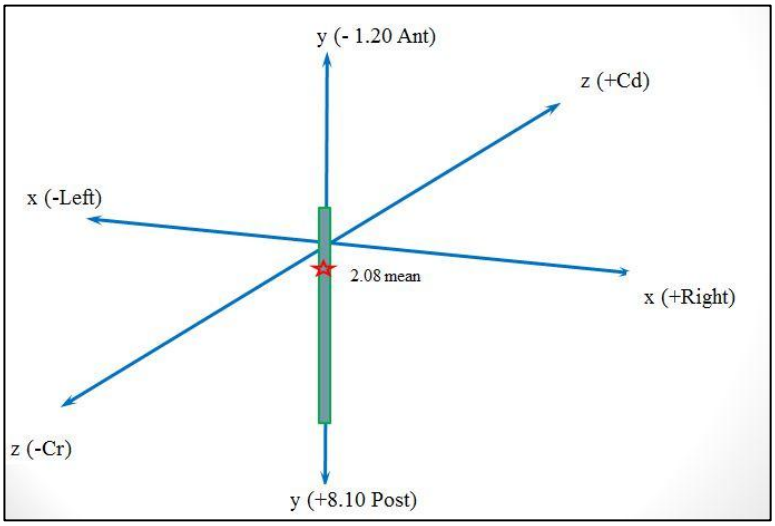


Figure 23: Average prostate movement in y axis for all dogs measured on CT.

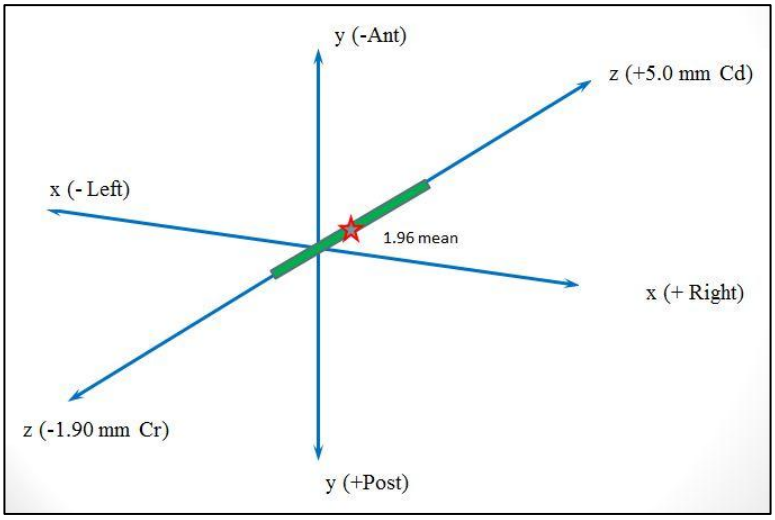


Figure 24: Average prostate movement in z axis for all dogs measured on CT.

Table 2: Descriptive statistics of prostate movements based on CBCT (cm), n=10 (ED1, 2, 4-11)

Movement	CBCT	N	Mean	Std	Min.	Median	Max.
Left to right	1	10	0.046	0.216	-0.360	0.040	0.430
	2	10	0.022	0.286	-0.490	-0.030	0.620
	3	10	0.125	0.197	-0.160	0.080	0.490
	4	10	-0.008	0.328	-0.760	-0.025	0.440
	5	10	0.020	0.259	-0.350	-0.055	0.580
	Overall	50	0.041	0.255	-0.760	-0.005	0.620
Anterior to posterior	1	10	0.130	0.207	-0.230	0.120	0.480
	2	10	0.096	0.339	-0.630	0.085	0.500
	3	10	0.169	0.269	-0.030	0.135	0.880
	4	10	0.242	0.289	-0.050	0.185	0.960
	5	10	0.322	0.296	-0.070	0.235	0.860
	Overall	50	0.192	0.284	-0.630	0.135	0.960
Cranial to caudal	1	10	0.031	0.113	-0.130	0.030	0.260
	2	10	0.062	0.095	-0.040	0.045	0.210
	3	10	0.053	0.234	-0.260	0.010	0.530
	4	10	0.072	0.154	-0.100	0.020	0.420
	5	10	0.067	0.162	-0.090	0.030	0.450
	Overall	50	0.057	0.153	-0.260	0.025	0.530

Table 3: Descriptive statistics of prostate movements based on CT in (cm) (ED12-16)

Movement	CT	N	Mean	Std	Min.	Median	Max.
Left to right	1	5	-0.210	0.333	-0.780	-0.070	0.070
	2	5	-0.106	0.283	-0.490	0.050	0.160
	3	4	-0.110	0.231	-0.440	-0.030	0.060
	4	2	-0.175	0.092	-0.240	-0.175	-0.110
	Overall	16	-0.148	0.254	-0.780	-0.085	0.160
Anterior to posterior	1	5	0.238	0.284	-0.010	0.150	0.700
	2	5	0.182	0.311	-0.120	0.160	0.670
	3	4	0.083	0.145	-0.040	0.045	0.280
	4	2	0.445	0.516	0.080	0.445	0.810
	Overall	16	0.208	0.286	-0.120	0.125	0.810
Cranial to caudal	1	5	0.280	0.212	0.000	0.280	0.500
	2	5	0.092	0.245	-0.190	0.080	0.480
	3	4	0.240	0.103	0.120	0.250	0.340
	4	2	0.160	0.170	0.040	0.160	0.280
	Overall	16	0.196	0.197	-0.190	0.170	0.500

In summary, this study documents substantial inter-fraction prostate movement, up to 9 mm. The mean displacement was most pronounced in the ventrodorsal (y) direction by both CBCT and diagnostic CT scans. The range of displacement was pronounced in all axes but especially dorsal (y) and left (x).

Comparison of treatment plans with and without HC:

The dogs' doses for various tissues, with and without HC, are shown in the Appendix. There were no statistically significant differences between doses with the HC on versus off, when evaluated with the Signed Rank t test which assumes a non-normal distribution. Using the less conservative t test, a few tissue doses differed statistically between HC on and off. Those included the PTVOLR, and the anterior and lateral rectal wall for some scans (CT1, 2, and 3 for anterior rectal wall and CT1, 2, 3 and the planning CT for the lateral rectal wall), and for a few scans for the femoral heads. There was a trend for doses to be higher when calculated without HC, except for the first CT scan (CT1) of Dog 13.

Dose to the target prostate volume, PTVOLR:

The optimal dose of 95% of PTVOLR is 50 Gy. The differences of the mean dose to the PTVOLR ranged from 0.45 to 0.65%, when comparing HC on versus off during treatment plans derived from the original planning CT scans. Doses ranged from 49.9 to 49.96 Gy with HC and from 49.7 to 50.7Gy.without CT, when planning was done from the original treatment planning CT scans (Figure 26). 95% of the PTVOLR received 0.11 to 0.35 Gy lower with HC than the optimal dose (50 Gy). PTVOLR doses were higher than 50Gy for 3 of 4 dogs without HC in use, because dose increases without HC (Figure 25).

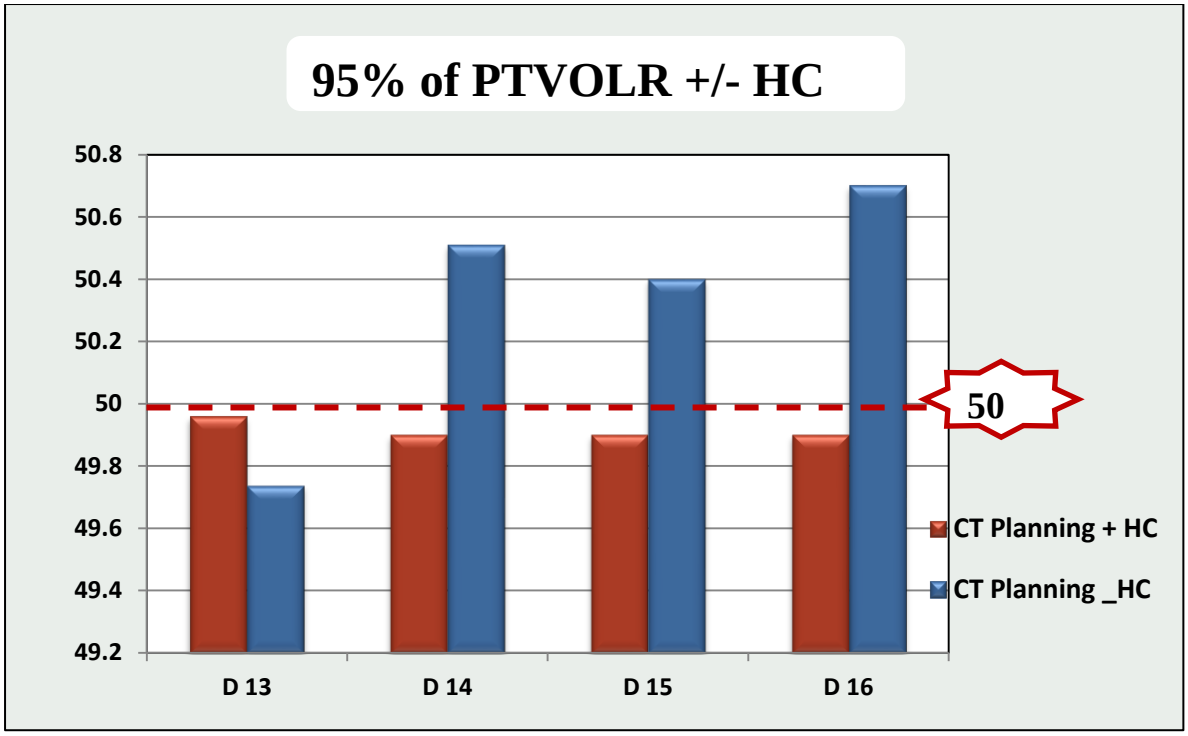


Figure 25: Doses from treatment planning CTs for the 95% of PTVOLR with and without HC in all 4 dogs

Figure 26 shows the effect of prostate movement (during the subsequent CT scans) on PTVOLR doses without HC. Although the doses exceeded 50Gy without HC for the treatment planning CT, due to the documented prostate movements during the subsequent CT scans, the PTVOLR doses were more suboptimal even without HC. Dog 14 had the lowest PTVOLR prostate dose although all dogs had less than 50 Gy on their multiple CTs. The lowest dose to the target was 47.97 Gy in CT1 of Dog 14, in which prostate displacement was -2.0, -0.1 , and 2.8 mm to left , ventral and caudal respectively. For Dog 14, under-dosing of the PTVOLR was associated mainly with caudal prostate displacement, however Dog 14's prostate movement was not as great as was documented for Dog 13.

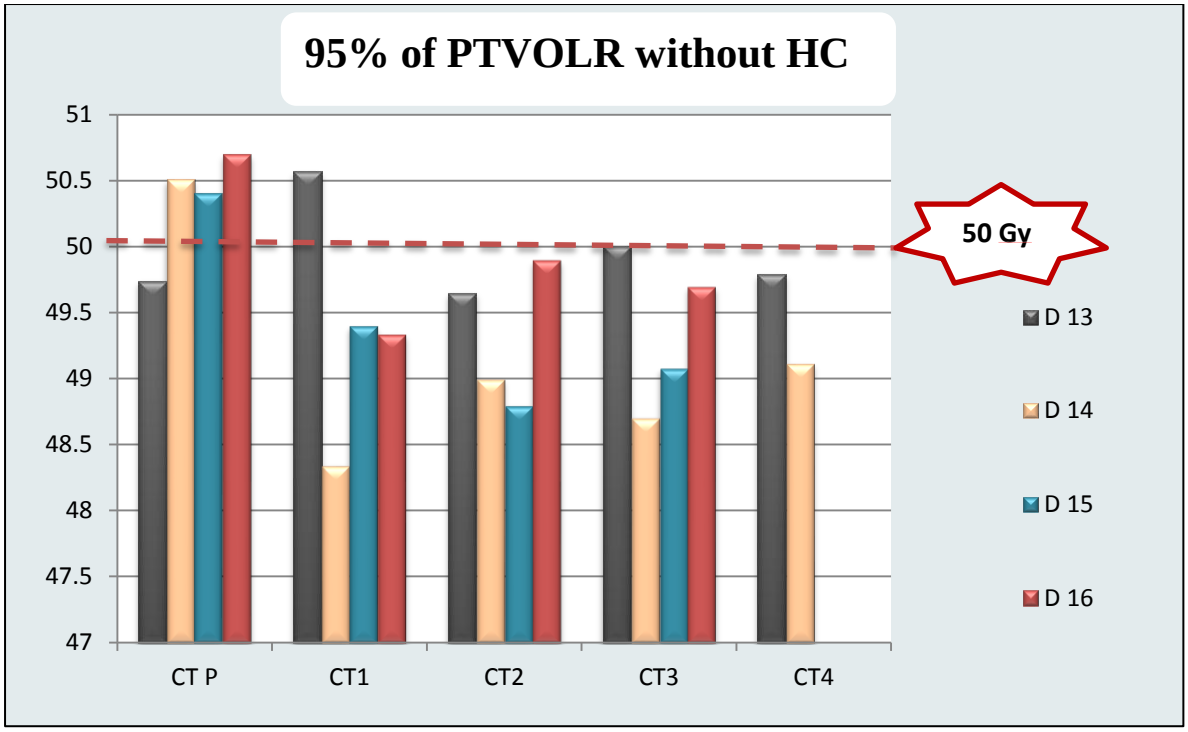


Figure 26: Doses from the subsequent CT scans generated when planning the dose to 95% of PTVOLR without HC in all 4 dogs.

