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Dosimetric Comparison of Hypofractionated Prostate Radiation with Simultaneous Integrated Boost and Conventional Fractionation with Sequential Boost

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Abstract

Introduction

Hypofractionated treatment delivery regimens are associated with better overall long-term disease control for prostate cancer. For patients with high-risk disease, there may be an indication for treatment of the surrounding pelvic lymph nodes for better over-all disease control. In order to achieve a hypofractionated regimen with treatment to the surrounding pelvic lymph nodes a simultaneous integrated boost technique is employed. There are concerns regarding achievability of target dose coverage and limitation of dose to the surrounding organs at risk with this fractionation.

Methods

This study is a retrospective dosimetric analysis of 7 randomly selected patients with high-risk prostate cancer. Each patient had a CT simulation performed, and two comparative treatment plans created, one with a conventional technique, the other with a hypofractionated technique.

Results

The results indicated that there was not a significant difference between target dose coverage and dose to surrounding organs at risk with the use of a hypofractionated treatment regimen with simultaneous integrated boost as compared to a conventional regimen with sequential boost. Use of a hypofractionated regimen with simultaneous integrated boost is a viable regimen to choose for patients with prostate cancer and indication of need for radiation to the surrounding pelvic lymph nodes.

Conclusion

Hypofractionated treatment regimens offer patients better long-term biochemical disease-free survival. Although patients may experience acute side effects earlier, and at an increased level, those side effects typically resolve more quickly than with conventional treatment delivery.

Introduction

The prostate is a gland located in the biologically male pelvis. It is bordered superiorly and posteriorly by the seminal vesicles, superiorly and anteriorly by the bladder, posteriorly by the rectum, and the urethra passes through its middle. The prostate gland is comprised of 5 lobes, and functions to create a fluid that is part of semen. Prostate cancer is the most commonly occurring cancer in adult males, and the second leading cause of cancer death. Average age at diagnosis is 66, and occurrence is rare in men under 40 [1]. Currently in the United States there are an estimated 3.1 million men alive with a prostate cancer diagnosis. Ultimately, about 1 in 41 men will die from prostate cancer. Typically, prostate cancer is discovered via routine screening that consists of a lab test evaluating prostate specific antigen (PSA) levels and a digital rectal exam (DRE) performed by a physician [2,3]. If abnormalities are found on these exams, more workup will be involved including repeat lab testing, computed tomography (CT), magnetic resonance imaging (MRI), and/or bone scan. Fifty percent of prostate cancers present with no symptoms and are relatively low risk [1].

Patients with high risk disease are classified as having a stage T3-T4 disease, PSA >20, and a Gleason score or 8-10, according to the National Comprehensive Cancer Network (NCCN), and account for approximately 20% of prostate cancer diagnoses [2]. Patients with high risk disease are at risk for their cancer to grow and spread quickly, and it is recommended that these patients pursue treatment without delay[2]. Prostate cancer may spread via local invasion to the periprostatic tissue, seminal vesicles, bladder and/or ureters. Lymphatic spread occurs through the external iliac, common iliac, presciatic, and presacral nodes. Hematogenous

metastases may be present in advanced disease. The most common site of distant metastases is bone.

Treatment recommendations vary with stage at diagnosis. Options include but are not limited to active surveillance, prostatectomy, cryotherapy, androgen deprivation therapy, immunotherapy, external beam radiation therapy, and/or brachytherapy. Patients with high risk disease should consider radical prostatectomy including pelvis lymph node dissection, or external beam radiation therapy to the prostate and surrounding pelvic lymph nodes [3,4]. Additionally, for patients with intermediate or high-risk cancer,[5] EBRT to the prostate with or without seminal vesicle inclusion is the leading treatment of choice [5,6].

In the last 20 years there has been rapid development in radiation oncology technology and understanding of disease in terms of biochemical control and toxicities associated with treatment regimens [7]. This has radically changed how prostate cancer is treated with radiation. Conventional treatment delivery methods prior to the advent of 3D conformal techniques used bony landmarks to delineate target volumes, and treatments were typically delivered via open fields. Once CT and MRI became available, along with advance treatment planning software that helped evaluate dose to normal structures and targets, considerable improvements were made in accuracy and limiting treatment related toxicities[4,8,9]. The early 2000s were the "early era of intensity modulated radiation therapy (IMRT),"[7]. IMRT treatment delivery was less conformal than it is today, and daily image guidance practices were not yet established. Even as recently as 2016, there was still data coming out proving better biochemical control rates of late toxicities with 3D conformal radiation therapy, which according to Vianni, et al., was a "great advance in terms of oncologic results,"[4].

In 1995, it was first suggested that control of prostate cancer would benefit from escalating doses in order to gain disease control [10]. In 2003, Brenner and Hall suggested that α/β ratios were as low as 1.5, after observing control rates after low dose rate brachytherapy [10,11]. Additionally, late responding normal tissues, specifically the rectum, have an assumed α/β ratio 5.4 [6,7,12]. It is now widely agreed that the α/β ratios are low, and proven need for dose escalation is needed, which has led to a greater need for better accuracy in treatment delivery [3–6,6,9,10,12,13]. When determining doses for hypofractionated regimens it is important to understand the biologically equivalent dose in comparison to historic conventional fractionations, as well as when evaluating normal structures for dose tolerance. Typically doses in the range of 80-86 Gray (Gy) have been used for prostate disease control, so hypofractionated doses need to have dose equivalence to these values (EQD2) [4]. Giving high doses to the target and limiting dose to normal structures is achievable via IMRT and image guided radiation therapy (IGRT), which can help prevent severe toxicities when using high doses[9]. One study of note evaluated rates of toxicities for patients receiving whole pelvis radiation therapy to the pelvic lymph nodes (LNs) with simultaneous integrated boost (SIB) to the prostate. The study found that patients on the hypofractionated regimen did not experience a difference in rate of grade >/= 2 late toxicities, but that patients who received radiation to the LNs had rates of late toxicity rates of 18.1% compared to 10.8% for patients who received EBRT to the prostate only [7]. The longest follow-up study to date is the "Conventional versus hypofractionated high-dose intensity modulated radiotherapy for prostate cancer," referred to as the CHHiP trial [6]. The CHHiP trial was a randomized study that allocated prostate cancer patients of various risk levels to a conventional or hypofractionated course of treatment[6]. Through long-term follow-up with the study subjects, the researchers determined that patients may initially suffer acute side effects at higher rates.