Dose to the various regions of the rectal wall and associated prostatic displacement:

For most dogs, some portion of the rectal wall had excessive doses when considering prostate displacement while treatment planning with HC. The recommended dose constraint for the posterior rectal wall is that the maximal dose % should not exceed 45% of the prescribed dose. Figures 27, 28, and 29 shows the maximal % dose to the posterior rectal wall for the dogs, with and without HC. These effects were slightly greater without HC (Figure 29) in general, since doses tended to be a little higher without HC. For all dogs, the maximal dose % to the posterior rectal walls exceeded dose limit constraints except for Dog 14. In Dog 13, all of the CTs with prostate displacement exceeded the tolerance limit and this was most pronounced for CT1 and CT4 (Figure 27). In Dog 15, the posterior rectal wall maximal dose % was higher than the dose tolerance limit for CT1 and CT 3. For CT1, prostatic displacement was the greatest to the left (7.8 mm) and caudally (5 mm) with a

maximum dose of 76.3 %. Also, had a maximal prostate displacement dorsally by 2.8 mm. Also, CT 4 for Dog 15 had the second highest dose (63.9%), in which the displacement was again worse in the dorsal direction (8.1mm). In comparison, for only CT 1 in Dog 16 did the posterior rectal wall just slightly exceed the dose tolerance limit at 45.3% of prescribed dose (Figure 28), where the prostate displacement was posterior by 1.5 mm.

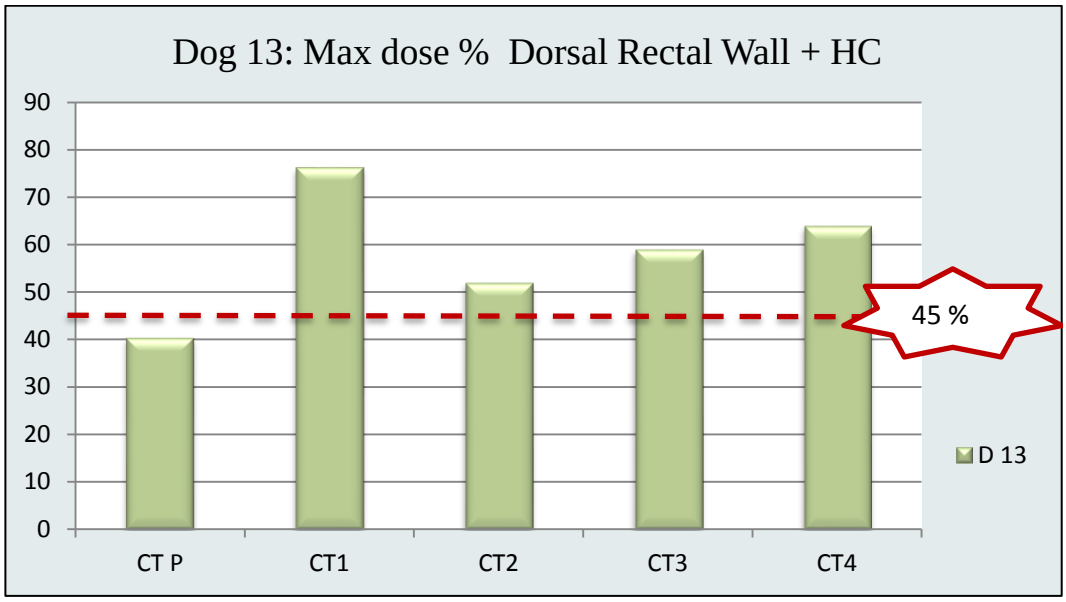


Figure 27: The bars on this graph represent the maximal dose % to the dorsal rectal wall with HC for the series of CT scans for Dog 13

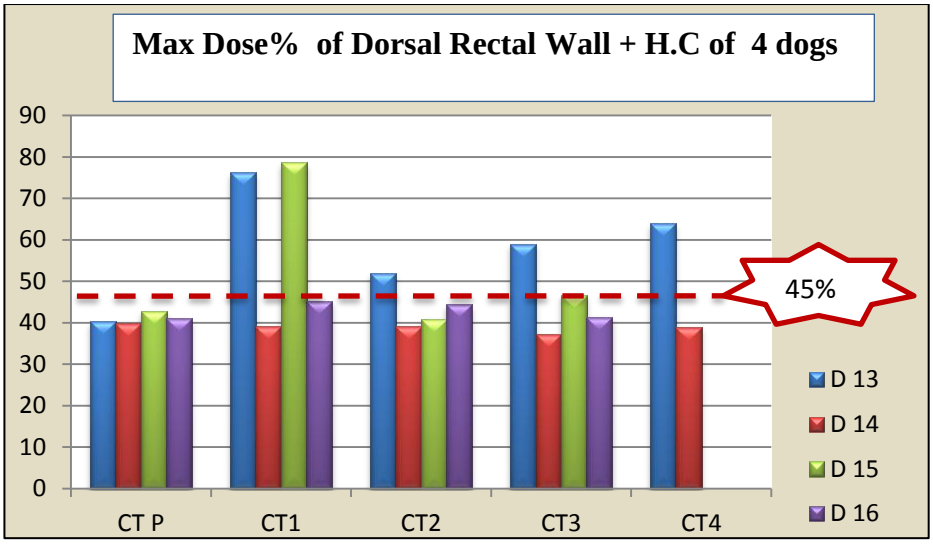


Figure 28: Maximal dose % of dorsal rectal wall with HC for the multiple CT scans in 4 dogs.

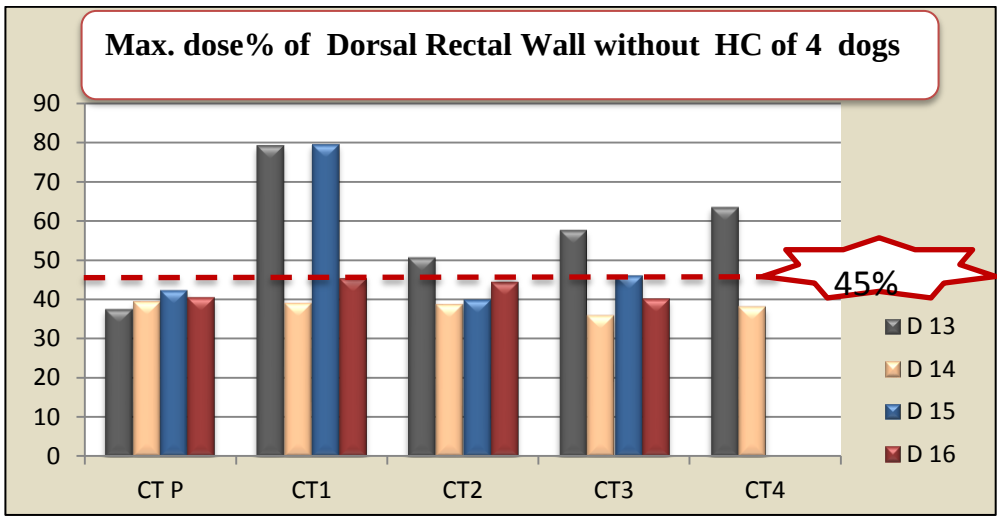


Figure 29: Maximal dose % of dorsal rectal wall without HC for the 3 to 4 scans in 4 dogs

Figures 30, 31 and 32 show the maximum dose % for the lateral rectal wall. The recommended dose constraint value for the lateral and anterior rectal walls are 100 % and 105 % of the prescribed dose respectively. This constraint dose was exceeded for only a few scans. With prostate movement, the range of maximal dose % to the anterior rectal wall was -2.32 to -1.35 % of the prescribed dose, while for the lateral rectal wall the range was

-2.70 to -1.27 % of prescribed dose. Three cc of the lateral rectal wall had a mean dose range of -1.28 to -0.67. However, the dose received by those areas of rectum exceeded the dose limit constraints only in Dog 13 (Figures 30, 31, and 32). Three cc of lateral rectal wall also exceeded the constraints of 45 Gy in CT2 and CT3 for Dog 13, by 0.37-3.4 Gy, and the prostate displacement for those scans was mainly to the left for Dog 13. For CT 2, the prostate was displaced - 4.9 mm to the left and maximum dose % was 1.7 % in excess, and for CT3 the prostate was displaced -4.4 mm to the left with a 104.2 % max dose.

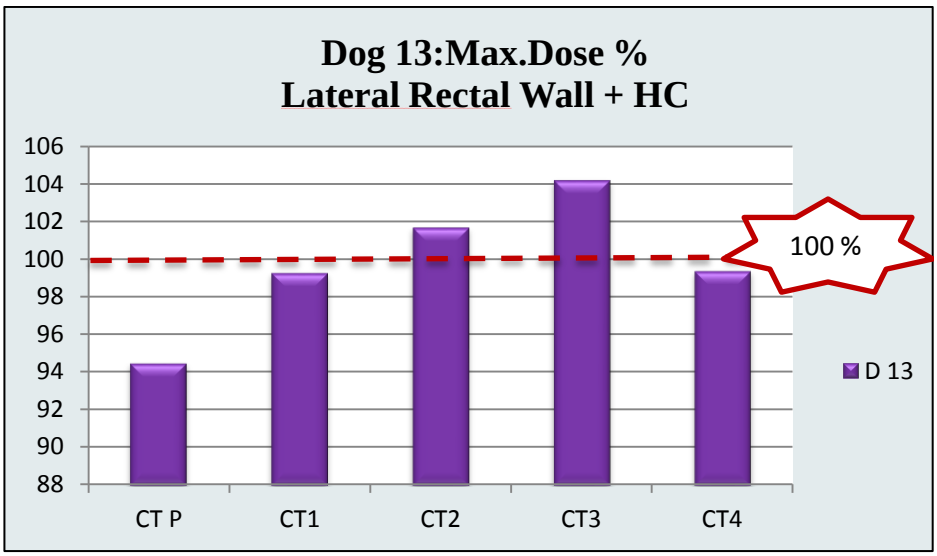


Figure 30: Maximal dose % of lateral rectal wall + HC in Dog 13

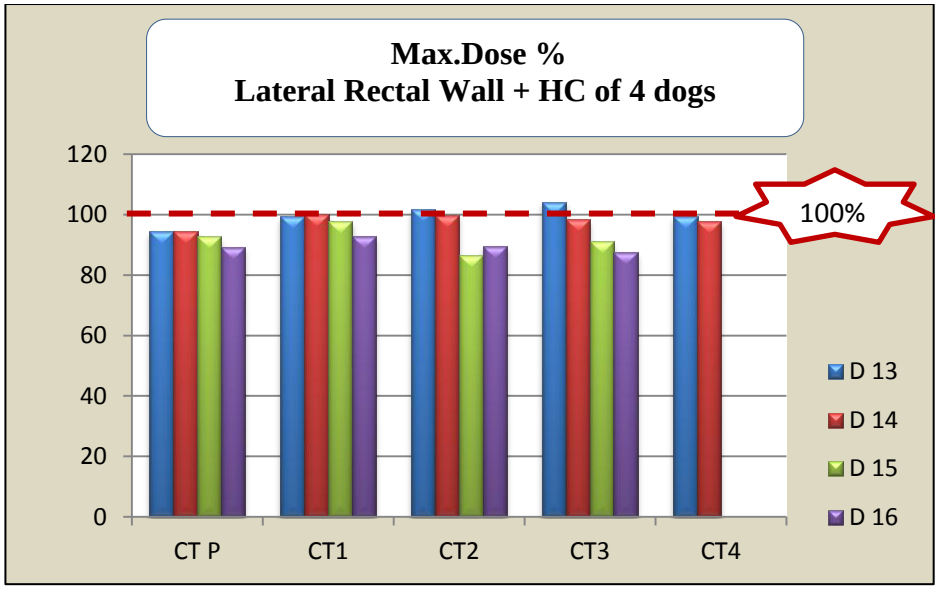


Figure 31: Maximal dose % of lateral rectal wall with HC for the multiple scans from the 4 dogs.

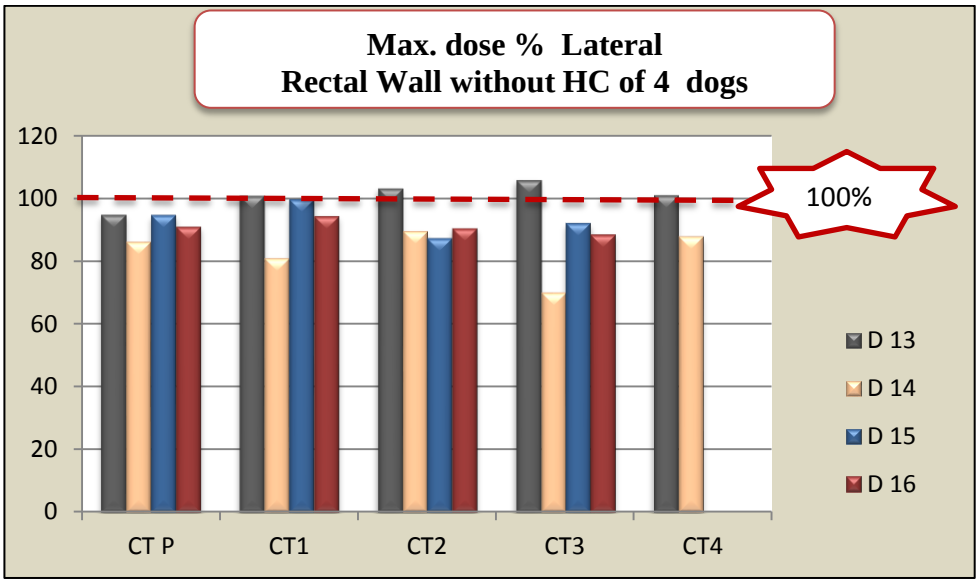


Figure 32: Maximal dose % of lateral rectal wall without- HC for the multiple scans from the 4 dogs.

Dose to other critical pelvic tissues:

Proximal rectum, urethra, and femoral heads did not exceed constraint for any scans with prostate displacement. Because the proximal rectum is distant from prostate, constraints were never exceeded even with prostate movement. The urinary bladder wall doses only increased slightly above constraint levels without HC twice in all four dogs' scans, exceeding the limit by 0.1-0.4 more maximum dose % in CT3 for Dog 13 and CT1 for Dog 15.

There were no significant differences when comparing doses with and without HC for femoral heads by Signed Rank test, and although there were a few significant differences for the CT planning scan and CT1, still, the femoral head values did not exceed constraint recommendations. For other critical pelvic tissues, there were no significant differences when HC was used.