Typically, these side effects resolve earlier than they do on conventional schedules. At an average of 4 years post treatment, rates of toxicities were the same for conventional delivery and hypofractionated delivery with better biochemical control of the primary disease for the hypofractionated arm[5]. Many other studies also noted the same information in regards to acute and late toxicities and control rate [5,12,14]. The CHHiP trial also helped to establish that doses in the realm of 3Gy per fraction offered good control rates and comparable levels of late toxicities to conventional treatment for patients, based on toxicity profiles [6]. 10 year data also supported a 10% mean increase in overall survival for patients who were treated with a hypofractionated regimen[5].

When determining dose fractionation for EBRT, historically dose fractionation for external beam radiation therapy was based on our understanding of alpha (irreparable) and beta (repairable) damage to the cancer cells and the normal surrounding tissue [15]. Most cancers have a high α/β ratio, as compared to the normal surrounding tissues, and the general window of opportunity, for causing irreparable harm to cancer cells, but not to surrounding normal tissues falls between180-220 centigray (cGy) per fraction [15]. Prostate cancer is an exception, and has a relatively low α/β ratio, as compared to the surrounding normal tissues, [16]. The window of opportunity for killing cancer cells with a low α/β ratio is higher than the standard, and prostate cancers have better biochemical control with higher doses per fraction [5,16]. Recent research indicates that the α/β ratio of adenocarcinoma of the prostate is low in comparison to other diseases and that the surrounding tissues, namely the rectum, can tolerate more dose per fraction [17,18].

The American Society for Radiation Oncology (ASTRO) published new guidelines in November 2018 indicating that men with localized prostate cancer will benefit from a

hypofractionated dose scheme for EBRT. Hypofractionated dose regimens have larger daily doses for a fewer number of total treatments, at least >200 cGy per fraction, moderately hypofractionated more specifically is between 240-340cGy per fraction [17]. A common technique for targeting pelvis lymph nodes for locally advanced or high-risk patients in a hypofractionated dose scheme is a simultaneous integrated boost (SIB). This allows the creation of two target volumes and the delivery of different doses at the same time. These regimens have the potential to offer better disease control, produce less overall toxicity for the patients, as well as offer reduced economic burden [9,12,19]. Although much research indicates that for high-risk patients, long-term outcomes show better biochemical control and no evidence of increased late toxicities, there is yet to be a recommendation to treat these patients with a hypofractionated dose scheme [6,20]. Specifically, the ASTRO recommendations states that for men with high-risk prostate cancer hypofractionated EBRT to the prostate, *excluding* the LNs should be considered[17].

Dose fractionation for patients with high risk prostate cancer considered for this study averaged an initial 180cGy per day for 26 days to a total dose of 4680cGy to the prostate and surrounding pelvic LNs, followed by a boost of 180cGy per day for 13 days to the prostate, for a total combined treatment dose of 7020cGy to the prostate. Institutional practice follows a hypofractionated dose scheme of 270cGy per day to the prostate for 26 days while simultaneously delivering 180cGy to the surrounding LNs via SIB for a total of 4680 to the surrounding pelvic LNs, and 7020cGy to the prostate, based on the Fox Chase trials[7]. Historically radiation treatment was delivered with step-and-shoot IMRT with daily IGRT. More recently with technological upgrades treatments are now delivered with volumetric modulated arc therapy (VMAT) or Tomotherapy. Risks of receiving radiation therapy treatment to the

prostate and surrounding pelvic LNs are primarily late toxicities to the gastrointestinal (GI) and genitourinary (GU) systems[7].

Patients considered for this study were previously treated adult male patients with high risk prostate cancer. VMAT with IGRT was the comparative treatment modality. Two treatment plans were created for each patient; one plan with the standard dose fractionation with sequential boost and a second plan with hypofractionation and SIB. Plans were created for each patient with VMAT treatment technique. Plans were evaluated for conformity of dose distribution and how well they achieved meeting dose constraints to organs at risk (OARs). The researcher hypothesizes that better dose conformity will be achieved via hypofractionated dose fractionation with simultaneous integrated boost.

Null hypothesis (H_0): Treatment planning with hypofractionated dose scheme will not show no difference in dose conformity and ability to meet dose constraints to the prostate and surrounding tissues.

Alternative hypotheses (H_A): Treatment planning with hypofractionated dose scheme and simultaneous integrated boost will show a difference in dose conformity with ability to meet dose constraints to the prostate and surrounding tissues.

Methods and Materials

This retrospective study is based on a comparison of planning techniques comparing standard fractionation of 180cGy with sequential boost for a total of 39 treatment fractions (7020cGy to the prostate and 4680cGy to the surrounding pelvic LNs) to a hypofractionated simultaneous integrated boost, 270cGy delivered to the prostate, and 180cGy delivered to the

surrounding pelvic lymph nodes simultaneously for a total of 26 treatment fractions (7020cGy to the prostate, 4680cGy to the surrounding pelvic LNs). Patients that qualified for this study were selected via in house data base of previously treated patients at a midwestern institution. The database is maintained by the physics and dosimetry team employed there.

Ethical Considerations

Prior to seeking IRB approval, CITI certification was earned through Grand Valley State University, and additional courses required by the midwestern hospital were also completed. Research at this midwestern institution is a joint effort between the hospital system and the local university. IRB approval was requested through the IRB at the university. Exemption was granted, since no human subjects would be directly impacted by the results of the research. A second IRB exemption was requested through the IRB at Grand Valley State University and granted.

Patient data that was identified as useful for this study was stored within the private institutional Microsoft Outlook. Any information that was stored outside of outlook anonymized each patient, replacing identifiers with a simple patient numbering system, unique to the researcher (1, 2, 3, etc.), free from all personal identifiers.

Sample Population

The sample population consists of a total of seven patients with a diagnosis of high-risk prostate cancer, who had initiated treatment between January 2010 and November 2019. The included patients had an intact prostate and qualified for treatment to their prostate and surrounding pelvic lymph nodes, with or without coverage to the seminal vesicles. The patients

were all male biologic gender, and 18 years of age or older. Patients who received radiation to the prostate only, prostate bed only, prostate bed plus pelvis lymph nodes, were excluded.

Patient Setup

For patients who received radiation therapy treatment, a simulation was performed. Patients were instructed to arrive for their appointment with a full bladder and empty rectum. Each patient was simulated in the supine position with their arms resting high on their chest, away from the pelvis. Immobilization for the legs was accomplished using a Vac-Lok device. Three-point setup marks were given to each patient on their pelvis, to aid in reproducing the setup daily for treatment. Each patient had a CT scan performed on the Philips AcQ Sim CT scanner.