DISCUSSION

Prostate Movement:

There are a number of reasons for inter-fraction prostate movement in the dog and man. The position of the prostate changes with age, and in the dog the prostate moves more cranially beyond the pubic brim with age and increasing prostate size.[60] Prostate volume is age-dependent, increasing in older men and dogs due to benign hypertrophy. Prostatic neoplasia will increase prostate size further. During a course of radiation, a positively responding cancerous prostate will shrink in volume which will also result in altered prostate location. The dogs in this study were intact young males, without cancer, therefore their prostate size did not completely model that of an older prostate cancer patient. During the course of the 5 radiation fractions a significant change in prostate size did not occur (Table 4).

Table 4: Prostate volume changes with every fraction.

Dog #	**Image**	**Prostate Volume based on CT image cm^3**
Dog 1	CT Planning	17.29
	Fraction 1	17.69
	Fraction 2	16.25
	Fraction 3	15.07
	Fraction 4	15.9
	Fraction 5	15.38
Dog 2	CT Planning	29.3
	Fraction 1	34.38
	Fraction 2	33.33
	Fraction 3	30.6
	Fraction 4	29.41
	Fraction 5	26.68
Dog 4	CT Planning	18.85
	Fraction 1	21.67
	Fraction 2	22.96
	Fraction 3	19.66
	Fraction 4	21.84

	Fraction 5	18.84
Dog 5	CT Planning	19.09
	Fraction 1	16.73
	Fraction 2	17.94
	Fraction 3	17.2
	Fraction 4	18.85
	Fraction 5	14.44
ED 6	CT Planning	27.76
	Fraction 1	28.83
	Fraction 2	30.07
	Fraction 3	28.39
	Fraction 4	29.17
	Fraction 5	29.08
ED 7	CT Planning	20.88
	Fraction 1	19.58
	Fraction 2	17.68
	Fraction 3	18.17
	Fraction 4	20.7
	Fraction 5	20.26
ED 8	CT Planning	7.01
	Fraction 1	8.34
	Fraction 2	9.29
	Fraction 3	6.46
	Fraction 4	7.8
	Fraction 5	8.74
ED 9	CT Planning	17.29
	Fraction 1	17.92
	Fraction 2	17.12
	Fraction 3	17.96
	Fraction 4	16.54
	Fraction 5	17.31
ED 10	CT Planning	27.8
	Fraction 1	24.58
	Fraction 2	25.5
	Fraction 3	23.3
	Fraction 4	23.37
	Fraction 5	23.87
ED 11	CT Planning	17.34
	Fraction 1	14.66
	Fraction 2	15.66
	Fraction 3	13.35
	Fraction 4	13.18
	Fraction 5	16.84

The prostate gland is a relatively mobile pelvic organ within the retroperitoneal space and its position also depends partly upon the organs to which it attaches. The changes in the

urinary bladder and rectum also contribute to prostatic shrinkage, expansion, and constant movement.[2] The prostate gland is physically connected to the urinary bladder at its cranial extent where it wraps around the neck of the bladder, and by the urethra caudally. The urinary bladder varies considerably with urine volume, and the prostate gland and bladder both adjust in position on a daily basis with this change. Furthermore, the urethra is long and flexible, and the descending colon which lies dorsal to the prostate will vary in volume and can shift ventrally when full of feces. Even so, a recent human study showed that rectal filling did not impact prostate stability with statistical significance correlation with inter fraction of prostate. In addition, immobilization with a rectal balloon was used in those patients to reduce inter-fraction prostate displacement. Even with the rectal balloon, there was enough prostatic displacement to require shifting the table ≥ 3mm for more than 90% of prostate radiation therapy treatments, and intra-fraction movement still occurred.[30,61]

The dogs in this study were fasted and fed a standard low residue diet, received an enema four hours prior to each radiation fraction and were treated at approximately the same time of each day to minimize the effect of fecal volume on prostate position. A rectal balloon catheter was also used. No attempts were made to control urine volume, since image guidance was being used to adjust the radiation field based on prostate position as determined by the CBCT.

Despite these differences and the precautions that were taken, marked prostate movement occurred in natural treatment situations during 5-fraction SRT, up to 9.6 mm in at least one dog. For both sets of dogs (documented retrospectively with CBCT or prospectively with diagnostic CT scans), the most severe displacement was in the ventrodorsal or y plane and the shift was most frequent and largest dorsally. Significant displacement also occurred in the left-right plane, and although there were an equivalent number of shifts towards left or right, the greatest movement was in the left direction.

There was slightly less magnitude of displacement in the crandiocaudal direction, but still there were also significant shifts in that direction with the greatest being caudal.

This degree of prostate movement would result in partial geographic miss during radiation therapy and potentially over-treatment of critical surrounding tissues if left uncorrected, and emphasizes the importance of methodology to track the prostate gland. That is ideally done in clinical practice using either surgically implanted fiducial markers, or non-invasive forms of image-guided radiation therapy in which CBCT is used for daily adjustment of the radiation fields to compensate for this motion.

Our mean canine results are similar to previous published human studies documenting prostate displacement. Mean human displacement was -0.5 mm (-4.4 to 3.4 mm) in the anterior-posterior direction, -0.6 mm (-4.5 to 3.3 mm) in the craniocaudal direction and -0.2 (-1.8 to 1.4 mm) left-right direction. The maximum displacement was 9.4, 8.1, and 4.4 mm for AP, CC, and RL respectively.[39,62] In the canine model the magnitude of displacement was slightly greater but similar to the human data. There are several ways that our methods differed from these human studies. First, the way prostate displacement was measured differed from our method relative to bony anatomy. Also, human patients lie down in the supine position, so the direction of coordinates differed compared to the canine results since dogs are in prone position. In addition, for those human prostate plans, treatment plans were based on contouring with the guidance of MRI images that were fused to CT scans. MRI is superior to CT for visualizing soft tissues and that provides more accurate contouring of pelvic organs. Bladder and rectal wall can be difficult to distinguish on the CT scans on some slices.[62] In our project that was especially true for Dog 13 in which the urinary bladder was distended during the treatment.

Differences in experimental method used in this project influenced the degree of prostate movement. Prostate movement from the first set of dogs was measured

retrospectively on CBCTs at the time of radiation fraction delivery. Prostate movement was measured prospectively instead on the diagnostic CT scans for the last 4 dogs (Dog 13 – 16). This was done in order to examine the influence of prostate movement on HC and the treatment plans overall, and diagnostic CT scan quality (rather than CBCT) was required in order to accurately recalculate treatment plans based on the new prostate positions. Diagnostic CT scans are superior in image quality over CBCT, making measurements more reliable based on CT. Also, image registration of diagnostic CT to diagnostic CT would use the same algorithm than registration compared to CBCT, further improving the reliability.

For those 4 dogs in which displacement was measured on the additional diagnostic CTs, Dogs 13 and 14 had similar degree of prostate movement as the dogs in the natural treatment situation measured by CBCT. Dogs 13 and 14 were moved back to the CT suite in their radiation therapy positioning cushions in order to repeat a diagnostic CT scan after each treatment. The increased time interval as well as the movement required to transport the dogs from radiotherapy to the CT suite likely contributed to their prostatatic movement.

In comparison, prostate movement for Dog 15 and Dog 16 was less than for the dogs measured by CBCT and it was also less than for Dogs 13 and 14. In Dogs 15 and 16, the displacement was created manually at the time that the CT planning was acquired. That method did not result in as much as movement as the other dogs and may not be as representative of a real treatment situation.

Effect of HC on Treatment Planning:

The ultimate goal of this study was to understand the impact of prostate movement relative to bony pelvic anatomy on the doses experienced by the prostate and critical surrounding normal tissues, and the role of HC in situations with documented prostate movement.

This first required determining the impact of HC on the initial prostatic treatment plans, which indirectly indicates the importance of accounting for the bony pelvis when plans are calculated. If the use of HC alone led to significant differences on the initial treatment planning scans, then that would indicate the importance of prostate position relative to the pelvic bones and make it more likely that prostate movement would significantly affect radiation doses to the pelvic organs.

Planning with HC takes into account the different tissue densities compared to a water medium standard. When radiation travels through the body, it is attenuated differently by the various tissues it passes through, and each tissue receives a different amount of dose based on how much radiation it attenuates. Without HC, the dose is calculated as if the radiation is passing through a standardized water medium without accounting for the potential attenuation by the higher density bones within that anatomy. As this relates to prostate treatment, the bones of the pelvis form a rectangle encompassing the pelvic soft tissue organs. With HC applied, attenuation of the radiation by these bone structures is accounted for in calculating the radiation dose to various intrapelvic tissues. Without HC, the treatment plan calculations would not factor the attenuation by the bones of the pelvis. This would result potentially in an increase in dose being received by the surrounding tissue.[54,63]

There were not statistically significant differences between treatment plans with and without HC, supporting our original hypothesis. However, there was a trend for doses to be slightly higher without HC, with increases ranging from 0.5-3 Gy (Figure 33). These results are consistent with another report in which it was found that the human maximal volume dose distribution to prostate, rectum and urinary bladder with and without HC was clinically insignificant with differences < 2.6%. Thus, the use of HC alone shouldn't impact pelvic tissue dose disruption biologically. Also, the impact of rectal air and also the presence of

iodine contrast media used during CT was minimal in another report, with only a slightly decrease in dose delivered to area filled with gas without HC (2-4%).[53] In contrary, in situations with a large amount of rectal gas, planning with HC is better since dosimetric error can be 8 % higher without HC.[52,53,64]

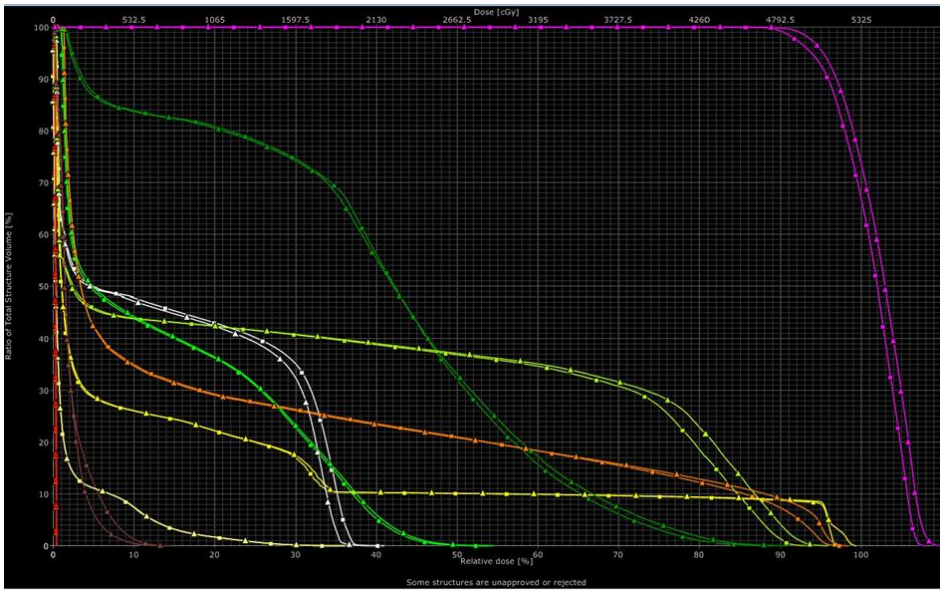


Figure 33: ED 16, DVH of comparison of Planning with/without HC. Each isodose line represents the dose constraints to specific tissue (2 isodose lines /each tissue). Square symbol is for planning with HC while triangle symbol is for planning without HC. It shows that the doses to the tumor and some of normal tissue in planning without HC were slightly higher than planning with HC most of the time.

Effect of prostate movement on Treatment Planning:

The goal of radiation therapy is to maximize the dose to the target (prostate, in this situation) while not exceeding the radiation tolerance limits of critical surrounding normal tissues. The recommended goal is achieve a target dose (95% of PTVOLR) of 50 Gy. The prostate movement documented for the 4 dogs with diagnostic CT scans would have resulted in a lower dose to that organ by as much as 3% on subsequent fractions, if movement was

unaccounted for. The prostate dose (PTVOLR) was less than the original treatment planning dose for all four dogs with the exception of 2 CTs for Dog 13. This lower dose to the PTVOLR was likely due to the treatment planning software being forced to lessen radiation delivery to that area of the pelvis in order to remain within tolerance constraint limits for the normal surrounding tissues, particularly the rectum. Under-treatment could potentially lead to decreased probability of local tumor control.

Another biological concern was that portions of the rectal wall doses exceeded constraint limits in some dogs with certain prostatic positions. The maximal prostate shift correlated with overdose to the surrounding tissue. Since the prostate is located ventral to the rectum, the rectum will be affected by dorsoventral displacement of the prostate, and the urinary bladder doses would be affected by craniocaudal prostatic displacement (Figure 34). It is less clear or predictable how left or rightward prostate displacement will affect rectal doses, but this is likely linked to additional shifts in the ventrodorsal plane.

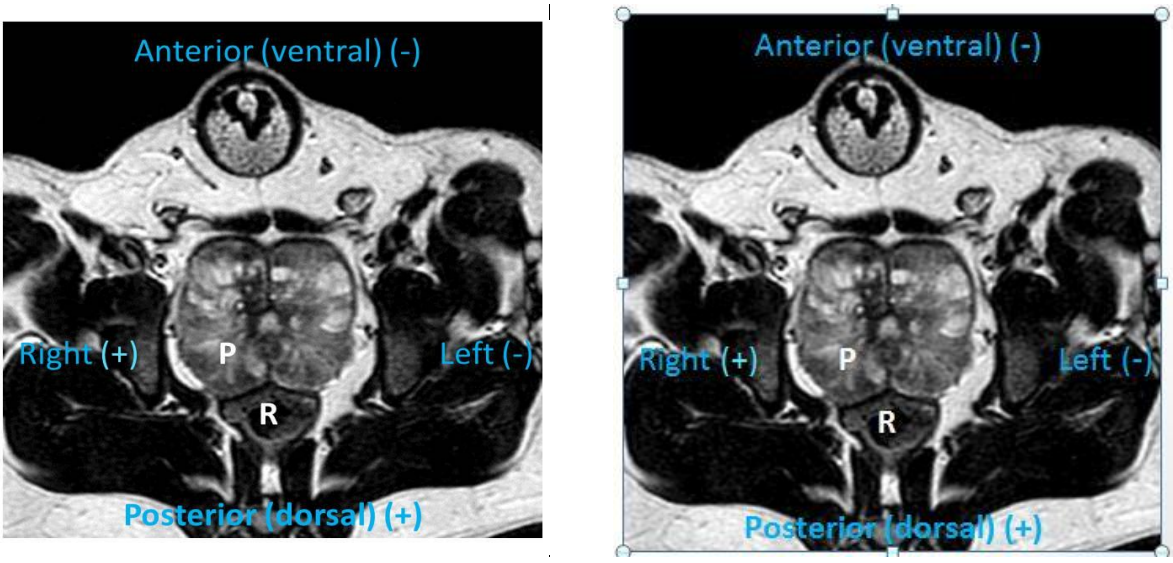


Figure 34a (left) and 34b (right): a. MRI sagittal, b. transverse views of prostate pelvic anatomy showing the anatomical relationship of the prostate (P) to the rectum (R).

The tolerance limits in Dog 13 were exceeded for the anterior rectal wall, lateral rectal wall and proximal rectum. This correlated with the degree and direction of displacement. For example, Dog 13's lateral rectal wall doses exceeded constraints on the CTs in which the prostate had leftward displacement. The posterior rectal wall limits were exceeded on CTs in which the prostate became displaced mainly caudally towards the left or dorsal. For Dogs 15 and 16, just the posterior rectal wall exceeded tolerance in one or two of the CTs, again, related to caudally and leftward in those dogs. Dog14's plans were optimal. That dog's doses remained within tolerance limits and the prostate displacement was less than the other dogs.

The dose to other critical pelvic tissues was not exceeded even with prostate displacement. The urinary bladder wall doses were only slightly above constraint values without HC twice for all four dog scans. The range in increased doses was only 0.1- 0.3 % above the constraint value, therefore not likely to have predictable biological significance. The doses to the urethra, femoral heads and proximal rectum did not exceed constraint values. This is because those anatomic structures shifted comparably or were distant enough from the prostate so as to not receive higher dose with movement.

A review of the biological significance of radiation toxicity:

Clinically, over-treatment of the rectum can cause acute and/or late toxicity of GI tract. Precise treatment planning increases the probability of local tumor control, and ideally decreases acute and late effects. The degree of expected toxicity is a primary consideration for radiation therapy of prostate cancer, as toxicity can have serious consequences on morbidity and quality of life. Each institute uses its own protocol for radiation therapy and those will vary with the location and type of tumor.[65] Many studies have been conducted and published about the toxicity of radiotherapy in general, from a particular regimen or

combination regimens, although there is a paucity of toxicity data for SRT specifically.[66,67] The most common adverse effects are associated with external beam radiotherapy of the prostate are on the gastrointestinal (GI) and genitourinary (GU) systems. Those are considered the limiting tissues for pelvic irradiation and the limits of dose escalation remain controversial.[41,68,69]

Tables 5 and 6 provide guidelines that are used to judge and grade radiation effects in human patients, which have been established by the RTOG. This group has conducted clinical and laboratory trails across the United State and Canada to help improving the outcome of cancer treatment by increasing the survival rate and quality of life of patients.[70] Acute toxicity is defined as that toxicity which originates either during RT or within a short period after completion of RT (usually weeks, or up to < 2 months after RT completion). Late toxicity develops at longer time periods after RT (usually > 6 months or even years after RT is completed).[71] Acute toxicity is reversible and self-limiting while late toxicity irreversible. Grades 3 and 4 acute toxicity are considered severe toxicity.

Table 5: Radiation Therapy Oncology Group Scale for Acute Toxicity Effects[72]

Type of toxicity	GI	GU
Grade 1	Increasing Frequency of bowel movements/change in bowel habit Rectal discomfort No medicine is required	Frequency/nocturnal No medicine is required
Grade 2	Diarrhea/mucous discharge/rectal pain	Frequency/nocturia < every hour. Dysuria/spasm Hematuria
Grade 3	Diarrhea/ sever mucous discharge/rectal pain/abdominal distention. GI bleeding	Frequency/nocturia < every hour. Dysuria/spasm Gross hematuria Urinary obstruction
Grade 4	Acute or subacute obstruction. Fistula/perforation GI bleeding Abdominal pain/tenesmus	Hematuria Sepsis/obstruction/ulceration/ necrosis of bladder

Table 6: Radiation Therapy Oncology Group Scale for Late Toxicity Effects[72]

Type of toxicity	GI	GU
G1	Increase of frequency of bowel movement at least twice baseline. Slight discharge/blood	Nocturia/ micro hematuria light mucosal atrophy. Minor telangiectasia
G2	Diarrhea/bleeding/ulceration Dilation mucous discharge/rectal pain	Frequency/nocturia General telangiectasia/ micro hematuria
G3	Severe diarrhea/ ulceration	Severe frequency and dysuria frequency hematuria
G4	Dysfunction. perforation Life threatening bleeding	Severe hemorrhagic Cystitis/ ulceration Require urinary diversion or cystectomy

Tables 7 and 8 provide the current grading system to judge acute and late toxicity for veterinary patients, developed by the Veterinary Radiation Therapy Oncology Group. Again, these grading systems allow for the systematic characterization of various radiation effects when evaluating the use of various treatments.

Table 7: Veterinary Radiation Therapy Oncology Group Scale for Acute effects [73]

Organ	G0	G1	G2	G3
Lower GI	No Change	Change in quality of bowel habits Rectal discomfort	Diarrhea Rectal discomfort	Diarrhea Bloody discharge Fistula Perforation
GU	No Change	change in frequency of urination	Change in frequency of urination	Gross hematuria Bladder obstruction
Medication	-	-	Required	Required

Table 8: Veterinary Radiation Therapy Oncology Group Scale for Late effects[73]

Organ	G0	G1	G2	G3
Bladder	No Change	Microscopic hematuria	Pollakiuria Dysuria Hematuria	Contracted bladder
Medication	-	Required	Required	Required

Much is known now about the tolerance limits and the likelihood of acute and late toxicity for IMRT, which has been well studied because this technique has been in use longer than SBRT for body radiation. IMRT delivers a precise dose to the target PTV and the volume of irradiated surrounding tissues is reduced. In patients receiving IMRT of the prostate is associated with significantly less toxicity to the GI and GU systems compared to conventional external beam 3D-CRT radiotherapy. Fortunately, most of acute toxicity resolves within 3 months, therefore, IMRT is well tolerated.[74,75] Rectal bleeding associated with late Grade 2, and Grade 3 effects is decreased and it can be safe to escalate the prostate dose up to 81 Gy with ≤ 20% developing Grade 2 late effects to the GI and GU systems, with excellent tumor control and 7-year distant metastasis free survival.[76] However, escalation dose of IMRT can still lead to late urinary toxicity comparable to 3D-CRT. As a consequence, this has impact on the quality of patient's life. [77-81]

The incidence of acute toxicity of the GI tract has been found to be a function of prostate volume for IMRT and prostate size may be a predictor of severe acute GU toxicity. A patient with a prostate volume larger than 50 cm^3 is more likely to experience severe GU toxicity or to develop Grade 3 effects like urgency/ increased frequency.[74] Furthermore, to reduce or limit the toxicity, there are other factors that are taken into consideration for IMRT of the prostate. Those include the use of a rectal balloon, reduction of the dorsal part of PTV, field size, radiation dose, and method of delivering radiation.[75,82-84] In a study using rectal balloons during prostatic IMRT, the incidence of rectal toxicity was low and the most common complication was bleeding. The incidence of fistula (which requires treatment with a colostomy) was rare, and mild to moderate complications were in the range of 20-25% after IMRT.[75,81,85] In that study, there was no significant correlation between acute toxicity and rectal and bladder volume and dose.[39,72]

There is little established data as of yet to establish definite constraint values using

SBRT for prostate irradiation, and the few studies that are published from the human clinical trials have not yet matured in order to fully understand late toxicity effects.[17] In this project, the doses associated with prostate movement with or without HC have been calculated, these are only theoretical. In reality, Dogs 13 through 16 had adjustments made to the radiation delivery through the use of image guidance to account for prostate displacement. Therefore, this project did not directly study the radiation toxicity that might result from SBRT to the prostate. In general, tolerance limits and doses that can be used for SBRT are lower than for IMRT due to its hypofractionated nature, which could lead to far greater late toxicity particularly due to difference in dose/ fraction size for SBRT.

In one recent SBRT study for prostate cancer irradiation on 48 patients, the dose tolerance was evaluated in three patient groups receiving different doses: 45 Gy, 47.5 Gy, and 50 Gy given in 5 fractions. The follow up period ranged from a year, two years, and two years and a half in those groups. Acute toxicity associated with prostate SBRT was evaluated and then the dose was escalated to the next level for the subsequent treatment group. Maximum tolerated dose for SBRT was 50 GY, and dose limiting toxicity started at Grade 3 for the GI or GU systems. Grade 1 acute GI toxicity was experienced in 40%, 13 %, and 47% of patients received 45 Gy, 47.5 Gy, and 50 Gy respectively. Grade 2 acute GI toxicity was experienced in patients received 47.5 and 50 Gy by 13 %, and 7 % respectively. No Grade 3 or Grade 4 effects were seen within 90 days after SBRT.[16]

On the other hand, late GI toxicity was seen in all groups. Grade1 late toxicity was experienced in 7% of patients who received 45 Gy and 47.5 Gy. Grade 2 late toxicity was seen in 7% and 27% of patients received 45 and 47.5 respectively. No Grade 3 or Grade 4 effects were seen in those two groups. For patients receiving 50 Gy, 33 % of patients experienced Grade 1 late toxicity and 7 % of patients experienced Grade 4 late toxicity with

no Grade 2 or Grade 3. One patient developed a GI ulcer shortly after treatment. There was tolerable acute Grade 1and Grade 2 GI toxicity with rare Grade 3 toxicity in that study.[16]

The toxicity associated with Cyperknife- SBRT (35 Gy in 5 fractions) based on the same RTOG scoring system has also been reported. The follow up range was between 6- 42 months in 45 patients. The most severe grade of acute toxicity was Grade 2, occurring with an incidence of 24.4% GI and 11.1 GU. Late toxicity was rare with only 2.2% of Grade 2 for the GI tract and Grade 3 for the GU system.[11] The most common rectal toxicity in that particular study was rectal urgency or stool frequency which occurred within the first month of treatment.[16]

The toxicity associated with hypo-fractionated IMRT within 2 years of follow up was assessed by RTOG scoring system. Although there was better tumor control than 3D_CRT in human patients, acute and late toxicity was experienced. Acute Grade 2 toxicity was reported as 10% for GU and 15% for GI toxicity with no Grade 3 or Grade 4 of acute GI and GU effects. In another study, most patients had Grade 0 or Grade 1 of GI and GU acute toxicity. Late GU or GI toxicity effects occurred in less than 5% of patients study.[79,86]

CONCLUSION

This study aimed to address the impact of prostate displacement and HC on the SBRT radiotherapy planning of the canine prostate patient. The results of this study have allowed us to evaluate the effect that inter-fractional prostate variations would have on modeled dose distribution. Also, the results of this study have allowed us to examine the impact of HC on dose distribution from prostate RT. The statistical tests used in the analysis of the data accounted for the size of sample when determining significance, and some conclusions could be made despite the small sample size. In future studies, a larger sample size and follow up, might allow for addressing whether planning without HC could affect the occurrence of severe late GI toxicity in canine patients undergoing EBRT modalities such as IMRT and SBRT. Also, the impact of prostate size and rectal distention on the accuracy of planning could be assessed.

Prostate inter-fraction displacement was pronounced especially in the dorsoventral direction and this was representative of a true clinical situation. There were only a few statically significant differences when comparing plans with and without HC of the prostate area. That indicates that using the HC does not have a huge impact on the dose evaluation of prostate planning. Still, there was a trend for doses to increase slightly when not using HC during treatment planning, due to mild radiation attenuation contributed by the pelvic bones.

In terms of prostate displacement, the results of this project indicated that prostatic displacement could have a significant effect if not accounted for during SBRT fraction delivery. Tissue tolerance constraints were exceeded with prostate displacement especially in the caudal, left and dorsal directions and there was a correlation between the prostate

displacements and dose to the tissues. PTOVLR (target) doses were usually lower than the goal while the posterior rectal wall doses exceeded constraints, especially where the displacement caudally toward left. Despite that, there was no statistically significance between doses after prostate displacement in the absence of HC. Inter (and intra) fraction prostate movement could limit the accuracy of IMRT or SBRT unless image guidance is used during therapy. Thus, tracking and accounting for prostate movement is very important during radiotherapy.

External beam radiotherapy (IMRT and SBRT) is well tolerated by the tissues when heeding known tissue constraints. However our goal should take into account tumor control, which means optimizing the dose to the target while keeping the likelihood of tissue toxicity to a minimum so as to preserve quality of life of the patients. As the constraint limits for SBRT become better understood, we will get closer to achieving that goal.