Planning

All compared patient plans were created in Pinnacle version 16.2 with the aid of autoplan by the researcher. The original plans created by the staff dosimetrists were not used in the study. The contours of the target volumes were created by the physician at time of treatment and were maintained for the study. The contoured organs included bladder, rectum, penile bulb, and the left and right femoral heads. Two plans were created by the researcher for each patient; one with a conventional regimen with sequential boost and a second with a hypofractionated regimen with SIB. Both plans employed a VMAT technique with opposing full arcs. The collimators were rotated 10-20 degrees in opposing directions for each arc, dependent upon patient anatomy, to limit interleaf leakage delivered to the patient in the same plane. The conventional plan consisted of initial fields encompassing the prostate and pelvic lymph nodes. 180cGy was delivered per fraction for 26 fractions. This was followed by a boost to the prostate of 180 cGy per fraction for

13 fractions. The hypofractionated plan targeted both the prostate and pelvic lymph nodes simultaneously to different dose levels. The prostate received 270cGy per day and the surrounding pelvic lymph nodes receiving 180cGy per day for a total of 26 fractions. With both regimens, the prostate received a total of 7020 cGy and the surrounding pelvic lymph nodes received 4680 cGy. Patient plans were created for the Varian TrueBeam. Autoplanning technique in Pinnacle was used with the criteria that can be found in Figures 1-3. Planning criteria was based on institutional practice at the midwestern institution. The autoplanning technique using the same objectives for all patients was chosen in order to limit manual manipulation and variation between plans. When treatment planning was complete, the dose volume histograms for each patient and plan were evaluated at dose points that can be found in Figure 1-3. Additionally, 95% dose coverage of 95% of the treatment volume was evaluated, as well as the conformity index (CI) for each target. Patient specific data was tabulated by use of a Microsoft Excel spreadsheet, where each patient was anonymized.

Statistical Analysis

For this analysis, an independent variable was tested with many levels of dependent variables. The independent variable, treatment planning technique, included two levels: conventional delivery with a sequential boost, and hypofractionated delivery with a SIB. Dose points and coverages were compared. The analysis performed to determine interaction was one-way ANOVA. A one-way ANOVA compares levels of categorical independent variables with continuous dependent variables. The tests for each subset of OARs, 95% coverage values, and CIs evaluated were performed separately. Equal variance was verified for each test, with evaluation of the Levene's value. To determine if there was significant interaction, the *F* value

with a significance (α) of $p < 0.05$ was used. For any groups showing significant interaction, a post-hoc analysis was performed. The software used for these comparisons was SPSS v. 20.

Results

The goal of this study is to evaluate and compare treatment techniques to determine if one treatment delivery method offered better dose conformity over the other, and reduction to dose in the nearby organs at risk. Seven previously treated high-risk biologically male prostate cancer patients were selected for this study. Patients who were selected had an intact prostate and indication to receive treatment to the pelvic lymph nodes.

PTV 7020

PTV 7020 was the treatment volume encompassing the prostate, +/- the seminal vesicles. With conventional treatment delivery, the prostate received 180cGy per day for 39 total treatment fractions. Hypofractionated treatment delivered 270cGy for 26 total fractions. Both regimens offered the same overall total dose of 7020cGy to the PTV. The points of evaluation selected for this volume were conformity index (CI), mean dose, and 95% coverage to 95% of the target volume.

PTV 7020 Conformity Index

CI was determined by calculating the sum of the area of the 100% isodose line volume/PTV. CI values ranged from 0.33 to 1.58 for conventional delivery, with a mean CI of 0.76, and a range of 1.25. With hypofractionated delivery, CI values ranged from 0.51 to 0.92, with a mean CI of 0.72 and a range of 0.41(refer to Table 1). The main effect of treatment modality was not significant, $F(1, 12)=.083$, $p=0.779$. Conventional treatment regimens and

hypofractionated regimens did not differ significantly in relation to CI for PTV 7020. No post-hoc analysis was performed.

Mean dose to PTV 7020

Mean dose to PTV 7020 was evaluated for both plans. The mean dose to the PTV 7020 differed slightly between the treatment techniques, with a 0.6% of prescribed dose variation between mean doses. Mean dose for conventional delivery was 7023.6cGy (*SD*=43.06). Mean dose for hypofractionated delivery was 7070.04cGy (*SD*=56.49). The main effect of treatment modality was not significant, $F(1, 12)=2.993$, $p=.109$. Conventional regimens and hypofractionated regimens did not differ significantly in relation to mean dose to PTV 7020. No post hoc analysis was performed.

Minimum 95% coverage to 95% of PTV 7020

The minimum target coverage goal for PTV 7020 was for a minimum of 95% of the prescribed dose (6669 cGy) to be delivered to at least 95% of the target volume. Mean target coverage with conventional delivery was 98.3% (*SD*=2.2). Mean target coverage with hypofractionated delivery was 97.3% (*SD*=2.65) for hypofractionated. Variance between 95% coverage differed by 1%. The main effect of treatment modality was not significant, $F(1, 12)=.666$, $p=.430$. Conventional regimens and hypofractionated regimens did not differ significantly in relation to the target coverage goal of 95% of the PTV receiving 95% of the prescription dose. No post hoc analysis was performed.

PTV 4680

PTV 4680 was comprised of the pelvic lymph nodes surrounding the prostate. The points of evaluation selected for this volume were CI, mean dose, and 95% coverage to 95% of the target volume. Refer to Table 1 for distributions.

Conformity Index PTV 4680

CI was determined by calculating the sum of the area of the 100% isodose line volume/PTV. CI values ranged from 0.41 to 1.7, with a mean value of 1.25 (*SD*=0.41), and range of 1.29 for conventional delivery. CI values ranged from 0.69 to 1.39, with a mean value of 1.1 (*SD*=0.33) and a range of 0.7 for hypofractionated delivery. The main effect of treatment modality was not significant, $F(1, 12)=.692$, $p=.422$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to CI for PTV 4680. No post-hoc analysis was performed.