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APPENDIX A

RAW DATA OF PROSTATE DISPLACEMENT ON CBCT

# Dog	TX Date/ Time	CBCT Scan Time	X	Y	Z
ED 1		RAB_CT2_Bone(040710	0	0	0
	6/1/2009, 11:22 A	CBCT#1.11:19	-0.06	0.4	-0.07
	6/2, 9:47 A	CBCT#2,9:32	-0.02	0.5	0.06
	6/3, 9:37 A	CBCT#3,9:22	0.26	-0.02	-0.26
	6/4, 9:37 A	CBCT#4, 9:25	0.27	0.23	0.03
	6/5 , 9:44 A	CBCT#5,9:38	-0.04	0.65	-0.02
Average			0.068333	0.293333	-0.04333
ED 2		RAB_ CT2_Bone	0	0	0
	6/8,12:24 P	CBCT#1.12:13	0.43	-0.23	-0.13
	6/9, 9:58 A	CBCT#2,9:49	0.62	0.42	0.06
	6/10, 9:47 A	CBCT#3,9:36	0.49	-0.03	-0.21
	6/11, 9:24 A	CBCT#4, 9:14	0.44	0.17	-0.02
	6/12, 9:34 A	CBCT#5,9:22	0.58	-0.07	-0.09
Average			0.426667	0.043333	-0.065
ED 4		RAB_ CT2_Bone	0	0	0
	9/14/2009,10:28 A.	CBCT#1,10:14	-0.36	0.11	0.06
	9/15,9:52 A	CBCT#2,9:42	-0.49	-0.24	-0.04
	9/16, 10:40 A	CBCT#3,10:33	0	0	0
	9/17,10:26 A	CBCT#4, 10:17	-0.76	0.13	-0.1
	9/18,10:50A	CBCT#5,10:36	-0.35	0.37	0.45
Average			-0.32667	0.061667	0.061667
ED 5		RAB_CT2_Bone	0	0	0
	1/25/2010, 1:14 P	CBCT#1,1:03	0.23	0.13	-0.04
	1/26, 10:05 A	CBCT#2,10:00	0.17	0.06	-0.02
	1/27, 12:23 P	CBCT#3,12:17	0.12	0	-0.07
	1/28, 12:27 P	CBCT#4,12:17	0.16	-0.05	-0.01
	1/29, 12:06 P	CBCT#5, 11:57	0.16	0.14	0.02
Average			0.14	0.046667	-0.02
ED 6		RAB_ CT2_Bone	0	0	0
	3/8/2010,11:54 A	CBCT#1.11:44	-0.09	0.06	-0.04
	3/9,9:26 A	CBCT#2,9:13	-0.11	0.1	-0.03
	3/10,10:26 A	CBCT#3,10:12	-0.06	0.17	-0.03
	3/11;11:54 A	CBCT#4, 11:42	-0.1	0.04	-0.05
	3/12,10:32 A	CBCT#5,10:22	-0.09	0.23	0.04
Average			-0.075	0.1	-0.01833
ED 7		RAB_ CT2_Bone	0	0	0
	7/16/2010,3:18P	CBCT#1, 3:10	-0.03	-0.08	0.07
	7/19, 2:25P	CBCT#2,2:13	-0.14	-0.63	0.21
	7/21, 2:09P	CBCT#3,2:00	-0.16	0.14	0.13

	7/23 ,3:19 P	CBCT#4, 3:13	-0.05	0.03	0.13
	7/26, 11:42 A	CBCT#5,11:28	-0.12	0.07	0
			-0.08333	-0.07833	0.09
ED 8		RAB_ CT2_Bone	0	0	0
	12/10/2010, 10:25 A	CBCT#1, 10:16	-0.07	0.48	0.26
	12/13, 11:38 A	CBCT#2, 11:33	0.22	0.36	0.18
	12/16, 10:13 P	CBCT#3, 10:04	0.31	0.88	0.53
	12/17, 3:57 P	CBCT#4, 3:45	-0.2	0.96	0.42
	12/20, 11:20 A	CBCT#5, 11:14	-0.07	0.61	-0.07
Average			0.031667	0.548333	0.22
ED 9		RAB_ CT2_Bone	0	0	0
	12/10/2010, 11:24 A	CBCT#1, 11:48	0.14	0.22	0.14
	12/13, 1:16 P	CBCT#2, 1:11	-0.04	0.07	-0.01
	12/15, 9:16 P	CBCT#3, 8:23	0.04	0.13	0.02
	12/17,10:00 A	CBCT#4, 9:46	-0.04	0.2	0.08
	12/21, 9:51 A	CBCT#5, 9:36	-0.19	0.86	0.06
Average			-0.015	0.246667	0.048333
ED 10		RAB_ CT2_Bone	0	0	0
	3/4/2001,11:30 A	CBCT#111:20:00	0.16	0.13	0
	3/7;10:19 A	CBCT#210:08:00	0.06	0.01	0.03
	3/9,10:45 A	CBCT#310:37:00	0.24	0.14	0.12
	3/11:05 A	CBCT#410:56:00	0.21	0.46	0.01
	3/14, 9:14 A	CBCT#59:07:00	0.11	0.24	0.24
Average			0.13	0.163333	0.066667
ED11		RAB_CT2_Bone	0	0	0
	6/29/2011, 12:25 P	CBCT#1.12:13	0.11	0.08	0.06
	7/1, 9:30 A	CBCT#2,9:26	-0.05	0.31	0.18
	7/5, 8:59 A	CBCT#3,8:47	0.01	0.28	0.3
	7/6, 9:44 A	CBCT#4, 9:36	-0.01	0.25	0.23
	7/8, 10:52 A	CBCT#5,10:47	0.21	0.12	0.04
Average			0.045	0.173333	0.135

APPENDIX B

RAW DATA OF PROSTATE DISPLACEMENT ON CT

ED13	CT Planning	0	0	0
	CT 1	-0.78	0.3	0.5
	CT 2	-0.49	-0.12	-0.19
	CT 3	-0.44	-0.01	0.31
	CT 4	-0.11	0.81	0.28
Average		-0.364	0.196	0.18
ED14	CT Planning	0	0	0
	CT 1	-0.2	-0.01	0.28
	CT 2	-0.32	-0.05	0.1
	CT 3	-0.1	-0.04	0.34
	CT 4	-0.24	0.08	0.04
Average		-0.172	-0.004	0.152
ED15	CT Planning	0	0	0
	CT 1	-0.07	0.05	0.15
	CT 2	0.07	0.25	0.08
	CT 3	0.04	0.28	0.12
Average		0.01	0.145	0.0875
ED16	CT Planning	0	0	0
	CT 1	-0.07	0.15	0
	CT 2	0.05	0.16	-0.01
	CT 3	0.06	0.1	0.19
Average		0.01	0.1025	0.045

marks the greatest movement per dog in each dimension

X direction is left to right (+ = right)

Y direction is A to P (+ = posterior)

Z direction is cranial to caudal (+ = caudal)

APPENDIX C

RAW DOSE DATA

Legend for the Raw Dose Data Tables

Green highlights those tissues that have constraints defined by volume.
Blue highlights columns of data derived Without the use of HC.
Pink highlights those values which differ greatly from the other related data.

		CT Planning + HC	CT Planning _HC	CT1 +HC	CT1_HC	CT2+HC	CT2_HC	CH3+HC	CH3_HC	CH4+HC	CH4_HC
ED13		Max Dose%	Max Dose%	Max Dose%	Max Dose%	Max Dose%	Max Dose%	Max Dose%	Max Dose%	Max Dose%	Max Dose%
	PTVO Less R.	111	110.3	111.9	112.5	111.7	112.6	111.9	112.7	112	113.2
	Ant. Rectal Wall	97	97.2	103.8	105.7	104	105.5	105.4	106.8	101.3	103.1
	Lat. Rectal Wall	94.5	94.9	99.3	100.9	101.7	103.3	104.2	105.9	99.4	101.1
	Pos. Rectal Wall	40.4	37.6	76.3	79.2	52	50.8	59	57.7	63.9	63.5
	Prox.Rectum	16.9	17.1	5.1	4.3	6.5	6.5	9.3	8.2	4.8	4.8
	Urethera	98.8	98.6	101.7	101.5	103.8	103.8	103.6	103.6	100.2	101.4
	Bladder Wall	101.1	100.3	104.8	104.8	104	104.1	105	105.1	103.7	104.5
	F.Hs	50.3	50.8	52.8	53.2	61.6	61.2	49.7	50.6	46.1	65.7
ED14											
	PTVO Less R.	107.1	107.5	106.7	106.1	107.2	106.3	107	106.6	106.9	106.1
	Ant. Rectal Wall	94.3	97.3	100.2	100.9	99.9	101.2	98.4	101	97.8	100
	Lat. Rectal Wall	84	86.2	79.6	81	86	89.6	68.8	70	84.2	87.9
	Pos. Rectal Wall	39.8	39.3	39.1	38.9	39.2	38.6	37.2	35.8	39	38
	Rectum	9.5	8.8	8.6	5.5	10.7	8.3	9.4	5.3	10	10.1
	Urethera	96.3	98.1	96.1	96.8	96.2	96.9	96.3	97.2	96.6	96.7
	Bladder	97.3	97.5	91.1	90	97	95.8	90.8	89.1	97.1	96.5
	F.Hs	49.1	50.3	51.6	52	48.4	48.4	54	54.4	45.9	45.6
Skin											
ED15											
	PTVO Less R.	111.3	112.3	111.9	112	110.7	111	110.7	111		
	Ant. Rectal Wall	101	102.5	101.1	102.7	98.6	99.6	98.8	100		
	Lat. Rectal Wall	92.8	94.7	97.7	99.7	86.6	87.3	91	92.1		
	Pos. Rectal Wall	42.9	42.4	78.7	79.5	40.9	40	46.7	46.1		
	Rectum	13.1	13.5	10.7	10.9	13	13.2	12.7	12.9		
	Urethera	100.1	100.4	100.7	99.9	100.5	100.1	100.1	99.8		
	Bladder	93.9	94.3	104.7	105.4	99.9	100.3	99.9	100.3		
	F.Hs	53.3	54.6	56.9	58.2	56.3	57.4	56.3	57.2		
ED16											
	PTVO Less R.	108	110	108.2	110.1	107.5	109.5	108.1	109.6		
	Ant. Rectal Wall	93.8	96.1	99.1	100.3	97.5	100.7	94	98.1		
	Lat. Rectal Wall	89.3	91	92.8	94.4	89.6	90.5	87.5	88.6		
	Pos. Rectal Wall	41	40.4	45.3	45.2	44.4	44.3	41.4	40.1		
	Rectum	14.7	14.3	18.1	15.5	18.7	16	28.1	28		
	Urethera	97.4	99.4	98.6	100.1	97.9	99.6	98.3	99.3		
	Bladder	97.7	98.4	101.9	101.7	98.8	98.2	97.5	96.8		
	F.Hs	54	54.6	58.4	59.1	60.7	62.3	58	58.1		
			Numbers in pink are way different than the rest of that organs data								

	CT Planning + HC	CT Planning _HC	CT1 +HC	CT1_HC	CT2+HC	CT2_HC	CH3+HC	CH3_HC	CH4+HC	CH4_HC
	Min Dose%	Min Dose%	Min Dose%	Min Dose%	Min Dose%	Min Dose%	Min Dose%	Min Dose%	Min Dose%	Min Dose%
PTVO Less R.	77.5	77.8	81.8	82.9	68.6	68.8	79.2	80.3	62.9	64.3
Ant. Rectal Wall	0.6	0.6	1	0.9	2.3	1.7	1	1	1.1	0.9
Lat. Rectal Wall	1.2	1	0.9	0.8	1.6	1.3	0.8	0.8	0.9	0.7
Pos. Rectal Wall	0.6	0.6	0.9	0.8	1.7	1.4	0.8	0.8	0.9	0.7
Prox.Rectum	0.4	0.4	0.7	0.6	0.7	0.6	0.7	0.6	0.5	0.4
Urethera	0.3	0.3	0.2	0.2	0.3	0.3	0.2	0.3	0.3	0.3
Bladder Wall	0.3	0.3	0.8	0.8	0.6	0.6	0.5	0.5	0.5	0.5
F.Hs	1.7	1.8	0	0	0	0	0.1	0.2	0.6	0.6
PTVO Less R.	82.9	85.4	67	66.3	68.7	68.8	67.6	66.7	66.9	66.5
Ant. Rectal Wall	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Lat. Rectal Wall	1.1	1	1.3	1.3	0.3	0.3	1.1	1.1	0.8	0.7
Pos. Rectal Wall	0.3	0.3	0.2	0.2	0.2	0.2	0.4	0.4	0.3	0.3
Rectum	2	2.1	1	1	1.7	1.7	1.6	1.6	2.2	2.2
Urethera	0.1	0.2	0.1	0.2	0.1	0.2	0.1	0.2	0.1	0.2
Bladder	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
F.Hs	0	0	0.3	0.4	0.2	0.2	0.2	0.3	0.2	0.3
PTVO Less R.	80.9	82.4	72.8	74.7	70.1	71.2	66.7	67.4		
Ant. Rectal Wall	0.3	0.2	0	0	0.4	0.4	0.4	0.4		
Lat. Rectal Wall	0.9	0.8	0	0	0.4	0.4	0.4	0.4		
Pos. Rectal Wall	0.2	0.2	0	0	0.4	0.4	0.4	0.4		
Rectum	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6		
Urethera	0.2	0.3	0	0	0.2	0.3	0.2	0.3		
Bladder	0.7	0.7	0.8	0.9	0.8	0.8	0.8	0.8		
F.Hs	0.9	1	0	0	0	0	0.6	0.6		
PTVO Less R.	82.2	83.3	65.6	67.7	71.9	74.5	66.2	68		
Ant. Rectal Wall	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4		
Lat. Rectal Wall	1.5	1.4	1.6	1.5	0.5	0.5	1.5	1.5		
Pos. Rectal Wall	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4		
Rectum	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2		
Urethera	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2		
Bladder	1.2	1.3	0.3	0.3	0.3	0.3	0.3	0.3		
F.Hs	0.8	0.9	0.9	0.9	0.9	0.9	0.9	1		

	CT Planning + HC	CT Planning _HC	CT1 +HC	CT1_HC	CT2+HC	CT2_HC	CH3+HC	CH3_HC	CH4+HC	CH4_HC
	Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)
PTVO Less R.	49.96	49.74	50	50.57	49.06	49.65	49.53	50	48.9	49.79
Ant. Rectal Wall										
Lat. Rectal Wall	40.97	42.41	43.43	45	45.37	46.33	47.52	48.4	41.29	42.4
Pos. Rectal Wall										
Prox.Rectum	2.32	2.37	1.37	1.39	2.21	2.12	2.26	1.87	1.45	1.44
Urethera										
Bladder Wall										
F.Hs	17.49	17.44	18.16	18.29	16.63	16.78	16.92	17.13	22.82	23.04
PTVO Less R.	49.9	50.51	47.97	48.35	48.81	49	48.35	48.71	49.1	49.12
Ant. Rectal Wall										
Lat. Rectal Wall	32.22	33.74	33.58	34.32	33.67	34.19	30.8	31.42	33.96	34.88
Pos. Rectal Wall										
Rectum	3.77	3.3	3.35	1.91	4.08	2.93	3.9	2.21	3.44	3.48
Urethera										
Bladder										
F.Hs	14.9	15.19	17.1	17.14	15.38	15.45	17.3	17.33	15.9	15.97
PTVO Less R.	49.9	50.4	48.9	49.4	48.5	48.8	48.74	49.08		
Ant. Rectal Wall										
Lat. Rectal Wall	41.4	42.4	38.7	39.11	36.4	37.04	34.16	34.6		
Pos. Rectal Wall										
Rectum	3.1	3.23	2.84	2.88	3.1	3.13	3.02	3.01		
Urethera										
Bladder										
F.Hs	19.5	19.8	19.8	19.93	19.3	19.32	19.85	19.88		
PTVO Less R.	49.9	50.7	48.13	49.34	49.3	49.9	48.93	49.7		
Ant. Rectal Wall										
Lat. Rectal Wall	40	41.14	37.85	38.68	39.28	40.05	36.19	36.93		
Pos. Rectal Wall										
Rectum	2.97	2.15	3.4	2.14	3.46	2.15	3.53	2.71		
Urethera										
Bladder										
F.Hs	19.4	19.9	21.04	21.27	20.63	20.84	20.54	20.72		

	CT Planning + HC	CT Planning _HC	CT1 +HC	CT1_HC	CT2+HC	CT2_HC	CH3+HC	CH3_HC	CH4+HC	CH4_HC
	Absolute Value(G	Absolute Value(G	Absolute Value(G	Absolute Value(G	Absolute Value(G	Absolute Value(G	Absolute Value(G	Absolute Value(G	Absolute Value(G	Absolute Value(G
PTVO Less R.	58.5	58.18	59.01	59.32	58.92	59.4	59	59.47	59.05	59.7
Ant. Rectal Wall	51.1	51.2	54.73	55.77	54.85	55.64	55.62	56.32	53.44	54.39
Lat. Rectal Wall	49.8	50.04	52.38	53.22	53.64	54.5	54.99	55.84	52.45	53.34
Pos. Rectal Wall	21.3	19.81	40.27	41.75	27.43	26.78	31.14	30.45	33.68	33.51
Prox.Rectum	8.9	9.01	2.69	2.27	3.42	3.44	4.93	4.34	2.53	2.53
Urethera	52.12	52.01	53.64	53.55	54.73	54.74	54.67	54.66	52.84	53.48
Bladder Wall	53.3	52.9	55.29	55.27	54.85	54.9	55.38	55.45	54.68	55.14
F.Hs	26.5	26.81	27.85	28.03	32.48	32.28	26.22	26.7	33.81	34.67
PTVO Less R.	57.79	58.01	57.54	57.25	57.84	57.35	57.7	57.49	57.69	57.26
Ant. Rectal Wall	50.87	52.47	54.06	54.42	53.89	54.57	53.09	54.46	52.76	53.96
Lat. Rectal Wall	45.33	46.48	42.97	43.67	46.4	48.38	37.1	37.74	45.43	47.4
Pos. Rectal Wall	21.47	21.18	21.11	20.98	21.14	20.81	20.07	19.29	21.01	20.49
Rectum	5.13	4.74	4.62	2.96	5.77	4.46	5.05	2.84	5.39	5.45
Urethera	51.9	52.9	51.86	52.25	51.88	52.26	51.97	52.44	52.1	52.14
Bladder	52.48	52.62	49.14	48.53	52.31	51.68	48.96	48.04	52.37	52.08
F.Hs	26.51	27.13	27.85	28.07	26.1	26.13	29.11	29.34	24.74	24.6
PTVO Less R.	57.16	57.6	57.47	57.5	56.8	56.9	56.8	56.98		
Ant. Rectal Wall	51.8	52.6	51.93	52.7	50.6	51.12	50.74	51.33		
Lat. Rectal Wall	47.6	48.6	50.15	51.18	44.4	44.83	46.7	47.31		
Pos. Rectal Wall	22	21.7	40.41	40.79	20.9	20.54	23.9	23.67		
Rectum	6.7	6.93	5.52	5.58	6.68	6.78	6.54	6.62		
Urethera	51.4	51.5	51.6	51.29	51.5	51.4	51.41	51.25		
Bladder	48.2	48.4	53.7	54.09	51.3	51.5	51.3	51.528		
F.Hs	27.3	28.04	29.2	29.86	28.9	29.4	28.9	29.36		
PTVO Less R.	57.5	58.56	57.63	58.62	57.23	58.31	57.56	58.37		
Ant. Rectal Wall	49.9	51.14	52.77	53.39	51.93	53.6	50.07	52.24		
Lat. Rectal Wall	47.5	48.43	49.42	50.28	47.71	48.19	46.57	47.15		
Pos. Rectal Wall	21.8	21.49	24.14	24.05	23.62	23.6	22.03	21.36		
Rectum	7.8	7.6	9.64	8.23	9.98	8.53	14.97	14.92		
Urethera	51.8	52.93	52.52	53.3	52.12	53.02	52.35	52.87		
Bladder	52	52.38	54.25	54.18	52.62	52.31	51.92	51.54		
F.Hs	28.7	29.07	31.12	31.45	32.34	33.17	30.89	30.92		

APPENDIX D

STATISTICAL DATA ANALYSIS

Table 9: PTV0 less rectal wall

Measure	Comparison	N	Mean	Std	t-test p-value	SignedRank test p-value
Dose						
	With HC vs. without HC for					
	CT1	4	-0.67	0.37	0.0373	0.1250
	CT2	4	-0.42	0.21	0.0270	0.1250
	CT3	4	-0.48	0.20	0.0164	0.1250
	CT4	2	-0.45	0.62	0.4857	0.5000
	CT Planning	4	-0.42	0.45	0.1544	0.2500
	Results with HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	1.16	0.90	0.0812	0.2500
	CT Planning vs.CT2	4	1.00	0.34	0.0095	0.1250
	CT Planning vs.CT3	4	1.03	0.47	0.0216	0.1250
	CT Planning vs.CT4	2	0.93	0.18	0.0884	0.5000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	0.92	1.26	0.2408	0.2500
	CT Planning vs.CT2	4	1.00	0.70	0.0657	0.1250
	CT Planning vs.CT3	4	0.97	0.88	0.1160	0.2500
	CT Planning vs.CT4	2	0.67	1.02	0.5229	1.0000
Absolute value						
	With HC vs. without HC for					
	CT1	4	-0.26	0.54	0.4103	0.3750
	CT2	4	-0.29	0.66	0.4404	0.6250
	CT3	4	-0.31	0.43	0.2447	0.3750

CT4	2	-0.11	0.76	0.8721	1.0000
CT Planning	4	-0.35	0.57	0.3077	0.3750
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-0.18	0.32	0.3579	0.3750
CT Planning vs.CT2	4	0.04	0.35	0.8355	1.0000
CT Planning vs.CT3	4	-0.03	0.36	0.8882	1.0000
CT Planning vs.CT4	2	-0.22	0.46	0.6145	1.0000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-0.08	0.79	0.8430	1.0000
CT Planning vs.CT2	4	0.10	0.90	0.8426	0.8750
CT Planning vs.CT3	4	0.01	0.89	0.9834	0.8750
CT Planning vs.CT4	2	-0.39	1.61	0.7918	1.0000
Maximum					
With HC vs. without HC for					
CT1	4	-0.50	1.06	0.4132	0.5000
CT2	4	-0.57	1.21	0.4118	0.5000
CT3	4	-0.55	0.80	0.2638	0.3750
CT4	2	-0.20	1.41	0.8743	1.0000
CT Planning	4	-0.68	1.13	0.3179	0.3750
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-0.33	0.56	0.3312	0.3750
CT Planning vs.CT2	4	0.07	0.60	0.8193	1.0000
CT Planning vs.CT3	4	-0.08	0.62	0.8255	1.0000
CT Planning vs.CT4	2	-0.40	0.85	0.6257	1.0000
Results without HC					

CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-0.15	1.51	0.8549	1.0000
CT Planning vs.CT2	4	0.18	1.69	0.8490	0.8750
CT Planning vs.CT3	4	0.05	1.67	0.9561	0.8750
CT Planning vs.CT4	2	-0.75	3.04	0.7863	1.0000

Mean

With HC vs. without HC for					
CT1	4	-0.55	0.53	0.1307	0.2500
CT2	4	-0.47	0.57	0.1929	0.2500
CT3	4	-0.45	0.37	0.0930	0.2500
CT4	2	-0.65	1.48	0.6471	1.0000
CT Planning	4	-0.60	0.61	0.1418	0.2500
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.32	0.69	0.4156	0.3750
CT Planning vs.CT2	4	0.40	0.55	0.2403	0.3750
CT Planning vs.CT3	4	0.28	0.71	0.4970	0.5000
CT Planning vs.CT4	2	0.55	0.21	0.1695	0.5000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.37	1.63	0.6763	0.7500
CT Planning vs.CT2	4	0.52	1.40	0.5066	0.7500
CT Planning vs.CT3	4	0.43	1.56	0.6230	0.8750
CT Planning vs.CT4	2	0.15	2.05	0.9344	1.0000

Minimum

With HC vs. without HC for					
CT1	4	-1.10	1.28	0.1830	0.2500
CT2	4	-1.00	1.16	0.1825	0.1250
CT3	4	-0.68	1.14	0.3231	0.3750

CT4	2	-0.50	1.27	0.6772	1.0000
CT Planning	4	-1.35	0.91	0.0599	0.1250

Results with HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	9.08	9.71	0.1585	0.2500
CT Planning vs.CT2	4	11.05	2.25	0.0022	0.1250
CT Planning vs.CT3	4	10.95	8.47	0.0813	0.2500
CT Planning vs.CT4	2	15.30	0.99	0.0291	0.5000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	9.33	10.73	0.1807	0.2500
CT Planning vs.CT2	4	11.40	3.63	0.0082	0.1250
CT Planning vs.CT3	4	11.63	9.56	0.0933	0.2500
CT Planning vs.CT4	2	16.20	3.82	0.1051	0.5000

Table 10: Anterior rectal wall

Measure	Comparison	N	Mean	Std	t-test p-value	SignedRank test p-value
Absolute value						
	With HC vs. without HC for					
	CT1	4	-0.70	0.28	0.0162	0.1250
	CT2	4	-0.91	0.52	0.0381	0.1250
	CT3	4	-1.21	0.73	0.0452	0.1250
	CT4	2	-1.08	0.18	0.0737	0.5000
	CT Planning	4	-0.94	0.65	0.0627	0.1250
	Results with HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-2.46	1.58	0.0531	0.1250
	CT Planning vs.CT2	4	-1.90	2.18	0.1802	0.2500
	CT Planning vs.CT3	4	-1.46	2.45	0.3177	0.3750
	CT Planning vs.CT4	2	-2.11	0.32	0.0675	0.5000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-2.22	1.83	0.0943	0.1250
	CT Planning vs.CT2	4	-1.88	2.46	0.2246	0.2500
	CT Planning vs.CT3	4	-1.73	2.64	0.2806	0.3750
	CT Planning vs.CT4	2	-2.34	1.20	0.2218	0.5000
Maximum						
	With HC vs. without HC for					
	CT1	4	-1.35	0.52	0.0138	0.1250
	CT2	4	-1.75	0.99	0.0383	0.1250
	CT3	4	-2.32	1.34	0.0400	0.1250
	CT4	2	-2.00	0.28	0.0635	0.5000
	CT Planning	4	-1.75	1.20	0.0618	0.1250
	Results with HC					

	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-4.52	3.01	0.0575	0.1250
	CT Planning vs.CT2	4	-3.48	4.14	0.1921	0.2500
	CT Planning vs.CT3	4	-2.63	4.64	0.3404	0.3750
	CT Planning vs.CT4	2	-3.90	0.57	0.0651	0.5000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-4.13	3.41	0.0941	0.1250
	CT Planning vs.CT2	4	-3.48	4.67	0.2333	0.2500
	CT Planning vs.CT3	4	-3.20	5.00	0.2909	0.3750
	CT Planning vs.CT4	2	-4.30	2.26	0.2268	0.5000
Mean						
	With HC vs. without HC for	4	-0.93	0.50	0.0341	0.1250
	CT1	4	-0.90	0.48	0.0337	0.1250
	CT2	4	-0.75	0.44	0.0412	0.1250
	CT3	2	-0.65	0.21	0.1444	0.5000
	CT4	4	-0.72	0.38	0.0311	0.1250
	CT Planning					
	Results with HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-3.65	8.76	0.4660	0.7500
	CT Planning vs.CT2	4	-7.93	8.11	0.1456	0.2500
	CT Planning vs.CT3	4	-4.65	8.22	0.3403	0.2500
	CT Planning vs.CT4	2	-3.80	7.50	0.6040	1.0000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-3.85	9.54	0.4788	0.8750
	CT Planning vs.CT2	4	-8.10	8.61	0.1565	0.2500
	CT Planning vs.CT3	4	-4.68	8.71	0.3617	0.3750
	CT Planning vs.CT4	2	-3.80	8.34	0.6357	1.0000

Minimum

With HC vs. without HC for					
CT1	4	0.03	0.05	0.3910	1.0000
CT2	4	0.15	0.30	0.3910	1.0000
CT3	4	0.00	0.00	.	.
CT4	2	0.10	0.14	0.5000	1.0000
CT Planning	4	0.03	0.05	0.3910	1.0000
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-0.03	0.29	0.8729	1.0000
CT Planning vs.CT2	4	-0.45	0.83	0.3599	0.5000
CT Planning vs.CT3	4	-0.13	0.19	0.2783	0.5000
CT Planning vs.CT4	2	-0.25	0.35	0.5000	1.0000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-0.03	0.21	0.8240	1.0000
CT Planning vs.CT2	4	-0.33	0.53	0.3039	0.5000
CT Planning vs.CT3	4	-0.15	0.19	0.2152	0.5000
CT Planning vs.CT4	2	-0.15	0.21	0.5000	1.0000