Mean Dose PTV 4680

Mean dose to PTV 4680 was evaluated for both plans. Mean dose delivered to PTV 4680 was 5182.9 cGy (*SD*=239.41). Doses delivered had a minimum of 4868.4 cGy and maximum of 5477 cGy, for a range of 424.4 cGy for conventional delivery. With hypofractionated delivery, mean dose to PTV 4680 was 5034.1cGy (*SD*=231.82), with a minimum of 4790.47 cGy to a maximum of 5305.3 cGy, total range 449.6 cGy (see Table 1). There was a total difference of 148.8cGy between mean doses, which comprised of 3.2% of the prescription value. The main effect of treatment modality was not significant, $F(1, 12) = 1.395$, $p=0.260$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to mean dose to PTV 4680.

Minimum 95% coverage to 95% of PTV 4680

The minimum target coverage goal was for a minimum of 95% of the prescription dose (4446cGy) to be delivered to at least 95% of the target volume. The main effect of treatment modality on 95%coverage to PTV 4680 was not significant, F(1, 12)=.444, p =.518. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to the coverage goals of 95% of the prescription being delivered to 95% of PTV 4680. No post hoc analysis was performed. Mean coverage values differed by 0.2%. See Table 1 for mean dose volume distribution.

Bladder

V7020<10%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the bladder receiving 7020cGy to 10% or less. The main effect of treatment modality was not significant $F(1, 12) = .369$, p =0.555. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V7020<10% for the bladder. Mean volume of bladder receiving 7020cGy was 4.11% (*SD*=1.14) with conventional delivery and 4.81% (*SD*=2.80) with hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V5000<15%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the bladder receiving 5000cGy to 15% or less. A main effect of treatment modality was not significant for V5000<15% $F(1, 12) = .420$, p =.529. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V5000<15% for the bladder. Mean volume of the bladder receiving 5000cGy was 22.57% (*SD*=11.0) for

conventional delivery and 19.03% (*SD*=9.42) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V4500<25%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the bladder receiving 4500cGy to 25% or less. A main effect of treatment modality was not significant for V4500<25%, $F(1, 12) = 0.49$, $p = .828$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V4500<25%. Mean volume of the bladder receiving 4500cGy was 27.32% (*SD*=11.89) for conventional delivery and 25.98% (*SD*=10.7) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V3500<35%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the bladder receiving 3500 cGy to 35% or less. A main effect of treatment modality was found to be not significant for 3500<35% $F(1, 12) = .035$, $p = .854$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V3500<35%. Mean volume of the bladder receiving 3500cGy was 37.24% (*SD*=13.72) for conventional delivery and 38.54% (*SD*=12.08) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V2500<50%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the bladder receiving 2500 cGy to 50% or less. A main effect of treatment modality on V2500<50% was not significant, $F(1, 12) = .123$, $p = .732$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V2500<50%. Mean

volume of the bladder receiving 2500cGy was 52.31% (*SD*=19.01) for conventional delivery and 55.7% (*SD*=17.21) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

Rectum

Planning goals for the rectum at the midwestern institution are comprised of the following dose limitation guidelines: V7020<10%, V5000<15%, V4000<25%, V3000<35%, V2000<50%. Mean dose coverage was evaluated at each dose point.

V7020 <10%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the rectum receiving 7020cGy to 10% or less. A main effect of treatment modality on V7020<10% was not significant, $F(1, 12) = .000$, $p = .996$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V7020<10%. Mean volume of the rectum receiving 7020cGy was 1.31% (*SD*=1.75) for conventional delivery and 1.31% (*SD*=1.64) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V5000<15%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the rectum receiving 5000 cGy to less than 15%. A main effect of treatment modality on V5000<15% was not significant, $F(1, 12) = .198$, $p = .664$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V5000<15%. Mean volume of the rectum receiving 5000cGy was 10.8% (*SD*=7.96) for conventional delivery and 9.18% (*SD*=5.42) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V4000<25%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the rectum receiving 4000cGy to less than 25%. A main effect of treatment modality on V4000<25% was not significant, $F(1, 12) = .459$, $p = .511$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V4000<25%. Mean volume of the rectum receiving 4000cGy was 20.96% (*SD*=7.42) for conventional delivery and 18.6% (*SD*=5.47) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V3000 <35%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the rectum receiving 3000cGy to less than 35%. A main effect of treatment modality on V3500<35% was not significant, $F(1, 12) = .417$, $p = .531$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V3000<35%. Mean volume of the rectum receiving 3000cGy was 31.96% (*SD*=7.77) for conventional delivery and 29.73% (*SD*=4.82) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V2000 <50%

A planning goal for EBRT to the prostate and surrounding pelvic LNs is to limit the volume of the rectum receiving 2000 cGy to less than 50%. A main effect of treatment modality on V2000<50% was not significant, $F(1, 12) = .445$, $p = .517$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V2000<50%. Mean volume of the rectum receiving 2000cGy was 50.11% (*SD*=10.04) for conventional delivery and

47.48% (*SD*=2.93) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

Penile Bulb

Treatment planning objects for EBRT to the prostate and surrounding pelvic LNs regarding the penile bulb are to limit mean does to the penile bulb to <3000 cGy. A main effect of treatment modality on mean dose to the penile bulb <3000 was not significant. $F(1, 12) = .312$, $p = .587$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to mean dose <3000cGy to the penile bulb. Mean dose to the penile bulb was 1314.21cGy (*SD*=543.85) for conventional delivery and 1521.31cGy (*SD*=816.23) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

Femoral Heads

Planning goals for the femoral heads are to limit the amount of the femoral head receiving 2500 cGy to less than 10%, and the amount of the femoral head receiving 1500 cGy to less than 25%.

Femoral Head Left

V2500 <10%

A main effect of treatment modality on V2500<10% was not significant, $F(1, 12) = .269$, $p = .613$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V2500<10%. Mean volume of the left femoral head receiving 2500cGy was 8.41% (*SD*=2.64) for conventional delivery and 9.79% (*SD*=6.56) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V1500 <25%

A main effect of treatment modality on V1500<25% was not significant. $F(1, 12) = 1.448$, $p = .252$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V1500<25%. Mean volume of the left femoral head receiving 1500cGy was 24.01% (*SD*=4.52) for conventional delivery and 31.97% (*SD*=16.91) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

Femoral Head Right

V2500 <10%

A main effect of treatment modality on V2500<10% was not significant, $F(1, 12) = .070$, $p = .795$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V2500<10%. Mean volume of the right femoral head receiving 2500cGy was 8.8% (*SD*=4.88) for conventional delivery and 9.62% (*SD*=6.56) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

V1500 <25%

A main effect of treatment modality on V1500<25% was not significant. $F(1, 12) = 1.321$, $p = .273$. Conventional treatment regimens and hypofractionated regimens did not differ significantly in relation to V1500<25%. Mean volume of the right femoral head receiving 1500cGy was 23.51% (*SD*=4.26) for conventional delivery and 31.51% (*SD*=17.91) for hypofractionated delivery. See Table 2 for distributions. No post hoc analysis was performed.