Table 11: Lateral rectal wall

Measure	Comparison	N	Mean	Std	t-test p-value	SignedRank test p-value
Absolute value						
	With HC vs. without HC for					
	CT1	4	-0.89	0.49	0.0361	0.1250
	CT2	4	-0.72	0.19	0.0046	0.1250
	CT3	4	-0.67	0.19	0.0056	0.1250
	CT4	2	-1.02	0.13	0.0594	0.5000
	CT Planning	4	-1.28	0.25	0.0019	0.1250
	Results with HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	0.26	2.55	0.8530	0.8750
	CT Planning vs.CT2	4	-0.03	3.96	0.9879	1.0000
	CT Planning vs.CT3	4	1.48	5.86	0.6484	0.6250
	CT Planning vs.CT4	2	-1.03	1.00	0.3842	0.5000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	0.64	2.72	0.6681	0.8750
	CT Planning vs.CT2	4	0.52	3.85	0.8044	0.8750
	CT Planning vs.CT3	4	2.08	5.84	0.5270	0.6250
	CT Planning vs.CT4	2	-0.57	0.81	0.5056	1.0000
Absolute value						
	With HC vs. without HC for					
	CT1	4	-0.86	0.14	0.0011	0.1250
	CT2	4	-0.94	0.72	0.0803	0.1250
	CT3	4	-0.67	0.12	0.0016	0.1250
	CT4	2	-1.43	0.76	0.2299	0.5000
	CT Planning	4	-0.83	0.40	0.0261	0.1250

Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-1.17	2.37	0.3962	0.3750
CT Planning vs.CT2	4	-0.48	2.90	0.7625	0.6250
CT Planning vs.CT3	4	1.22	5.49	0.6874	0.6250
CT Planning vs.CT4	2	-1.38	1.80	0.4760	0.5000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-1.20	2.73	0.4438	0.6250
CT Planning vs.CT2	4	-0.59	3.48	0.7581	0.8750
CT Planning vs.CT3	4	1.38	5.94	0.6742	0.6250
CT Planning vs.CT4	2	-2.11	1.68	0.3269	0.5000
Maximum					
With HC vs. without HC for					
CT1	4	-1.65	0.25	0.0010	0.1250
CT2	4	-1.70	1.32	0.0827	0.1250
CT3	4	-1.27	0.29	0.0030	0.1250
CT4	2	-2.70	1.41	0.2258	0.5000
CT Planning	4	-1.55	0.79	0.0298	0.1250
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-2.20	4.45	0.3953	0.3750
CT Planning vs.CT2	4	-0.82	5.53	0.7848	0.6250
CT Planning vs.CT3	4	2.27	10.18	0.6852	0.6250
CT Planning vs.CT4	2	-2.55	3.32	0.4740	0.5000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-2.30	5.11	0.4346	0.6250
CT Planning vs.CT2	4	-0.97	6.67	0.7890	0.8750

CT Planning vs.CT3	4	2.55	11.10	0.6773	0.6250
CT Planning vs.CT4	2	-3.95	3.18	0.3296	0.5000

Mean

With HC vs. without HC for

CT1	4	0.10	0.12	0.1817	0.5000
CT2	4	0.10	0.08	0.0917	0.2500
CT3	4	0.17	0.15	0.1018	0.2500
CT4	2	0.00	0.14	1.0000	1.0000
CT Planning	4	-0.10	0.35	0.6042	0.7500

Results with HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	1.95	5.47	0.5270	0.6250
CT Planning vs.CT2	4	4.03	4.70	0.1855	0.2500
CT Planning vs.CT3	4	3.80	7.04	0.3594	0.3750
CT Planning vs.CT4	2	5.85	11.10	0.5923	1.0000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	2.15	5.32	0.4784	0.6250
CT Planning vs.CT2	4	4.23	4.78	0.1752	0.2500
CT Planning vs.CT3	4	4.08	7.06	0.3322	0.3750
CT Planning vs.CT4	2	5.85	10.39	0.5720	1.0000

Minimum

With HC vs. without HC for

CT1	4	0.05	0.06	0.1817	0.5000
CT2	4	0.08	0.15	0.3910	1.0000
CT3	4	0.00	0.00	.	.
CT4	2	0.15	0.07	0.2048	0.5000
CT Planning	4	0.13	0.05	0.0154	0.1250

Results with HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.23	0.50	0.4338	0.6250
CT Planning vs.CT2	4	0.48	0.62	0.2221	0.2500
CT Planning vs.CT3	4	0.23	0.26	0.1856	0.5000
CT Planning vs.CT4	2	0.30	0.00	.	0.5000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.15	0.48	0.5760	0.8750
CT Planning vs.CT2	4	0.43	0.53	0.2040	0.2500
CT Planning vs.CT3	4	0.10	0.24	0.4740	0.6250
CT Planning vs.CT4	2	0.30	0.00	.	0.5000

Table 12: Posterior rectal wall

Measure	Comparison	N	Mean	Std	t-test p-value	SignedRank test p-value
Absolute value						
	With HC vs. without HC for					
	CT1	4	-0.41	0.75	0.3542	0.6250
	CT2	4	0.34	0.26	0.0776	0.1250
	CT3	4	0.59	0.25	0.0171	0.1250
	CT4	2	0.35	0.25	0.2988	0.5000
	CT Planning	4	0.60	0.60	0.1382	0.1250
	Results with HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-9.84	10.28	0.1515	0.2500
	CT Planning vs.CT2	4	-1.63	3.24	0.3890	0.6250
	CT Planning vs.CT3	4	-2.64	4.98	0.3668	0.3750
	CT Planning vs.CT4	2	-5.96	9.08	0.5236	1.0000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-10.85	11.28	0.1501	0.2500
	CT Planning vs.CT2	4	-1.89	3.66	0.3786	0.6250
	CT Planning vs.CT3	4	-2.65	5.56	0.4110	0.6250
	CT Planning vs.CT4	2	-6.51	10.18	0.5320	1.0000
Maximum						
	With HC vs. without HC for					
	CT1	4	-0.85	1.44	0.3225	0.6250
	CT2	4	0.70	0.47	0.0584	0.1250
	CT3	4	1.15	0.37	0.0084	0.1250
	CT4	2	0.70	0.42	0.2578	0.5000
	CT Planning	4	1.10	1.13	0.1478	0.1250
	Results with HC					

CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-18.83	19.76	0.1529	0.2500
CT Planning vs.CT2	4	-3.10	6.11	0.3850	0.6250
CT Planning vs.CT3	4	-5.05	9.40	0.3615	0.3750
CT Planning vs.CT4	2	-11.35	17.18	0.5217	1.0000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-20.78	21.63	0.1505	0.2500
CT Planning vs.CT2	4	-3.50	6.99	0.3906	0.6250
CT Planning vs.CT3	4	-5.00	10.49	0.4107	0.6250
CT Planning vs.CT4	2	-12.30	19.23	0.5319	1.0000
Mean					
With HC vs. without HC for					
CT1	4	0.78	0.42	0.0344	0.1250
CT2	4	0.75	0.34	0.0219	0.1250
CT3	4	0.65	0.31	0.0249	0.1250
CT4	2	0.50	0.14	0.1257	0.5000
CT Planning	4	0.75	0.33	0.0202	0.1250
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.48	2.52	0.7315	0.8750
CT Planning vs.CT2	4	-0.38	1.68	0.6852	1.0000
CT Planning vs.CT3	4	0.43	1.87	0.6803	0.6250
CT Planning vs.CT4	2	-1.10	3.39	0.7264	1.0000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.50	2.37	0.7019	0.8750
CT Planning vs.CT2	4	-0.37	1.68	0.6852	1.0000
CT Planning vs.CT3	4	0.33	1.81	0.7438	0.8750

CT Planning vs.CT4	2	-1.55	3.89	0.6733	1.0000

Minimum

With HC vs. without HC for

CT1	4	0.03	0.05	0.3910	1.0000
CT2	4	0.08	0.15	0.3910	1.0000
CT3	4	0.00	0.00	.	.
CT4	2	0.10	0.14	0.5000	1.0000
CT Planning	4	0.00	0.00	.	.

Results with HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.00	0.22	1.0000	1.0000
CT Planning vs.CT2	4	-0.30	0.55	0.3534	0.5000
CT Planning vs.CT3	4	-0.13	0.10	0.0796	0.2500
CT Planning vs.CT4	2	-0.15	0.21	0.5000	1.0000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.02	0.17	0.7888	1.0000
CT Planning vs.CT2	4	-0.23	0.40	0.3456	0.5000
CT Planning vs.CT3	4	-0.13	0.10	0.0796	0.2500
CT Planning vs.CT4	2	-0.05	0.07	0.5000	1.0000

Table 13: Proximal rectal wall

Measure	Comparison	N	Mean	Std	t-test p-value	SignedRank test p-value
Dose						
	With HC vs. without HC for					
	CT1	4	0.66	0.80	0.1976	0.6250
	CT2	4	0.63	0.70	0.1686	0.2500
	CT3	4	0.73	0.72	0.1373	0.1250
	CT4	2	-0.02	0.04	0.6560	1.0000
	CT Planning	4	0.28	0.45	0.3043	0.6250
	Results with HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	0.30	0.57	0.3691	0.6250
	CT Planning vs.CT2	4	-0.17	0.28	0.3006	0.5000
	CT Planning vs.CT3	4	-0.14	0.30	0.4230	0.6250
	CT Planning vs.CT4	2	0.60	0.38	0.2692	0.5000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	0.68	0.62	0.1149	0.1250
	CT Planning vs.CT2	4	0.18	0.16	0.1144	0.2500
	CT Planning vs.CT3	4	0.31	0.69	0.4291	0.6250
	CT Planning vs.CT4	2	0.38	0.78	0.6217	1.0000
Absolute value						
	With HC vs. without HC for					
	CT1	4	0.86	0.81	0.1254	0.2500
	CT2	4	0.66	0.83	0.2116	0.6250
	CT3	4	0.69	1.05	0.2797	0.3750
	CT4	2	-0.03	0.04	0.5000	1.0000
	CT Planning	4	0.06	0.28	0.6893	0.8750
	Results with HC					

CT Planning vs. CT1-4					
CT Planning vs.CT1	4	1.52	3.39	0.4370	0.6250
CT Planning vs.CT2	4	0.67	3.34	0.7149	1.0000
CT Planning vs.CT3	4	-0.74	4.66	0.7714	0.8750
CT Planning vs.CT4	2	3.06	4.69	0.5260	1.0000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	2.31	3.13	0.2369	0.2500
CT Planning vs.CT2	4	1.27	2.92	0.4491	0.6250
CT Planning vs.CT3	4	-0.11	5.13	0.9685	0.8750
CT Planning vs.CT4	2	2.89	5.08	0.5695	1.0000
Maximum					
With HC vs. without HC for					
CT1	4	1.58	1.54	0.1336	0.2500
CT2	4	1.22	1.54	0.2092	0.5000
CT3	4	1.28	1.96	0.2849	0.3750
CT4	2	-0.05	0.07	0.5000	1.0000
CT Planning	4	0.12	0.51	0.6590	0.7500
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	2.93	6.41	0.4285	0.6250
CT Planning vs.CT2	4	1.33	6.29	0.7018	1.0000
CT Planning vs.CT3	4	-1.33	8.76	0.7821	0.8750
CT Planning vs.CT4	2	5.80	8.91	0.5263	1.0000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	4.38	5.95	0.2380	0.2500
CT Planning vs.CT2	4	2.43	5.54	0.4458	0.6250
CT Planning vs.CT3	4	-0.17	9.65	0.9733	0.8750

CT Planning vs.CT4	2	5.50	9.62	0.5670	1.0000

Mean

With HC vs. without HC for

CT1	4	0.38	0.52	0.2441	0.5000
CT2	4	0.43	0.46	0.1647	0.2500
CT3	4	0.48	0.57	0.1963	0.2500
CT4	2	-0.05	0.07	0.5000	1.0000
CT Planning	4	0.10	0.23	0.4502	0.5000

Results with HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.50	0.57	0.1785	0.2500
CT Planning vs.CT2	4	-0.08	0.13	0.3189	0.3750
CT Planning vs.CT3	4	0.02	0.30	0.8777	0.7500
CT Planning vs.CT4	2	0.60	0.28	0.2048	0.5000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.78	0.78	0.1412	0.1250
CT Planning vs.CT2	4	0.25	0.25	0.1411	0.2500
CT Planning vs.CT3	4	0.40	0.67	0.3173	0.3750
CT Planning vs.CT4	2	0.45	0.64	0.5000	1.0000

Minimum

With HC vs. without HC for

CT1	4	0.03	0.05	0.3910	1.0000
CT2	4	0.03	0.05	0.3910	1.0000
CT3	4	0.03	0.05	0.3910	1.0000
CT4	2	0.05	0.07	0.5000	1.0000
CT Planning	4	-0.03	0.05	0.3910	1.0000

Results with HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.18	0.57	0.5813	1.0000
CT Planning vs.CT2	4	0.00	0.24	1.0000	1.0000
CT Planning vs.CT3	4	0.03	0.29	0.8729	1.0000
CT Planning vs.CT4	2	-0.15	0.07	0.2048	0.5000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.23	0.59	0.5017	1.0000
CT Planning vs.CT2	4	0.05	0.25	0.7177	1.0000
CT Planning vs.CT3	4	0.08	0.30	0.6500	1.0000
CT Planning vs.CT4	2	-0.05	0.07	0.5000	1.0000