Discussion

The purpose of this study was to observe and compare a conventional treatment regimen with sequential boost to a hypofractionated treatment regimen with SIB for the treatment of high-risk prostate cancer targeting the prostate and surrounding pelvic LNs with EBRT. The

comparison of the treatment regimens was done to evaluate if target dose coverage and avoidance of OARs could be achieved with both techniques. In order to ensure disease control, coverage of targets is the number one priority in treatment planning for treatment of prostate cancer, with a need to spare to surrounding structures. Radiation in excess of recommended dosing can cause acute and long-term side effects for the patients and be disruptive to daily living activities[9,12,21,22].

PTV coverage, PTV 7020 and PTV 4680

This study indicated that there was no evidence of significant effect of treatment modality on target coverage or dose limitation to nearby organs at risk. This result indicates that delivery of radiation with a hypofractionated regimen is dosimetrically comparable to delivery of radiation with a conventional regimen. Due to evidence of better rates of biochemical failure free survival with hypofractionated regimens for prostate cancer patients, it is important to evaluate if this is a modality that can be offered to high-risk patients as well as low-risk patients [5,7,23,24]. High-risk prostate cancer is unique when compared to low-risk prostate cancer due to the nature of the likelihood of quick progression of disease [17,24,25]. With a diagnosis of high-risk prostate cancer, it is imperative to start treatment without delay, due to the nature of and likelihood of quick progression of disease [2,3].

Regarding PTV 7020, both plans achieved target coverage goals of 95/95 and mean coverage differed by 1 %. An interesting comparison when evaluating PTV 7020 was that when reviewing the box plot and range of CI values, there was a smaller range when reviewing the conformity index for the hypofractionated plan with SIB, refer to Figure 4. The ANOVA for these values had a p=0.779 indicating that there was not a significant effect of treatment

modality on the CI, but further research with a larger sample size may be able to evaluate a statistical difference more effectively.

PTV 4680 also had a smaller distribution of difference for CI values with hypofractionated delivery, refer to Figure 5. The ANOVA for these values had a p=0.442, indicating that there was not a significant effect of treatment modality on CI for PTV 4680. Further research with a larger sample size may be able to more effectively evaluate the presence of any significant difference.

Bladder

The bladder is located directly anterior and superior to the prostate. Problems related to treatment toxicity from radiation include frequency, incontinence, and discomfort with urination[21] There was no significant effect of treatment modality on mean percentage of volume receiving radiation at the dose constraint targets seen in Table 2. In addition to there being no significant effect of treatment modality, there was also no observable trend of increase or reduction of volumes treated when comparing one modality to the other. Mean volumes differed by as little as 0.7% to a maximum of 3.39%. Literature indicates that there is no difference in rates of frequency of acute or late GU toxicity for patients treated with conventional or hypofractionated regimens [7,26]. This dosimetric comparison supports the literature findings.

Rectum

There was no significant effect of treatment modality on mean percentage of volume receiving radiation at the dose constraint targets seen in Table 2. Despite the absence of statistical significance, there was a general trend of mean volumes being slightly lower for the hypofractionated group, for all but one dose point, V7020<10%. Both treatment regimens were

observed to encompass a mean volume well below the constrain for this dose point, at 4.11% for conventional delivery and 4.81% for hypofractionated delivery. Although the decreases were with hypofractionation were not significant, (V5000=1.6%, V4000=2.36%, V3000=2.26%, V2000=2.6%), future research with a larger sample size may be able to evaluate an effect of treatment modality. Of greatest concern in the review of studies evaluating hypofractionation for EBRT to the prostate was resolution of treatment related toxicities as well as presence of grade 2 or greater GI toxicity as defined by the RTOG [7]. The long-term data evaluated indicated that many patients in hypofractionated trials experienced acute side effects earlier on average, than patients who received conventionally fractionated treatment delivery, with resolution of these side effects also taking place sooner [4,24,26,27]. The literature also indicated that there was not a significant impact on rates of rectal toxicity >/= grade 2 with treatment regimen [7,26]. This dosimetric comparison shows that there is no significant effect of treatment modality on achievability of dose constraints to the rectum which supports the findings in the literature.

Penile Bulb

In evaluation of the literature comparing conventional and hypofractionated treatment regimens, in relation to dose to the penile bulb, there was no relationship between treatment modality and reduced rates of sexual dysfunction following EBRT [28,29]. This dosimetric comparison found that mean dose delivered to the penile bulb was significantly lower than dose constraint goals for both treatment regimens, and that there was no significant effect of treatment modality on mean dose to the penile bulb.

Femoral Heads

Femoral heads were evaluated separately but given the same constraints. Dose points considered in evaluation were V2500<10 and V1500<25 per institutional guidelines. There was no significant effect of treatment modality on dose to the femoral heads, as can be seen in Table 2. Interestingly the left femoral head, doses trended higher with hypofractionated treatment for the left femur and the right femur for both dose points. Dose constraint goals for V2500<10% all fell within constraint goals for both treatment modalities. Mean volume restriction for V1500<25% was not met for the right or left femoral head with hypofractionated delivery. Although the referenced trials did not compare rates of toxicity based on treatment modality for the femoral heads, literature suggests that radiation dose to the femoral heads be limited 5000cGy to less than 5% of the organ, or a max dose of less than 4500cGy [15,30]. This results in long-term risk of degradation of bone, resulting in risk of radiation associated fractures[30]. There was no significant effect of treatment modality on dose distribution to the femoral heads. Figure 6 shows comparative isodose distributions for conventional and hypofractionated treatment techniques.

This study was based upon the current ASTRO recommendations in support of hypofractionation of EBRT for patients with low-risk prostate cancer [17]. The recommendations for hypofractionation are based on the increased understanding and consensus of lower α/β ratios for prostate tumors that was first suggested in the 1990s [11,25,31,32]. The ASTRO recommendations do not currently extend to patients in the high-risk category, nor to the elective coverage of the surrounding pelvic LNs. Interestingly three of five referenced studies evaluated for the ASTRO recommendations included high-risk patients, and one study exclusively included high-risk patients [5,6,17,33,34]. Specifically, the CHHiP trial and Dutch Hypofractionated versus conventionally fractionated radiotherapy for localized prostate cancer (HYPRO) trial enrolled

high-risk patients, and the Italian study performed by Arcangali, et. al enrolled exclusively high-risk patients [14,17,23,35]. Studies not referenced by the ASTRO recommendations, the Fox Chase trials and a study by Martinez et al, also had a subset of high-risk patients [20,24]. The studies that included high-risk patients showed a consensus of better long-term disease control with hypofractionated EBRT with or without pelvic LN radiation. An important note to add is that when increased understanding of lower α/β ratios was first realized, technology was not yet advanced enough to deliver high amounts of radiation per fraction and protect nearby critical OARs [4]. Technology for both EBRT treatment delivery and treatment planning software have evolved and made it possible to deliver high doses of radiation more conformally and more precisely, making hypofractionation achievable [4].

Limitations and Future Research

This study was limited by the small sample size available. The intended sample size for this study was 10 patients. Two databases had originally been available to the researcher at the initiation of this study, but extenuating circumstances limited database availability to one. Increased sample size could impact the relevance and significance of this data.

PTV volumes were not compared by size. Future research could assess whether volume of targets correlated to target coverage and dose limitation to nearby OARs. Additionally, future studies could evaluate the amount of organ overlap of target volumes and OARs to increase understanding of why planning objectives were not achievable in some instances. This do not fall within the scope of this study but could be useful knowledge as more is learned about hypofractionated treatment delivery for patients with high-risk prostate cancer with indication to radiate the surrounding pelvic LNs.

Conclusion

Current ASTRO recommendations for prostate cancer are in support of a hypofractionated treatment regimen for localized prostate cancer[17]. Although some patients treated with a hypofractionated regimen may experience acute side effects earlier, and at higher levels, typically these side effects resolve more quickly than with conventional treatment delivery[12,21]. Five and 10-year follow up data supports an increase in biochemical disease-free survival, and should be considered for patients with high-risk prostate cancer[5]. In addition to offering better overall disease control and comparable rates of late toxicities, hypofractionation offers the advantage of decreased cost of treatment to the patient due to fewer overall treatments, and a more limited overall disruption to life [9].

This dosimetric comparison showed that there was no significant effect of treatment modality on target coverage or dose constraint to OARs. This is promising, as it indicates that treating high risk prostate cancer patients with indication of treatment to the surrounding pelvic lymph nodes is achievable. Offering high risk patients a hypofractionated treatment regimen gives the benefit of better long term biochemical failure free survival.

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Appendix

Figure 1. Dose planning constraints used in Pinnacle autoplan for the conventionally fractionated prostate + pelvic lymph node dose, treating 180 cGy per day to a total dose of 4680 cGy.

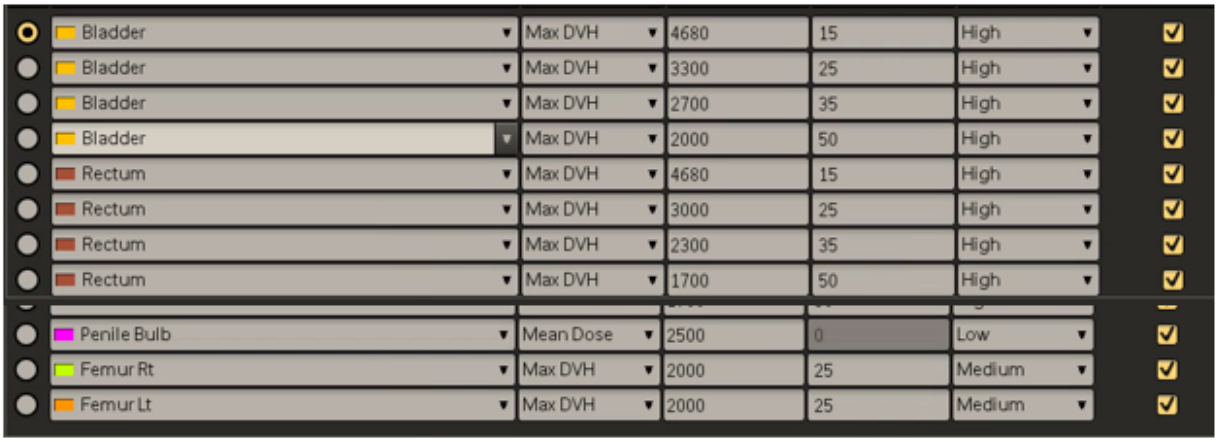

Figure 2. These are the planning constraints used in Pinnacle autoplan for the conventionally fractionated plan, treating 180cGy per day boosting the prostate an additional 2340cGy for a total dose of 7020 cGy.

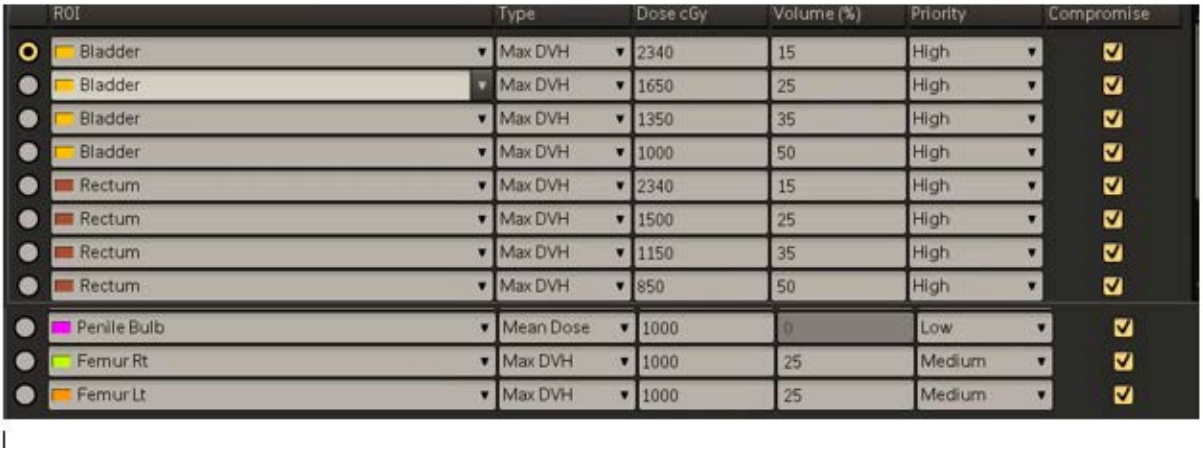

Figure 3. These are the planning constraints used in Pinnacle autoplan for the hypofractioanted SIB plan, treating 270cGy per day to the prostate and 180 per day to the surrounding pelvic lymph nodes.