Table 14: Urethra

Measure	Comparison	N	Mean	Std	t-test p-value	SignedRank test p-value
Absolute value						
	With HC vs. without HC for					
	CT1	4	-0.19	0.49	0.4883	0.6250
	CT2	4	-0.30	0.45	0.2788	0.3750
	CT3	4	-0.20	0.34	0.3155	0.6250
	CT4	2	-0.34	0.42	0.4603	0.5000
	CT Planning	4	-0.53	0.63	0.1889	0.3750
	Results with HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-0.60	0.69	0.1806	0.2500
	CT Planning vs.CT2	4	-0.75	1.25	0.3137	0.2500
	CT Planning vs.CT3	4	-0.80	1.19	0.2753	0.1250
	CT Planning vs.CT4	2	-0.46	0.37	0.3275	0.5000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-0.26	0.95	0.6185	0.8750
	CT Planning vs.CT2	4	-0.52	1.51	0.5393	1.0000
	CT Planning vs.CT3	4	-0.47	1.46	0.5661	0.8750
	CT Planning vs.CT4	2	-0.36	1.58	0.8038	1.0000
Maximum						
	With HC vs. without HC for					
	CT1	4	-0.30	1.01	0.5943	0.8750
	CT2	4	-0.50	0.92	0.3567	0.5000
	CT3	4	-0.40	0.65	0.3049	0.5000
	CT4	2	-0.65	0.78	0.4471	0.5000
	CT Planning	4	-0.98	1.09	0.1717	0.2500
	Results with HC					

CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-1.13	1.31	0.1856	0.2500
CT Planning vs.CT2	4	-1.45	2.38	0.3103	0.2500
CT Planning vs.CT3	4	-1.42	2.29	0.3016	0.5000
CT Planning vs.CT4	2	-0.85	0.78	0.3656	0.5000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-0.45	1.83	0.6563	0.8750
CT Planning vs.CT2	4	-0.97	2.88	0.5463	1.0000
CT Planning vs.CT3	4	-0.85	2.79	0.5849	0.8750
CT Planning vs.CT4	2	-0.70	2.97	0.7952	1.0000
Mean					
With HC vs. without HC for					
CT1	4	-0.07	0.10	0.2152	0.5000
CT2	4	-0.05	0.13	0.4950	0.7500
CT3	4	0.00	0.14	1.0000	1.0000
CT4	2	-0.15	0.21	0.5000	1.0000
CT Planning	4	-0.13	0.22	0.3416	0.5000
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-1.13	2.86	0.4886	0.8750
CT Planning vs.CT2	4	-1.15	1.97	0.3282	0.6250
CT Planning vs.CT3	4	-1.40	2.69	0.3751	0.6250
CT Planning vs.CT4	2	-6.05	11.38	0.5897	1.0000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-1.08	3.09	0.5370	0.8750
CT Planning vs.CT2	4	-1.08	2.19	0.3980	0.6250
CT Planning vs.CT3	4	-1.28	2.85	0.4364	0.6250

CT Planning vs.CT4	2	-6.20	11.88	0.5952	1.0000

Minimum

With HC vs. without HC for					
CT1	4	-0.03	0.05	0.3910	1.0000
CT2	4	-0.05	0.06	0.1817	0.5000
CT3	4	-0.08	0.05	0.0577	0.2500
CT4	2	-0.05	0.07	0.5000	1.0000
CT Planning	4	-0.05	0.06	0.1817	0.5000
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.08	0.10	0.2152	0.5000
CT Planning vs.CT2	4	0.00	0.00	.	.
CT Planning vs.CT3	4	0.03	0.05	0.3910	1.0000
CT Planning vs.CT4	2	0.00	0.00	.	.
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.10	0.14	0.2522	0.5000
CT Planning vs.CT2	4	0.00	0.00	.	.
CT Planning vs.CT3	4	0.00	0.00	.	.
CT Planning vs.CT4	2	0.00	0.00	.	.

Table 15: Bladder wall

Measure	Comparison	N	Mean	Std	t-test p-value	SignedRank test p-value
Absolute value						
	With HC vs. without HC for					
	CT1	4	0.08	0.41	0.7309	0.6250
	CT2	4	0.17	0.37	0.4228	0.6250
	CT3	4	0.25	0.52	0.4027	0.6250
	CT4	2	-0.09	0.53	0.8581	1.0000
	CT Planning	4	-0.08	0.34	0.6663	0.8750
	Results with HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-1.60	3.66	0.4463	0.6250
	CT Planning vs.CT2	4	-1.28	1.41	0.1672	0.2500
	CT Planning vs.CT3	4	-0.40	2.93	0.8048	1.0000
	CT Planning vs.CT4	2	-0.64	1.05	0.5506	1.0000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-1.44	4.07	0.5293	0.6250
	CT Planning vs.CT2	4	-1.02	1.85	0.3506	0.6250
	CT Planning vs.CT3	4	-0.06	3.56	0.9733	1.0000
	CT Planning vs.CT4	2	-0.85	1.97	0.6506	1.0000
Maximum						
	With HC vs. without HC for					
	CT1	4	0.15	0.74	0.7129	0.7500
	CT2	4	0.33	0.72	0.4322	0.6250
	CT3	4	0.48	0.94	0.3864	0.6250
	CT4	2	-0.10	0.99	0.9097	1.0000
	CT Planning	4	-0.13	0.65	0.7262	0.8750
	Results with HC					

CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-3.13	7.01	0.4382	0.6250
CT Planning vs.CT2	4	-2.43	2.72	0.1725	0.2500
CT Planning vs.CT3	4	-0.80	5.51	0.7903	1.0000
CT Planning vs.CT4	2	-1.20	1.98	0.5489	1.0000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	-2.85	7.71	0.5131	0.6250
CT Planning vs.CT2	4	-1.97	3.55	0.3468	0.6250
CT Planning vs.CT3	4	-0.20	6.63	0.9557	1.0000
CT Planning vs.CT4	2	-1.60	3.68	0.6488	1.0000
Mean					
With HC vs. without HC for					
CT1	4	0.03	0.10	0.6376	1.0000
CT2	4	0.10	0.08	0.0917	0.2500
CT3	4	0.08	0.05	0.0577	0.2500
CT4	2	0.00	0.14	1.0000	1.0000
CT Planning	4	-0.02	0.13	0.7177	1.0000
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.40	9.88	0.9406	1.0000
CT Planning vs.CT2	4	2.63	8.70	0.5889	1.0000
CT Planning vs.CT3	4	3.08	8.65	0.5284	0.8750
CT Planning vs.CT4	2	-4.65	5.73	0.4562	0.5000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.45	10.07	0.9344	1.0000
CT Planning vs.CT2	4	2.75	8.81	0.5767	1.0000
CT Planning vs.CT3	4	3.18	8.77	0.5215	0.8750

CT Planning vs.CT4	2	-4.70	5.94	0.4643	0.5000

Minimum

With HC vs. without HC for					
CT1	4	-0.03	0.05	0.3910	1.0000
CT2	4	0.00	0.00	.	.
CT3	4	0.00	0.00	.	.
CT4	2	0.00	0.00	.	.
CT Planning	4	-0.03	0.05	0.3910	1.0000
Results with HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.07	0.59	0.8160	1.0000
CT Planning vs.CT2	4	0.12	0.53	0.6702	1.0000
CT Planning vs.CT3	4	0.15	0.51	0.5954	1.0000
CT Planning vs.CT4	2	-0.10	0.14	0.5000	1.0000
Results without HC					
CT Planning vs. CT1-4					
CT Planning vs.CT1	4	0.08	0.65	0.8323	1.0000
CT Planning vs.CT2	4	0.15	0.58	0.6408	1.0000
CT Planning	4	0.18	0.56	0.5737	1.0000

vs.CT3					
CT Planning vs.CT4	2	-0.10	0.14	0.5000	1.0000

Table 16: Femoral heads

Measure	Comparison	N	Mean	Std	t-test p-value	SignedRank test p-value
Dose						
	With HC vs. without HC for					
	CT1	4	-0.13	0.08	0.0420	0.1250
	CT2	4	-0.11	0.08	0.0756	0.1250
	CT3	4	-0.11	0.10	0.1010	0.1250
	CT4	2	-0.14	0.11	0.3039	0.5000
	CT Planning	4	-0.26	0.23	0.1070	0.2500
	Results with HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-1.20	0.87	0.0704	0.1250
	CT Planning vs.CT2	4	-0.16	0.90	0.7413	0.8750
	CT Planning vs.CT3	4	-0.83	1.26	0.2788	0.3750
	CT Planning vs.CT4	2	-3.17	3.06	0.3819	0.5000
	Results without HC					
	CT Planning vs. CT1-4					
	CT Planning vs.CT1	4	-1.08	0.77	0.0691	0.1250
	CT Planning vs.CT2	4	-0.02	0.73	0.9700	1.0000
	CT Planning vs.CT3	4	-0.68	1.08	0.2951	0.3750
	CT Planning vs.CT4	2	-3.19	3.41	0.4119	0.5000
Absolute value						
	With HC vs. without HC for					
	CT1	4	-0.35	0.22	0.0497	0.1250
	CT2	4	-0.29	0.46	0.2992	0.3750
	CT3	4	-0.30	0.21	0.0667	0.1250
	CT4	2	-0.36	0.71	0.6027	1.0000
	CT Planning	4	-0.51	0.20	0.0154	0.1250
	Results with HC					

CT Planning vs. CT1-4

CT Planning vs.CT1	4	-1.75	0.52	0.0065	0.1250
CT Planning vs.CT2	4	-2.70	2.74	0.1431	0.2500
CT Planning vs.CT3	4	-1.53	1.27	0.0959	0.2500
CT Planning vs.CT4	2	-2.77	6.42	0.6512	1.0000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	-1.59	0.64	0.0158	0.1250
CT Planning vs.CT2	4	-2.48	2.88	0.1835	0.2500
CT Planning vs.CT3	4	-1.32	1.02	0.0814	0.2500
CT Planning vs.CT4	2	-2.67	7.35	0.6982	1.0000

Maximum

With HC vs. without HC for

CT1	4	-0.70	0.42	0.0457	0.1250
CT2	4	-0.57	0.93	0.3052	0.5000
CT3	4	-0.58	0.39	0.0618	0.1250
CT4	2	-9.65	14.07	0.5097	1.0000
CT Planning	4	-0.90	0.41	0.0216	0.1250

Results with HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	-3.25	0.93	0.0059	0.1250
CT Planning vs.CT2	4	-5.08	5.13	0.1424	0.2500
CT Planning vs.CT3	4	-2.83	2.41	0.1010	0.2500
CT Planning vs.CT4	2	3.70	0.71	0.0855	0.5000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	-3.05	1.24	0.0163	0.1250
CT Planning vs.CT2	4	-4.75	5.44	0.1789	0.2500
CT Planning vs.CT3	4	-2.50	1.90	0.0785	0.2500

CT Planning vs.CT4	2	-5.10	13.86	0.6945	1.0000

Mean

With HC vs. without HC for

CT1	4	-0.18	0.05	0.0060	0.1250
CT2	4	2.08	4.55	0.4290	1.0000
CT3	4	-0.15	0.06	0.0138	0.1250
CT4	2	-0.25	0.07	0.1257	0.5000
CT Planning	4	-0.17	0.13	0.0689	0.2500

Results with HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.23	3.01	0.8907	1.0000
CT Planning vs.CT2	4	-0.70	5.55	0.8171	0.6250
CT Planning vs.CT3	4	0.60	4.31	0.7986	1.0000
CT Planning vs.CT4	2	-1.00	0.42	0.1855	0.5000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.22	2.87	0.8854	1.0000
CT Planning vs.CT2	4	1.55	3.53	0.4446	0.6250
CT Planning vs.CT3	4	0.63	4.16	0.7833	1.0000
CT Planning vs.CT4	2	-1.10	0.14	0.0577	0.5000

Minimum

With HC vs. without HC for

CT1	4	-0.03	0.05	0.3910	1.0000
CT2	4	0.00	0.00	.	.
CT3	4	-0.08	0.05	0.0577	0.2500
CT4	2	-0.05	0.07	0.5000	1.0000
CT Planning	4	-0.08	0.05	0.0577	0.2500

Results with HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.55	0.93	0.3217	0.6250
CT Planning vs.CT2	4	0.58	0.90	0.2910	0.6250
CT Planning vs.CT3	4	0.40	0.83	0.4055	0.6250
CT Planning vs.CT4	2	0.45	0.92	0.6145	1.0000

Results without HC

CT Planning vs. CT1-4

CT Planning vs.CT1	4	0.60	0.99	0.3136	0.5000
CT Planning vs.CT2	4	0.65	0.93	0.2562	0.5000
CT Planning vs.CT3	4	0.40	0.85	0.4172	0.6250
CT Planning vs.CT4	2	0.45	1.06	0.6560	1.0000

LIST OF ABBREVIATIONS

AP	Anterior to Posterior
Ant.R.W	Anterior Rectal Wall
EBRT	External Beam Radiotherapy
ERB	Enodorectal Balloon
CTCAE	Cancer Institute Common Terminology Criteria for adverse Events
CBCT	Cone Beam Computed Tomography
cc	Cubic Centimeters
CC	Cranial to Caudal
CT	Computed Tomography
CRT	Conformal Radiation Therapy
CSU	Colorado State University
CSUVTH	Colorado State University Veterinary Teaching Hospital
CT	Computed Tomography
CTV	Clinical Target Volume
DVH	Dose Volume Histogram
F.Hs	Femoral Heads
GI	Gastrointestinal
GTV	Gross Target Volume
GU	Genitourinary
Gy	Gray
IACUC	The Institutional Animal Care and Use Committee
IGRT	Image Guided Radiotherapy
Lat.R W	Lateral Rectal Wall
LR	Left to Right
IMRT	Intensity Modulated Radiotherapy
kV	Kiolovoltage
mA	Miliamps
Max	Maximum
MeV	Mega Electronvolts
Min	Minimum
Mm	Millimeter
MRI	Magnetic Resonance Imaging
MV	Megavoltage
Post.R.W	Posterior Rectal Wall
Prox.R	Proximal Recum
PSA	Prostate specific Antigen
PTV	Planning Target Volume
PTVOLR	Planning Target Volume Less Rectal Wall

RT	Radiotherapy/Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SD	Standard Deviation
SBRT	Stereotactic Body Radiation Therapy
TCC	Transitional Cell Carcinoma
TPS	Treatment Planning System
US	Ultrasound
VRTOG	Veterinary Radiation Therapy Oncology Group