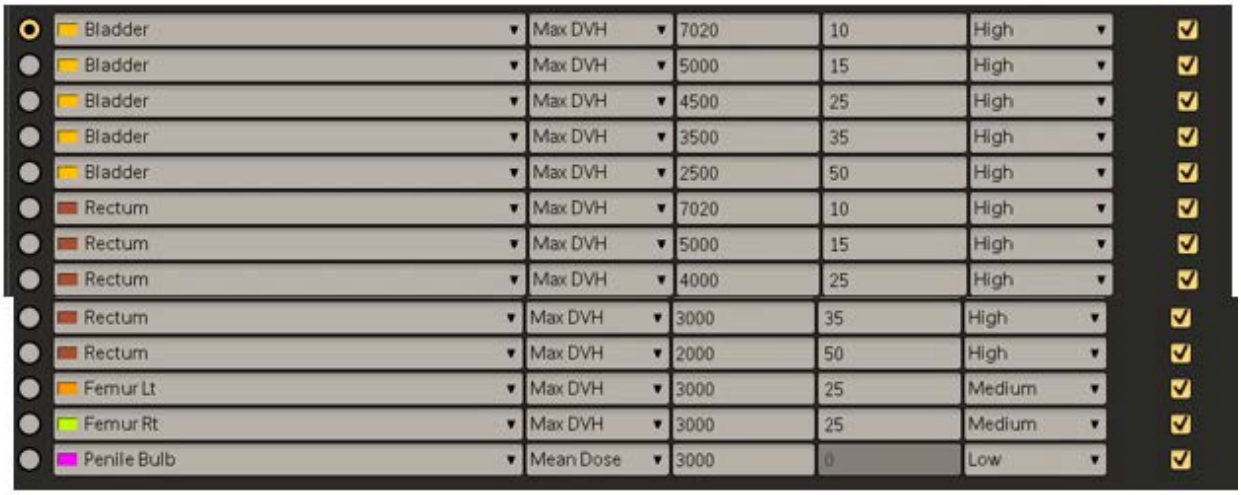

Table 1. Dose Evaluation for Targets

	Conventional			Hypofractionated			ANOVA
	Min	**Max**	**Mean**	**Min**	**Max**	**Mean**	***p* Value**
PTV 7020 Mean Dose	6956.10	7075.0	7023.6	7003.4	7119.4	7070.4	0.109
PTV 7020 95% to 95% volume	93.74%	99.92%	98.33%	92.4%	99.73%	97.27%	0.430
PTV 7020 CI	0.33	1.58	0.77	0.51	0.92	0.72	0.779
PTV 4680 Mean Dose	4866.4	5477.0	5182.9	4790.5	5305.3	5034.11	0.260
PTV 4680 95% to 95% volume	99.4%	100%	99.9%	98.23%	100%	99.7%	0.518
PTV 4680 CI	0.41	1.53	1.25	0.69	1.39	1.1	0.422

Table 2. Mean Dose Volume Constraints to Organs at Risk

	Conventional			Hypofractionatied			ANOVA
	Min	**Max**	**Mean**	**Min**	**Max**	**Mean**	***p* Value**
Bladder V7020 <10%	2.01%	5..75%	4.11%	1.45 %	10.61 %	4.81 %	0.555
Bladder V5000 <15%	12.41 %	45.92 %	19.03 %	10.51 %	39.23 %	19.03 %	0.529
Bladder V4500 <25%	16.8%	52.88%	27.32%	17.77%	49.45%	25.98%	0.828
Bladder V3500 <35%	26.48%	67.02%	37.24%	29.7%	65.1%	38.54%	0.854
Bladder V2500 <50%	40.66%	94.14%	52.31%	44.79%	46.9%	55.7%	0.732
Rectum V7020 <10%	0%	3.79%	1.31%	0%	3.92%	1.31%	0.996
Rectum V5000 <15%	2.07%	20.16%	10.8%	2.56%	14.92%	9.18%	0.664
Rectum V4000 <25%	9.29%	27.03%	20.96%	12.33%	24.8%	18.6%	0.511
Rectum V3000 <35%	20.09%	43.71%	31.96%	22.09%	34.92%	29.73%	0.531
Rectum V2000 <50%	36.77%	62.27%	50.11%	42.28%	50.84%	47.48%	0.517
Fem Head L V2500 <10%	4.65%	13.37%	8.41%	0.02%	19.88%	9.79%	0.613
Fem Head L V1500 <25%	19.5%	31.51%	24.01%	13.28%	65.14%	31.97%	0.252
Fem Head R V2500 < 10%	1.35%	15.11%	8.8%	0.95%	22.27%	9.62%	0.795
Fem Head R V1500 <25%	17.56%	29.37%	23.51%	10.23%	67.96%	31.51%	0.273
Penile Bulb Mean <3000	932.5 cGy	2436.1 cGy	1314.21 cGy	933.6 cGy	3194.7 cGy	1521.31 cGy	0.587

Figure 4. Boxplot comparing CIs for PTV 7020

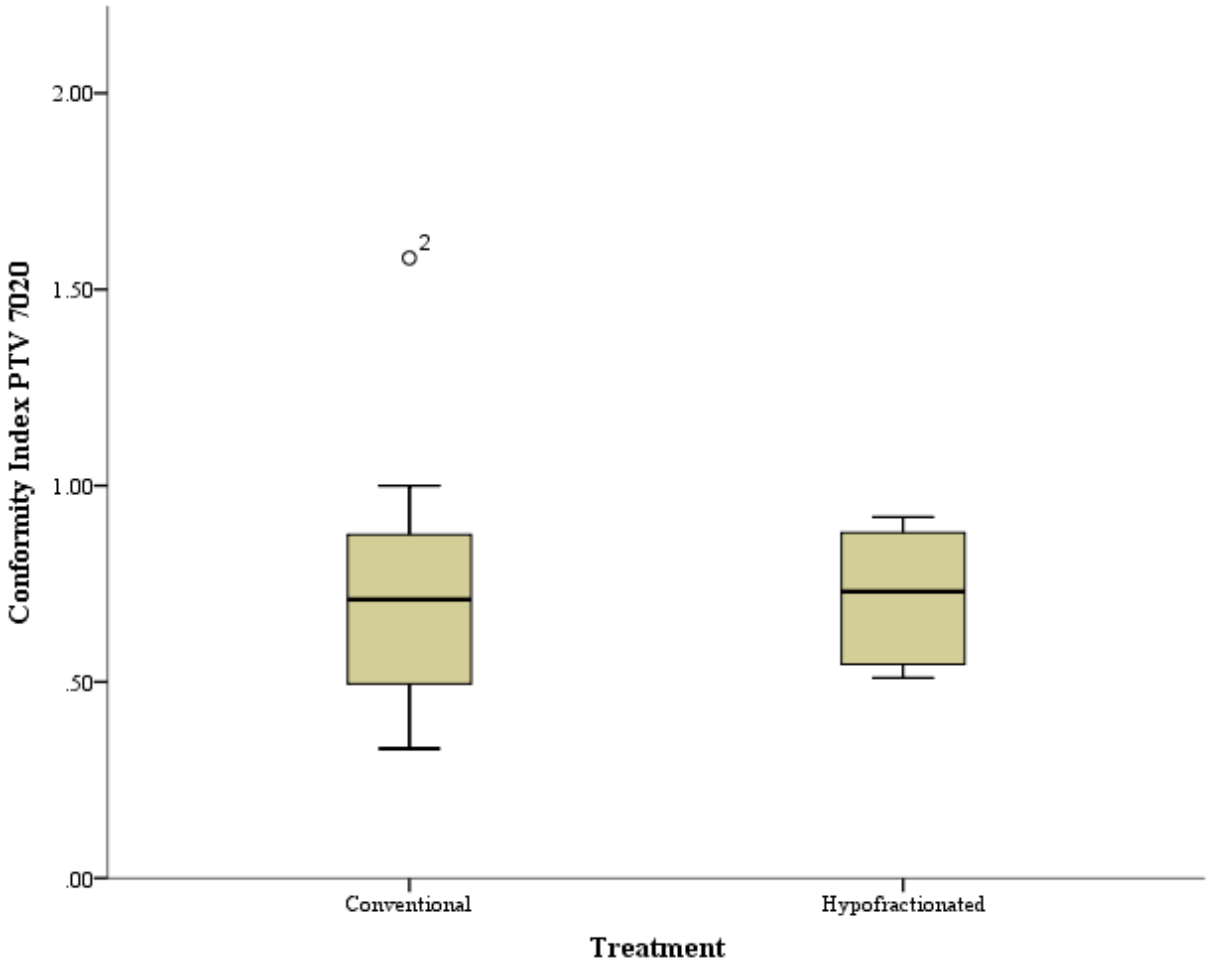

Figure 5. Boxplot comparing CIs for PTV 4680

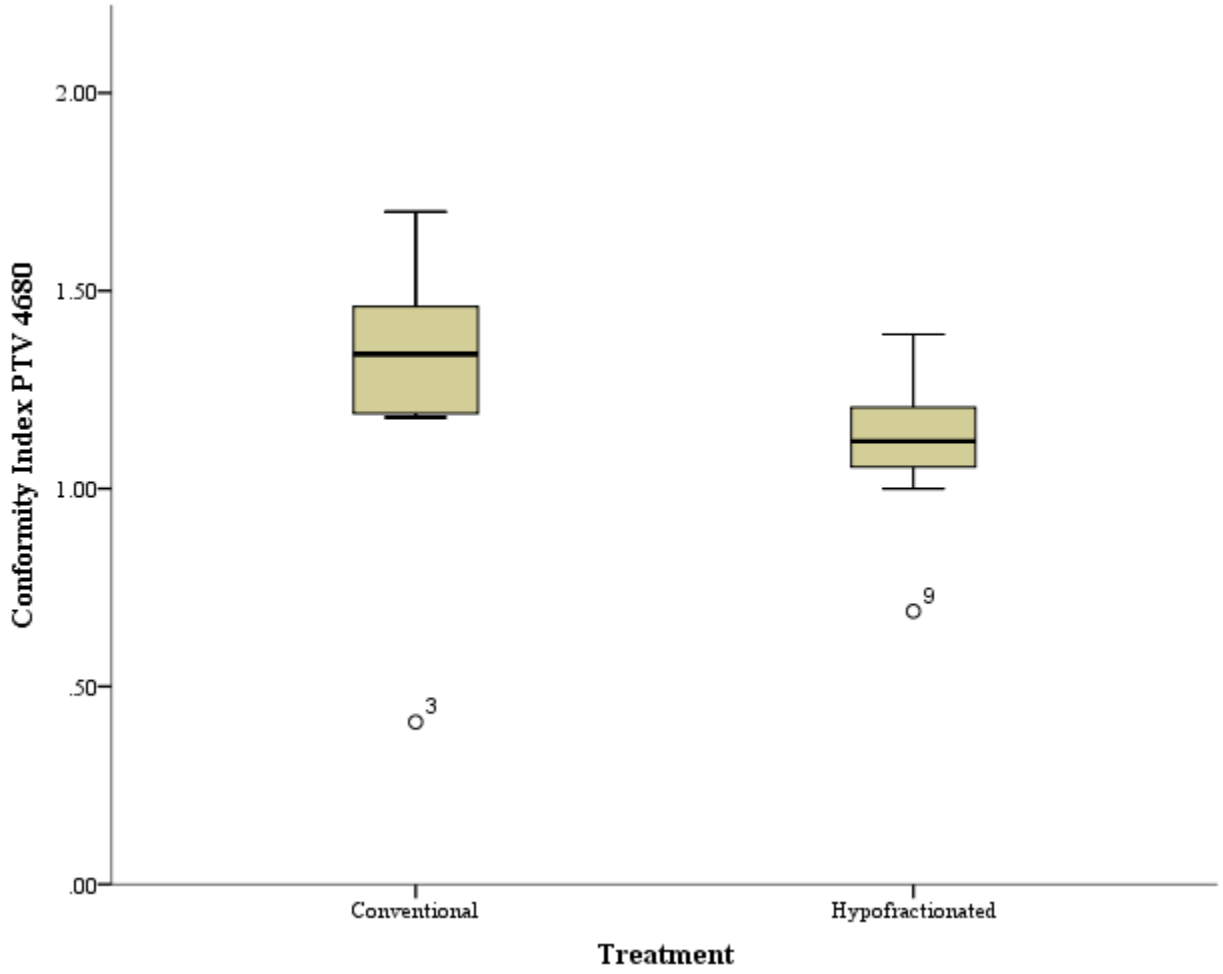

Figure 6. Isodose distributions for conventional and hypofractionated regimens. Special attention paid to distribution around femoral heads.